Carbon ion beam radiotherapy (CIRT) for cancer treatment

Systematic review

Ludwig Boltzmann Institut
Health Technology Assessment

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List of abbreviations

AA.....Anaplastic astrocytomas
AJCC .....American Joint Committee on Cancer
ARCHADE.....Advanced Resource Center for HADrontherapy in Europe
CGE.....Cobalt Gray Equivalents
CIB .....Carbon ion boost
CIRT .....Carbon ion radiotherapy
CSS.....Cause-specific survival
CSS.....Cause-specific survival
CT.....Controlled trial
CTCAE .....Common Terminology Criteria for Adverse Events
C-ion .....Carbon ion
DFS .....Disease-free survival
DSS .....Disease-Specific Survival
ENT.....Ear-Nose-Throat
EORTC-QLQ .....European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ESCC.....Esophagal squamous cell carcinoma
ETOILLE .....Espace de Traitement Oncologique par Ions Légers dans le cadre Européen
EU .....European Union
EUNETHTA .....European Network for Health Technology Assessment
FACT-G .....Functional Assessment of Cancer Therapy – General
FACT-P .....Functional Assessment of Cancer Therapy – Prostate
FU .....Follow-up
GBM.....Glioblastomas multiforme
GHMC .....Gunma University Heavy Ion Medical Centre
GI.....Gastrointestinal
GSI .....Gesellschaft für Schwerionenforschung
Gy .....Gray cobalt
GyE.....Gray cobalt equivalents
HIMAC .....Heavy Ion Medical Accelerator in Chiba
HIT..... Heidelberg Ion Beam Therapy Centre
HITFIL ..... Heavy Ion Therapy, Lanzhou
HTA..... Health technology assessment
IMRT..... Intensity-modulated radiation therapy
IMSRT ..... Intensity-modulated stereotactic radiation therapy
KCE..... Belgian Health Care Knowledge Centre
LBI-HTA ..... Ludwig Boltzmann Institute for Health Technology Assessment
MCS ..... Mental Component Score
MeV ..... Mega electron volt
HRQoL..... Health-related Quality of Life
MST..... Median survival time
NCI..... National Cancer Institute
NIRS..... National Institute of Radiological Science
NSCLC..... Non-small cell lung carcinomas
OS ..... Overall survival
PCS..... Physical component score
PFS ..... Progression-free survival
PRO..... Patient-reported outcomes
PRT ..... Proton radiotherapy
PTCOG ..... Particle Therapy Co-Operative Group
RBE ..... Relative Biological Effectiveness
RCT..... Randomised controlled trial
RFS..... Recurrence-free survival
RoB..... Risk of Bias
RS ..... Relative survival
RT..... Radiation therapy
SEER..... Surveillance, Epidemiology, and End Results
SR ..... Systematic review
TOI ..... Trial Outcome Index
UCLA-PCI..... UCLA Prostate Cancer Index
WHO ..... World Health Organisation
WHO-ICTRP..... WHO International Clinical Trials Registry Platform

Zusammenfassung

Einleitung: Hintergrund und Ziele des Assessments

In den letzten Jahrzenten wurden international einige Hadronen-Strahlentherapiezentren errichtet. Auch in Österreich wurde ein solches Therapiezentrum, MedAustron, in den letzten zwei Jahrzenten geplant bzw. in weiterer Folge gebaut und 2016 eröffnet. In MedAustron wird Krebsbehandlung mittels Partikeltherapie (mit Protonen und Kohlenstoff-Ionen) angeboten und entsprechende Forschung durchgeführt. Derzeit kommt bei MedAustron die Protonentherapie bereits zum Einsatz und zusätzlich ist ein Ausbau der Behandlung mittels Kohlenstoff-Ionentherapie in Planung. Das Krebstherapiezentrum begann mit PatientInnen-Behandlungen etwa vor einem Jahr und hat das Ziel ab 2020 ca. 1.000 Krebs-PatientInnen pro Jahr mit Protonen und/ oder Kohlenstoff-Ionen zu behandeln.

MedAustron:
seit 2016 in Betrieb

Strahkentherapie
mit Protonen und
Kohlenstoff-Ionen
(= CIRT)

Einerseits wird davon ausgegangen, dass die Kohlenstoff-Ionentherapie (engl. **c**arbon **i**on **r**adio**t**herapy = CIRT) – aufgrund der besseren Dosisverteilung und der höheren relativen biologischen Wirksamkeit (RBW) – im Vergleich zur herkömmlichen Strahlentherapie sowohl effektiver als auch sicherer ist. Es wird vermutet, dass CIRT im Vergleich zur herkömmlichen Strahlentherapie eine bessere lokale Tumor-Kontrolle ermöglicht, wodurch die Wahrscheinlichkeit, umliegendes gesundes Gewebe zu beschädigen, minimiert werden kann. Andererseits führt die höhere RBW auch dazu, dass die Ionisationsdichte höher ist als bei herkömmlicher Strahlentherapie und damit der lineare Energietransfer (LET) hoch ist. Die Eigenschaften von CIRT im Vergleich zur herkömmlichen Strahlentherapie werden deshalb auch als „zweischneidiges Schwert" bezeichnet: Manche dieser Unterschiede könnten Vorteile erbringen, während andere mit Nachteilen verbunden sein könnten, weil a) die behandelte Fläche größer ist als der Tumor und damit gesundes Gewebe der Bestrahlung ausgesetzt ist und b) Tumore in gesundes Gewebe eingebettet sind und dieses auch beschädigt wird.

Hoffnung in CIRT
wegen physikalischer
Eigenschaften:

präziser und schonender

aber ev. auch
schädlicher für
umliegendes gesundes
Gewebe

Es ist also wichtig zu klären, sowohl für welche Indikationen CIRT verwendet werden sollte, als auch, ob CIRT effektiver und sicherer als herkömmliche Strahlentherapie ist. Ein Ziel des vorliegenden Berichts ist es, mögliche Indikationen für die Verwendung der CIRT zu eruieren, indem alle Indikationen in (publizierten und laufenden) klinischen Studien identifiziert wurden. Ein weiteres Ziel ist es, die Evidenz hinsichtlich Wirksamkeit und Sicherheit von CIRT bei ausgewählten Indikationen zu prüfen. Es wurde dafür eine systematische Übersichtsarbeit der Studien zu Effektivität (Mortalität, Morbidität) und Sicherheit von CIRT für 54 onkologische Indikationen in 12 Körperregionen durchgeführt.

Ziel des
vorliegenden Berichts:

mögliche
CIRT-Indikationen

Evidenz zu
12 Indikationsbereichen
(54 Sub-Indikationen)

Beschreibung der Technologie

In der Strahlentherapie können Photonen und Hadronen zum Einsatz kommen. Allgemein geht es in der Strahlentherapie darum, die DNA eines Tumors zu beschädigen, sodass der Tumor zerstört wird. Während bei der Photonentherapie Röntgenstrahlung oder Gamma Strahlen zum Einsatz kommen, können bei der Hadronentherapie sowohl Protonen als auch *Kohlenstoff-Ionen* zur Bestrahlung verwendet werden.

Hadronentherapie:
Protonen &
Kohlenstoff-Ionen

LINAC und Synchotron erzeugen

Teilchenstrahlen für Tumor-Bestrahlungstherapie

Ein Linearbeschleuniger (engl. linear accelerator = LINAC) kommt bei der Strahlentherapie zum Einsatz. Bei der CIRT werden Kohlenstoff Ionen durch den LINAC – auf gerader Strecke durch elektrische Wechselfelder – beschleunigt bevor es in den sog. Synchrotron injiziert wird. Der Synchrotron – ein Kreisbeschleuniger mit einem Umfang von in etwa 80 Metern – beschleunigt sodann die Teilchen auf eine Endgeschwindigkeit von ca. 200.000 km/s. Dann kommt der Teilchenstrahl über eine sog. Extraktionslinie in einen der 3 Bestrahlungsräume, die bei MedAustron für die CIRT verwendet werden können. Starke Magnetfelder kommen dabei zum Einsatz, um den Teilchenstrahl in Vakuumröhren durchführen zu können.

Hadronen- vs. Photonentherapie: unterschiedliche Wirkweise
CIRT: hochdosierte, präzise Bestrahlung

Hadronentherapie unterscheidet sich von der herkömmlichen Photonentherapie in der Wirkweise: Das Tiefendosisprofil der Hadronentherapie (der sog. Bragg Peak) ermöglicht eine höhere und präzisere Bestrahlung. Kohlenstoff-Ionen haben eine wesentlich höhere Ionisationsdichte und der lineare Energietransfer (LET) ist höher als bei der herkömmlichen Photonen und Protonentherapie. CIRT gehört damit zu den hohen LET Strahlentherapien.

Methoden

2 Forschungsfragen: Indikationenspektrum in klinischen Studien
Evidenz für Wirksamkeit und Sicherheit in 12 (resp. 54 Sub-) Indikationsbereichen

Der folgende Bericht widmet sich zwei Forschungsfragen:

1. Für welche Tumorindikationen wird CIRT derzeit (in klinischen Studien) angewendet? und
2. Welche Evidenz für eine vergleichbare oder höhere Wirksamkeit beziehungsweise Sicherheit von CIRT liegt bei 54 onkologischen Indikationen in 12 „Regionen“ vor?

Zur Beantwortung der Forschungsfragen wurde eine systematische Literatursuche in folgenden 4 Datenbanken durchgeführt:

systematische Literatursuche in 4 Datenbanken

- Cochrane (CENTRAL)
- Centre for Research and Dissemination (CRD)
- Embase
- Ovid MEDLINE

Handsuche in Referenzlisten und auf Websites (PTCOGC)

Es wurden klinische Studien, die die Effektivität und/oder Sicherheit der CIRT analysieren, systematisch gesucht. Zusätzlich wurde eine Handsuche in Referenzlisten der identifizierten systematischen Übersichtsarbeiten sowie im Internet durchgeführt: Die Websites der Krebstherapiezentren sowie der Particle Therapy Co-Operative Group (PTCOGC) wurden durchsucht, um weitere abgeschlossene und/oder laufende klinische Studien zu finden.

Forschungsfrage 1: alle prospektiven Studien publizierte und laufende Studien

Für die erste Forschungsfrage wurden alle publizierten Studien mit zumindest prospektivem Fallserien Studiendesign sowie laufende klinische Studien aufgearbeitet: Studien wurden gescreent und nach Indikationsgruppen (Regionen) sortiert. Anschließend erfolgte eine Kategorisierung der Studien nach Studiendesign sowie Phase der klinischen Studien und die Extraktion der Anzahl der PatientInnen, die an den Studien teilnahmen. Mit Hilfe dieser Daten wurde die Anzahl der CIRT-PatientInnen mit spezifischen Tumorindikationen bzw. Tumorregionen geschätzt.

Forschungsfrage 2: nur prospektive Studien mit low/moderate RoB, publiziert nach 2005

Für die zweite Forschungsfrage wurden striktere Einschlusskriterien gewählt: Die Evidenzsynthese wurde auf 54 onkologische Indikationen in 12 Tumorregionen eingeschränkt und auf nur jene Studien, die moderates oder niedriges Bias-Risiko aufwiesen sowie nach 2005 publiziert worden sind.

Die Studienauswahl sowie die Bewertung der methodischen Qualität der Studien wurden von zwei WissenschafterInnen (GG, MM) unabhängig voneinander durchgeführt ebenso wie die Datenextraktion von einer Person (GG) durchgeführt und von zweiter Person (MM) kontrolliert wurde.

alle Arbeitsschritte von 2 WissenschafterInnen durchgeführt

Auswahl der Endpunkte zur Wirksamkeit

Im Rahmen der Prüfung der CIRT auf Überlegenheit/Unterlegenheit hinsichtlich Wirksamkeit und/oder Sicherheit im Vergleich zur Photonentherapie wurden folgende wesentliche Wirksamkeits-Endpunkte gewählt:

wesentliche Endpunkte:

- Gesamtüberleben [engl. Overall Survival (OS)]
- Krankheitsspezifisches Überleben [engl. Cause-Specific Survival (CSS)/Disease-Specific Survival (DFS)]
- Rezidivfreies Überleben [engl. Recurrence Free Survival (RFS)]
- Progressionsfreies Überleben [engl. Progression Free Survival (PFS)]
- Krankheitsfreies Überleben [engl. Disease Free Survival (DFS)]
- Gesundheitsbezogene Lebensqualität [engl. Health-related Quality of Life (HRQoL)]
- Die lokale Tumorkontrolle [engl. Local Tumor Control (LCR)] wurde (nur) als Surrogat-Endpunkt in diesem Assessment aufgenommen.

6 Endpunkte zur Wirksamkeit:

Überleben (OS)
Lebensqualität (HRQoL)
etc.

und ein Surrogatendpunkt (LCR)

Auswahl der Endpunkte zur Sicherheit

Zur Bewertung der Sicherheit der CIRT wurden folgende wesentliche Endpunkte herangezogen:

2 Endpunkte zur Sicherheit:

- akute Strahlenbelastung
- späte Strahlenbelastung

akute & späte Strahlenbelastung

Ergebnisse zur Forschungsfrage 1: Indikationsspektrum

Weltweit wurden etwa 21.580 PatientInnen, die mit CIRT behandelt wurden, bis 2016 dokumentiert. Nach Schätzungen aus den identifizierten klinischen Studien nahmen in etwa 5.651 PatientInnen in (zumindest) prospektiven Fallserien teil (retrospektive Fallserien und Einzelfallstudien sind hier nicht berücksichtigt).

21.580 PatientInnen mit CIRT behandelt (bis 2016), davon 26 % in prospektiven Studien erfasst

In unserer systematischen Suche wurden insgesamt 56 publizierte und 65 laufende Studien identifiziert und aufbereitet, um die Frage der derzeitigen Verwendung von CIRT beantworten zu können. Die Ergebnisse zu den Tumorindikationen für CIRT legen nahe, dass diese Therapie bislang bei Tumoren im Hirn- und Schädelbasisbereich, der Prostata, der Lunge, im HNO Bereich, sowie bei gynäkologischen und gastrointestinalen Tumoren durchgeführt wurde bzw. derzeit durchgeführt wird.

56 publizierte (prospektive) Studien

65 laufende Studien

Die 56 publizierten klinischen Studien umfassen folgende Indikationsbereiche:

56 publizierte Studien:

- 14 Studien zu Tumoren im Hirn- und Schädelbasis-Bereich (mit ca. 543 CIRT-PatientInnen),
- 11 Studien zu Prostata-Krebs (mit ca. 3.206 CIRT-PatientInnen, die CIRT erhielten) sowie
- 9 Studien zu Lungenkrebs (mit ca. 631 CIRT-PatientInnen),
- 7 Studien zu HNO Tumoren (mit ca. 489 CIRT-PatientInnen) sowie
- 4 Studien zu GI Tumore (mit ca. 184 CIRT-PatientInnen).

14 Studien: Hirn- und Schädelbasis

11 Studien:Prostata

9 Studien: Lunge

7 Studien: HNO

4 Studien: GI Tumore;

2 Studien: Knochen- und Weichteiltumore
1 Studie: Auge

- Weniger häufig waren Studien zu Knochen- und Weichteiltumore sowie Tumore des Auges (Choroid Melanoma): Es wurden 3 Studien zu den beiden letzteren Tumorregionen gefunden, wobei jeweils weniger als 100 PatientInnen dokumentiert mit CIRT behandelt wurden.

7 Studien: Gynäkologie
1 Studie: Hautkrebs

- Zusätzlich konnten 2 potentielle Tumorindikationen für CIRT identifiziert werden, die nicht auf der MedAustron-Liste zu finden waren: 7 Studien zu gynäkologischen Tumoren (mit ca. 241 PatientInnen) und 1 weitere Studie zu Hautkrebs (mit 45 CIRT-PatientInnen).

65 laufende Studien mit 6.038 Pts &
1 Patientenregister

Die Suche nach laufenden (zumindest prospektiven) Fallserien resultierte in 1 Patientenregister und 65 derzeitig laufenden klinischen Studien mit ungefähr 6.038 StudienteilnehmerInnen. Davon hatten nur 10 Studien ein kontrolliertes Studiendesign: 8 laufende RCTs und 2 laufende CTs wurden identifiziert. Von den 65 laufenden Studien waren

davon nur
10 kontrollierte Studien:
8 laufende RCTs
2 laufende CTs

- 16 Studien zu CIRT bei Tumoren im GI-Bereich (mit 861 TeilnehmerInnen),
- jeweils 9 zu Prostatakrebs und HNO Tumore (Prostata: 1.858 Teilnehmer, HNO: 612 TeilnehmerInnen),
- 8 Studien zu gynäkologischen Tumoren (mit 197 Teilnehmerinnen),
- 8 Studien zu Knochen- und Weichteiltumore (mit 391 TeilnehmerInnen),
- 7 Studien zu Hirn und Schädelbasistumore (mit ca. 1.219 StudienteilnehmerInnen) sowie
- 5 Studien zu Lungenkrebs (mit ca. 860 PatientInnen).
- 3 weitere Studien behandelten Nierenkrebs-PatientInnen oder Brustkrebspatientinnen mit CIRT, jedoch waren in beiden dieser Regionen insgesamt weniger als 50 PatientInnen in den Studien inkludiert.

RCTs/CTs:

Die laufenden kontrollierten Studien beinhalten Studienpopulationen in folgenden Tumoindikationen

5 Studien zu Hirn- und Schädelbasis
2 Studien: sakrale Chordome
jeweils 1 Studie zu HNO-Tumore, GI-Tumore und Lungenkrebs

- 5 Studien zu Hirn- und Schädelbasis
- 2 Studien: sakrale Chordome
- 1 Studie zu HNO-Tumore
- 1 Studie zu GI-Tumore
- 1 Studie zu Lungenkrebs

kein RCT zu Prostata

Es fällt auf, dass die in den publizierten Studien (prospektive Fallserien ohne Kontrollgruppe) behandelten Tumorindikationen sich – in der Gewichtung/ Häufigkeit – nicht mit jenen der laufenden kontrollierten Studien deckt. So konnte kein RCT zu CIRT bei Prostatakrebs, und nur eine kontrollierte Studie zu CIRT bei Lungenkrebs, identifiziert werden.

Verbesserung der Evidenz in den nächsten Jahren durch Ergebnisse der RCTs/CTs

Es ist erwähnenswert, dass mit einer Verbesserung der Evidenzbasis im Zuge der nächsten Jahre zu rechnen ist: 4 identifizierte „laufende“ RCTs sind bereits abgeschlossen, jedoch nicht publiziert und weitere 6 kontrollierte Studien werden in den nächsten 4 Jahren abgeschlossen.

Ergebnisse zur Forschungsfrage 2: Verfügbare Evidenz zu 54 Indikationen in 12 Körperregionen

Es wurden 27 prospektive Studien eingeschlossen, um die Evidenz zur Wirksamkeit und Sicherheit der CIRT im Vergleich zur Photonentherapie zu überprüfen: Es konnte nur 1 randomisierte kontrollierte Studie, die sich vor allem der Sicherheit bzw. Durchführbarkeit von CIRT widmete, identifiziert werden. Die restlichen eingeschlossenen Studien waren Beobachtungsstudien: 3 Fall-Kontrollstudien, die sich vor allem der richtigen Dosis für CIRT/PRT widmeten, 3 Vorher-Nachher Studien, und 20 Fallserien.

27 prospektive Studien erfüllten Einschlusskriterien:

1 RCT zu Sicherheit
26 Beobachtungsstudien

Wirksamkeit und Sicherheit der CIRT

Die Ergebnisse dieses Berichts besagen Folgendes: Es konnte keine Evidenz zu 41 (von 54) Indikationen, sowie unzureichende Evidenz zu 13 (von 54) Indikationen in 7 Regionen gefunden werden:

keine Evidenz zu 41 Ind.
unzureichende Evidenz zu 13 Ind.

Schädelbasis-Tumore

Der Schädelbasis-Bereich umfasste in diesem Assessment 13 onkologische Indikationen. Insgesamt erfüllten 2 unkontrollierte prospektive Fallserien die Einschlusskriterien. 112 PatientInnen (53 PatientInnen mit Chordomen und 59 PatientInnen mit Chondrosarkomen) wurden in diesen Studien mit CIRT – mit einer Dosierung von 45 GyE bis 60.8 GyE – behandelt. Keine Evidenz wurde zu den weiteren 11 Schädelbasistumoren gefunden.

Schädelbasis:
13 Subindikationen,
3 Studien, 112 Pts,
45 GyE bis 60.8 GyE
unzureichende Evidenz für Chordome & Chondrosarkome
keine Evidenz für weitere 11 Indikationen

Augenkarzinom

Für Augentumore wurde die Evidenz zu einer onkologischen Indikation (Aderhautmelanom) überprüft. Weitere onkologische Indikationen im Augenbereich befinden sich in der MedAustron Liste im Schädelbasisbereich sowie im HNO Bereich. Es wurden keine Studien, die CIRT auf Wirksamkeit und/oder Sicherheit bei Aderhautmelanomen untersuchten, eingeschlossen. Deshalb konnte keine Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT für Aderhautmelanome gefunden werden.

Auge:
keine Evidenz für Aderhautmelanome

Hirntumore

Insgesamt wurden 2 unkontrollierte prospektive Fallserien eingeschlossen. In diesen Studien wurden 62 PatientInnen (14 PatientInnen mit WHO II Gliome (diffuse Astrozytome) und 48 PatientInnen mit hochgradigen Hirntumoren (WHO Grad III-IV)) mit CIRT – mit einer Dosierung von 16,8 bis 55,2 GyE – behandelt. Die letztere Patientengruppe bekamen CIRT als Boost nach einer Photonenbestrahlung. Co-Interventionen umfassten – vor, während oder nach der CIRT – operative Behandlungen, Bestrahlung mittels Röntgen sowie Salvage-Therapie (z.B. Chemotherapie).

Hirn:
5 Subindikationen
2 Studien ohne Vergleich, 62 Pts,
16.8-55.2 GyE

In Ermangelung einer Kontrollgruppe wurde unzureichende Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur herkömmlichen Strahlentherapie für Gliome (WHO grad I-II) und Glioblastome (WHO Grad III) gefunden. Keine Evidenz wurde für 3 weitere Hirntumore gefunden: Ependymoma, Medulloblastom, „andere kindliche Hirntumore“.

unzureichende Evidenz für Gliome (Grad I-II) und Glioblastome
keine Evidenz für weitere 3 Indikationen

Tumoren im Hals-Nase-Ohr (HNO) Bereich

HNO:
11 Subindikationen
5 Studien, 415 Pts,
18-72 GyE

Der HNO Bereich umfasste in diesem Assessment 11 onkologische Indikationen. Für Tumore im Hals-Nase-Ohr (HNO) Bereich wurden 5 Studien eingeschlossen: 1 Fall-Kontrollstudie und 4 Fallserien von 3 Krebstherapiezentren in Japan und Deutschland. Es nahmen insgesamt 415 PatientInnen an diesen Studien Teil, von welchen 381 mit CIRT (Dosisierung: 18 GyE bis 72 GyE) bekamen. Co-Interventionen umfassten, unter anderem, Photonentherapie, Salvage-Therapie (insb. Re-Bestrahlung), sowie Post-Chemotherapie.

unzureichende Evidenz
für 3 Indikationen

keine Evidenz für
8 Indikationen

In Ermangelung einer Kontrollgruppe wurde unzureichende Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur herkömmlichen Strahlentherapie für folgende Indikationen gefunden: Tumore der Nasenhöhle und Nasennebenhöhle, adenoidzystische Speicheldrüsenkarzinome und Sarkome im HNO-Bereich (inkl. Ewing Sarkome). Keine Evidenz wurde für die restlichen 8 onkologischen Indikationen im HNO Bereich gefunden.

Lungenkarzinome

Lunge:
3 Subindikationen

6 Studien, 559 Pts
(459 CIRT, 100 PRT),
52.8 - 76 GyE

In der „Lungen-Region" wurden folgende onkologische Indikationen in diesem Assessment berücksichtigt: Das nicht-kleinzellige Lungenkarzinom (NSCLC), mediastinale Tumore sowie pleurale Mesotheliome. Es wurden nur für NSCLC Studien identifiziert: 2 Fall-Kontrollstudien sowie 4 Fallserien, in denen insgesamt in etwa 559 PatientInnen teilnahmen. 459 PatientInnen erhielten CIRT mit einer Dosierung von 52.8 GyE bis 76 GyE. 100 PatientInnen erhielten PRT mit einer Dosis-Schwankung von 60-80 GyE.

unzureichende Evidenz
NSCLC, keine Evidenz:
mediastinale Tumore,
pleurale Mesotheliome

In Ermangelung einer Kontrollgruppe wurde unzureichende Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für das NSCLC. Es wurden keine Studien für mediastinale Tumore und pleurale Mesotheliome identifiziert: keine Evidenz.

Gastroinestinale (GI) Tumore

GI: 6 Subindikationen
2 Fallserien, 215 Pts
Rektumkarzinome:
184 Pts, 67,2-73,6 GyE
Ösophaguskarzinome:
31 Pts, 28,8-36,8 GyE

Es wurden 2 Fallserien mit 215 PatientInnen eingeschlossen: 184 PatientInnen hatten Rektumkarzinome und 31 PatientInnen Ösophaguskarzinome. Sie erhielten CIRT mit einer Dosis von 67,2 GyE-73,6 GyE (RektumCa), resp. 28,8 GyE bis 36,8 GyE ÖsophagusCa).

unzureichende Evidenz
für ÖsophagusCa und
RektumCA
keine Evidenz zu
4 weiteren Indikationen

In Ermangelung einer Kontrollgruppe wurde unzureichende Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für Ösophaguskarzinome und Rektumkarzinome ohne distante Metastasen gefunden. Es wurde keine Evidenz zu folgenden Indikationen gefunden: Pankreaskarzinom, Leberkarzinom, Schwannome/maligne Schwannome und Ewing Sarkome.

Knochen- und Weichteiltumore

Knochen- & Weichteile:
5 Subindikationen
1 Studie, 17 Pts
(Sarkome-Extremitäten),
52.8-70.4 GyE

Es wurde eine Fallserie mit 17 PatientInnen mit primären Sarkomen der Extremitäten eingeschlossen. Die PatientInnen erhielten CIRT mit einer Dosis zwischen 52,8 GyE und 70,4 GyE.

unzureichende Evidenz
für Weichteilsarkome
keine Evidenz für
weitere 4 Indikationen

In Ermangelung einer Kontrollgruppe wurde unzureichende Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für Weichteilsarkome (lokalisierte primäre Sarkome der Extremitäten) gefunden. Es wurde keine Evidenz zu folgenden Indikationen gefunden: Osteosarkome, Sakrale Chordome, sakrale Chondrosarkome sowie spinale Meningeome.

Prostatakarzinom

Es wurden 8 Studien eingeschlossen: 1 randomisierte Kontrollstudie (Fokus: vor allem Durchführbarkeit, Sicherheit der CIRT) und 3 Vorher-Nachher Studien (Fokus: Lebensqualität) sowie 4 Fallserien (Fokus: Wirksamkeit und/ oder Sicherheit der CIRT). Insgesamt nahmen ca. 2.715 PatientInnen an diesen Studien teil, von welchen 2.668 CIRT bekamen (Dosis: 51,6 GyE–72.0 GyE). Co-Interventionen waren vor allem Hormonenbehandlung und neoadjuvante Hormonenbehandlung. 14 der Patienten bekamen CIRT als Boost nach der Intenstitätsmodulierten Strahlentherapie (IMRT).

Prostata:
8 Studien, 1 RCT primär zu Sicherheitsendpunkte
7 Beobachtungsstudien
ca. 2.715 Patienten (2.668 CIRT-Pts)
51,6-72,0 GyE

In Ermangelung einer Kontrollgruppe, die mit Photonentherapie behandelt wurde, wurde unzureichende Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für Prostatakarzinome (mit unterschiedlichen Risikogruppen) gefunden.

unzureichende Evidenz

Mammakarzinom

Es wurde keine Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für das Mammakarzinom gefunden.

Brust: keine Evidenz

Nierenkarzinom

Es wurde keine Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für Nephroblastome gefunden.

Niere: keine Evidenz

Tumore des zentralen Nervensystems (ZNS)

Es wurde keine Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für Neuroblastome gefunden.

ZNS: keine Evidenz

Hämatologische Tumore

Es wurde keine Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für Non-Hodgkin's Lymphome und Hodgkin's Lymphome gefunden.

Hämatologische Tumore: keine Evidenz

Andere onkologische Indikationen

Es wurde keine Evidenz hinsichtlich der Überlegenheit/Unterlegenheit der CIRT im Vergleich zur konventionellen Strahlentherapie für solitäre Lebermetastasen bei kolorektalen Tumoren, retroperitonealen Metastasen bei kontrollierten Primärtumoren sowie Oligo-Metastasen bei kontrollierten Primärtumoren bei ausgesuchten Indikationen gefunden.

andere Indikationen: keine Evidenz

Diskussion

ethische Barrieren gegen die Durchführung von RCTs nicht akzeptabel, weil es viele andere neue Therapien gibt, die vielversprechend sind

In Anbetracht der Studienlage fällt auf, dass es eine Vielzahl an nicht randomisierten und unkontrollierten publizierten sowie laufenden Studien zur CIRT gibt. Ethische Barrieren werden häufig in Debatten zur Hadronentherapie erwähnt, diese greifen aber im Kontext der CIRT nicht, weil es eine Vielzahl an anderen vielversprechenden neuen Behandlungsmöglichkeiten (z. B. CyberKnife oder intensitätsmodulierte Strahlentherapie bei ProstataCa) gibt. Deshalb ist es unabdingbar, vergleichende Studien durchzuführen, um eruieren zu können, für welche onkologischen Indikationen CIRT tatsächlich patientenrelevante Vorteile im Vergleich zu anderen Behandlungsmodalitäten bringt.

Verstärkung der Kooperation innerhalb der EU wesentlich, um Evidenzstand zu stärken

Neben ethischen Barrieren könnte es noch andere bedeutende strukturelle Faktoren geben, die hinderlich für die Generierung von fundierter wissenschaftlicher Forschung im Hinblick auf Überlegenheit/Unterlegenheit der CIRT im Vergleich zur herkömmlichen Photonentherapie sind. Die Zusammenarbeit zwischen den Krebstherapiezentren in der EU und weltweit ist derzeit wenig ausgeprägt. Entsprechende Rahmenbedingungen für die Evidenzgenerierung sollten geschaffen bzw. gefördert werden.

Fragen zur Versorgungsforschung von Krebstherapien wichtig

Die Kooperation sollte jedoch nicht auf die Primärforschung eingeschränkt werden. Vielmehr sind auch Fragen der Versorgungsforschung sowie der ökonomischen Evaluation (insb. jene mit gesellschaftlicher Perspektive) in solchen Krebstherapiezentren zu stellen, um die wissenschaftliche Basis für Patienten-zentrierte Entscheidungen zu schaffen.

Schlussfolgerung

keine Aussagen zu Überlegenheit/ Unterlegenheit auf Basis der derzeitigen Evidenz möglich
unklar, ob theoretische Vorteile der CIRT mit patientenrelevante Vorteile einhergehen

In Anbetracht der Evidenzlage sind keine Aussagen zur Überlegenheit/Unterlegenheit der CIRT im Vergleich zur herkömmlichen Photonentherapie – auf Basis der gewählten Wirksamkeitsendpunkte (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) und Sicherheitsendpunkte (akute Strahlenbelastung, späte Strahlenbelastung) – möglich.

Die Ergebnisse dieses Berichts zeigen, dass es damit derzeit kein abgesichertes Wissen darüber gibt, ob die vielversprechenden theoretischen Vorteile der CIRT tatsächlich auch mit patientenrelevanten Vorteilen (längeres Überleben, verbesserte Lebensqualität, geringere Nebenwirkungen) einhergehen. CIRT ist deshalb derzeit als experimentelle Therapie anzusehen.

CIRT = experimentelles Verfahren

Ergebnisse aus (R)CTs notwendig

Ergebnisse aus (randomisierten) Kontrollstudien sind notwendig, um Vor- oder Nachteile der CIRT im Vergleich zur herkömmlichen Photonentherapie einschätzen zu können. Ziel muss es sein, die Evidenzbasis für CIRT zu stärken.

Executive summary

Introduction

Background and aims

In recent decades, many cancer therapy centres, using large and costly accelerators, were constructed internationally to implement a new form of cancer treatment using charged particles. In Austria, MedAustron – planned approximately 2 decades ago – aimed at focusing on cancer treatment using charged particles (proton and carbon ion radiotherapy) and research. The centre started treating cancer patients with proton radiotherapy a year ago, with approximately 30 treated patients as of September 2017, and has ambitious plans for the future: MedAustron aims at treating 1,000 patients per year with protons and carbon ions by 2020.

Hadron-therapy in MedAustron since 2016/17: proton and carbon ion radiotherapy (CIRT)

Carbon ion radiotherapy (CIRT) is claimed to be both more effective and safer than conventional radiotherapy due to its physical dose distribution and its higher relative biological effectiveness (RBE). Moreover, CIRT is expected to have a higher local control of the tumour than conventional radiotherapy while minimising the probability of damaging the surrounding healthy tissues. On the contrary, the higher RBE to be found in CIRT leads to a higher ionisation density, generating high linear energy transfer (LET), and can be described as a two-edged sword: some of those differences may constitute advantages, while others may be disadvantages. That is to say: CIRT may also have its negative aspects for certain indications, since a) the treated volume extends the gross tumour volume and thus, healthy tissues may be affected by high LET and b) tumours may be intertwined with, or embedded in, healthy tissues. Thus, it is necessary to elaborate for which indications CIRT should be used, as well as whether CIRT is more effective and safer than conventional cancer radiotherapy.

expectation in CIRT: higher relative biological effectiveness (RBE) – more effective and safer therapy

but also ev. destroying surrounding healthy tissues

The project aims at elaborating possible cancer types, being an indication for carbon ion therapy. As such, clinical studies, analysing the use of CIRT for specific cancer types, will be identified through a systematic literature search and will be reviewed and reported in this project.

Furthermore, a systematic analysis of the literature on the effectiveness (mortality, morbidity) and safety of CIRT for 54 oncologic indications in 12 regions (i.e., skull base, eye, brain, ear-nose-throat, lung, gastrointestinal, bone and soft tissue, prostate, breast, kidney, nervous system, hematologic cancer) will be conducted.

2 research questions (RQ): potential CIRT indications evidence for indications

Description of technology

Carbon ion radiotherapy (CIRT) is a type of radiation therapy and belongs, together with other charged particles such as protons, helium or neon, to the "family" of hadron therapy. The physical properties to be found in CIRT are different to those of conventional radiotherapy (i.e., photons). That is, a peak energy delivery (Bragg peak) enables a large fraction of the energy of CIRT to be deposited at the target while being less invasive to surrounding tissues due to a low entrance dose affecting healthy tissues. That is, the ionisation density and the relative biological effectiveness (RBE) increase with depth, meaning when travelling deeper into the body.

physical properties of CIRT: peak energy delivery – large fraction of the energy at target

precision

Methods

methods: systematic search in 4 databases handsearch at websites of CIRT centres

A systematic search was conducted in 4 databases, Cochrane [Cochrane (CENTRAL), Centre for Research and Dissemination (CRD), Embase and Ovid MEDLINE]. Studies focusing on the efficacy or safety of carbon ion radiotherapy (CIRT) were searched for. Moreover, a hand-search was conducted on the websites of the cancer therapy centres currently offering CIRT, and the particle therapy co-operative group (PTCOG) to identify further relevant published and ongoing studies respectively.

RQ1: only prospective studies
RQ2: prospective studies With low/moderate RoB

All prospectively conducted primary studies were reviewed, and ongoing controlled studies were identified to elaborate potential current indications for CIRT. For the evidence synthesis regarding the efficacy and safety of CIRT, all primary studies with low or moderate risk of bias, published between 2005 and 2017, were eligible to be included in this assessment.

Results

Available evidence

21.580 (documented) patients treated with CIRT: 5,651 in prospective studies

Until 2016, 21,580 patients were recorded to have been treated with CIRT worldwide. According to the identified studies in this assessment, approximately 5,651 patients were enrolled in at least prospective case series studies and received CIRT.

RQ1: spectrum of indications
56 prospective studies identified, most frequent indications: prostate, brain, skull base, lung

Overall, 56 studies elaborating on the efficacy and/or safety of CIRT have been identified: The majority of the studies chose samples with CIRT patients suffering from tumours in the brain and skull base, prostate and lung region, with 14, 11 and 9 identified studies in those regions respectively. Ear-nose-throat cancer was another significant cluster, consisting of 7 clinical studies. Less frequent clusters were in the bone and soft tissue and gastrointestinal (GI) region, with 2 and 4 clinical studies assessing the efficacy and safety of CIRT in those regions respectively. In addition, 1 study was identified including patients with choroid melanomas (eye) in their sample.

RQ2 evidence synthesis:

27 prospective studies with low/moderate RoB

no RCT or CT for efficacy
1 RCT for safety (control: protons)

some (but insufficient) evidence for 13 indications, no evidence in 41 indications

Of those 56 studies, 27 clinical studies were eligible for the qualitative synthesis of the efficacy and safety of CIRT when compared to standard irradiation: 1 randomised controlled trial focusing on toxicity and feasibility of CIRT/PRT with a high risk of bias using a historical control and no other controlled study was found. The other 26 included studies were either prospective case series (n=20) or – less frequently – case-control studies (n=3) or single-arm before-after studies (n=3), focusing on HRQoL. When assessing the superiority/inferiority of CIRT in comparison to standard irradiation regarding efficacy and safety on the basis of the selected oncologic endpoints, no scientific evidence was found for 41 indications, and insufficient scientific evidence was found for 13 indications in 7 regions: **skull base**: chordomas, chondrosarcomas; **brain**: glioma grade II, glioma grade III; glioblastoma; **ear-nose-throat**: sarcomas in the head and neck, tumours in the nasal cavity and paranasal sinus, adenoid cystic salivary gland carcinoma; **bone and soft tissue**: soft tissue sarcoma; **lung:** non-small cell lung carcinoma; **prostate:** prostate carcinoma; **gastrointestinal:** oesophageal carcinoma, rectum carcinoma.

skull base: insufficient evidence (chordomas and low-grade chondrosarcoma: 3 case series), no evidence: 11 further indications

- **Skull base**: insufficient scientific evidence indicating superiority/inferiority of CIRT for chordomas and low-grade chondrosarcoma when compared to conventional radiotherapy (evidence base: 3 uncontrolled prospective case series studies). No scientific evidence was found for 11 other skull base tumours.

- **Eye**: no scientific evidence indicating superiority/inferiority of CIRT for eye tumours when compared to conventional radiotherapy.

eye: no evidence

- **Brain**: insufficient scientific evidence indicating superiority/inferiority of CIRT for WHO grade II and WHO grade III-IV brain tumours when compared to conventional radiotherapy (evidence base: 2 studies). No scientific evidence regarding inferiority/superiority of CIRT was found for ependymoma, medulloblastoma, and "other childhood brain tumours".

brain: insufficient evidence (grade III-IV brain tumours: 2 case series), no evidence: 3 further indications

- **Ear-Nose-Throat** (ENT): insufficient scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety for sarcomas in the head and neck, tumours in the nasal cavity and paranasal sinus and adenoid cystic salivary gland carcinomas (evidence base: 1 case-control study and 4 prospective case series). No scientific evidence regarding superiority/inferiority of CIRT when compared to standard irradiation was found for 8 other specific indications in the ENT region: orbital tumours, maxillary sinus carcinoma, nasopharyngeal carcinoma, oropharyngeal carcinoma, tonsil carcinoma, tongue base carcinoma, pleomorphic salivary gland carcinoma, rhabdomyosarcoma.

ENT: insufficient evidence (sarcomas head & neck, nasal cavity, paranasal sinus adenoid cystic salivary gland carcinomas: 5 studies), no evidence: 8 further indications

- **Lung:** insufficient scientific evidence indicating superiority/inferiority of CIRT for non-small cell lung cancer (NSCLC) when compared to conventional radiotherapy (evidence base: 2 case-control studies and 4 prospective case series).

lung: insufficient evidence (NSCLC: 6 studies)

- **Gastrointestinal tumours:** insufficient scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety for thoracic oesophageal squamous cell carcinoma and rectal cancer without distant metastases when compared to conventional radiotherapy (evidence base: 1 prospective case series respectively). No scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety when compared to standard irradiation was found for pancreatic cancer, liver carcinoma, schwannomas/malignant schwannomas, and Ewing's sarcomas.

GI tumours: insufficient evidence (oesophageal and rectal carcinoma: 1 case series), no evidence: pancreatic & liver Ca, schwannomas, Ewing's sarcomas

- **Bone and soft tissue sarcoma:** insufficient scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety was found for soft tissue sarcoma (localised primary sarcoma of the extremities) when compared to conventional radiotherapy (evidence base: 1 prospective case series study). No scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety when compared to standard irradiation was found for osteosarcoma, sacral chordoma, sacral chondrosarcoma and spinal meningioma.

bone & soft tissue sarcoma: insufficient evidence (primary sarcoma of the extremities: 1 case series), no evidence: osteosarcoma, sacral chordoma, sacral chondrosarcoma & spinal meningioma

- **Prostate:** insufficient scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety (evidence base: 1 RCT focusing on feasibility and toxicity, 3 before-after studies focusing on HRQoL and 4 prospective case series).

prostate: insufficient evidence (1 RCT on safety, control: proton, 7 observational studies)

- **Breast:** no scientific evidence indicating superiority/inferiority regarding efficacy or safety of CIRT when compared to conventional radiotherapy.

breast: no evidence

- **Kidney:** no scientific evidence indicating superiority/inferiority regarding efficacy or safety of CIRT when compared to conventional radiotherapy for nephroblastoma.

kidney: no evidence

- **Central nervous system:** no scientific evidence indicating superiority/inferiority regarding efficacy or safety of CIRT when compared to conventional radiotherapy for neuroblastoma.

CNS: no evidence

hematologic cancer (NHL): no evidence

- **Hematologic cancer:** no scientific evidence indicating superiority/inferiority regarding efficacy or safety of CIRT when compared to conventional radiotherapy for Non-Hodgkin's lymphoma and Hodgkin's lymphoma.

other indications (liver metastases in colorectal cancer, retroperitoneal metastases in primary tumours): no evience

- **"Other oncologic indications":** no scientific evidence indicating superiority/inferiority regarding efficacy or safety of CIRT when compared to conventional radiotherapy for solitary liver metastases in colorectal cancer, retroperitoneal metastases in controlled primary tumours, and oligo-metastasis in controlled primary tumours in selected indications.

Upcoming evidence

65 ongoing studies: only 10 controlled studies brain & skull base, bone & soft tissue, GI & ENT. lung

The search for ongoing studies revealed that the great majority of currently undertaken studies are uncontrolled: 65 ongoing studies were identified of which 10 were at least controlled studies, with enrolled patients suffering from tumours in the following regions: brain and skull base, bone and soft tissue, gastrointestinal, and ENT as well as lung. Interestingly, no randomised controlled trials were found in the prostate or lung region, and only 1 controlled study enrolled lung cancer patients in their study.

4 RCTs finished, but not published

In addition, results from (randomised) controlled trials are expected to arise in the following years: the primary completion date of 4 of the ongoing RCTs has already passed (region: brain and skull base). The primary completion date of the other controlled and randomised controlled trials is in the next 4 years.

Discussion and conclusion

54 potential indications

In 2018, neither superiority nor inferiority on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the currently (un)available evidence for 54 oncologic indications.

but no comparative evidence available

While plans of many cancer therapy centres in the European Union exist to increase patient treatment with CIRT, sound scientific evidence to show superiority or inferiority of CIRT when compared to photon, or other forms of, radiotherapy is absent. Suffice to say that results from (randomised) controlled studies are urgently needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation.

CIRT = experimental treatment

As a treatment modality, CIRT can be described as a potentially less invasive cancer treatment due to its physical properties. Due to the lack of controlled trials, no conclusions may be drawn on the comparative effectiveness of CIRT when compared to conventional photon therapy.

As of today, CIRT must be considered as experimental treatment.

1 Introduction

1.1 Carbon ion therapy centres

Internationally, the Lawrence Berkeley National Laboratory (BEVALAC) in the United States was the first cancer therapy centre experimenting treatment with heavy ions [1]: patient treatment started in 1975. In 1992 – after treatment of approximately 433 patients – it was closed again [2]. Japan was the first country to introduce carbon ion radiotherapy (CIRT) at the Heavy Ion Medical Accelerator in Chiba (HIMAC), starting CIRT treatment in 1994. In 1997, the "Gesellschaft für Schwerionenforschung" (GSI) in Darmstadt (Germany) was the next facility to start treating cancer patients with CIRT. However, the GSI – similar to the BEVALAC – had a considerably short history of patient treatment and was closed in 2009, with 440 patients treated with CIRT at this cancer therapy centre [2] [1]. In the next 2 decades, additional facilities using CIRT for cancer treatment were constructed in Asia (Japan, China) and Europe (Germany, Italy and Austria) [2]. Table 1-1 gives an overview of the cancer therapy centres and the documented number of treated patients as of the end of 2016.

erstes Krebs-Schwerionen-Zentrum 1975 in USA erbaut, 1992 geschlossen

Japan: 1994 erste CIRT Behandlung in Chiba

Deutschland: 1997-2009 CIRT Behandlungen im GSI

Table 1-1: Patients treated with C-ions (per end of 2016) [2]

CIRT Centre	Country	Start of the treatment	Total patients treated
CNAO, Pavia	Italy	2012	816
GHMC, Gunma	Japan	2010	2,231
GSI, Darmstadt	Germany	1997 (-2009)	440
HIBMC, Hyoga	Japan	2002	2,527
HIMAC, Chiba	Japan	1994	10,692
HIMAT, Saga	Japan	2013	1,776
HIT, Heidelberg	Germany	2009	2,430
IMP-CAS, Lanzhou	China	2006	213
I-rock, Kanagawa	Japan	2015	105
SPHIC Fudan University Shanghai CC	China	2014	350
Sum		**1994-2016**	**21,580**

Data retrieved from PTOGC website [2], last updated: December 2017,
Abbreviations: C-ion – carbon ion; MeV – Mega electron volt;

To date, 11 cancer therapy centres worldwide offer CIRT, with the majority of these being located in Asia (5 in Japan, 2 in China) and a few in Europe (2 in Germany, 1 in Italy and 1 in Austria) (see Table 1-2 with more specific information regarding beam direction, max. energy). In addition, 4 new facilities aiming at offering CIRT in the near future, are under construction [3] and 1 is in the planning stage [4]: 2 facilities are under construction in China (HITFIL, Lanzhou and the Heavy Ion Cancer Treatment Center in Wuwei), and 1 facility is under construction in South Korea (KIRAMS, Busan) and in Japan (Yamagata University Hospital, Yamagata) respectively. The cancer therapy centres under construction plan to start patient treatments between 2018 and 2020. In addition, 1 further facility in South Korea (Yonsei University Hospital in Seoul) is currently in the planning stage and is estimated to start treating cancer patients by 2022 (see Table 1-3).

derzeit 11 Zentren weltweit, die CIRT anbieten

4 weitere in Bau/ Fertigstellung

Eröffnung: 2018-20

2 weitere Einrichtungen in Frankreich

in Literatur erwähnt, nicht aber von PTCOG

In addition, 2 cancer therapy treatment centres in France planning to use CIRT for cancer therapy are mentioned in the literature, but are not among the centres listed by the PTCOG (Particle Therapy Co-Operative Group): the ETOILLE (Espace de Traitement Oncologique par Ions Légers dans le cadre Européen), with an unknown status regarding patient treatment[1], and the Advanced Resource Center for Hadrontherapy in Europe (ARCHADE), having received permission for the construction of a proton therapy centre in 2014. On the website of this centre, it is stated that the accelerator will be used for therapeutic applications and will deliver both protons and C-ions[2].

21.580 PatientInnen bis 12/2016 mit CIRT dokumentiert behandelt

Until end of 2016, approximately 21,580 patients were recorded to have been treated with C-ions, with the majority of patients treated at HIMAC, in Chiba, Japan (10,692) followed by HIT, in Heidelberg, Germany (2,430) and HIBMC, in Hyogo, Japan (2,527) (see Table 1-1).

Table 1-2: CIRT facilities in operation [7]

Country	CIRT Centre	S/C/SC* Max. Energy (MeV)	Beam directions	Start of treatment
Austria	MedAustron, Wiener Neustadt	S 430/u	2 fixed beams**	2017
China	IMP-CAS, Lanzhou	S 400/u	1 fixed beam	2006
China	SPHIC, Shanghai	S 430/u	3 fixed beams**	2014
Germany	HIT, Heidelberg	S 430/u	2 fixed beams, 1 gantry**	2009, 2012
Germany	MIT, Marburg	S 430/u	3 horiz., 1 45-deg. fixed beams**	2015
Italy	CNAO, Pavia	S 480/u	3 horiz., 1 vertical, fixed beams	2012
Japan	HIMAC, Chiba	S 800/u	horiz.***, vertical***, fixed beams, 1 gantry	1994, 2017
Japan	HIBMC, Hyogo	S 320/u	horiz.,vertical, fixed beams	2002
Japan	GHMC, Gunma	S 400/u	3 horiz., 1 vertical, fixed beams	2010
Japan	SAGA-HIMAT, Tosu	S 400/u	3 horiz., vertical, 45-deg., fixed beams	2013
Japan	i-Rock Kanagawa Cancer Center, Yokohama	S 430/u	4 horiz., 2 vertical, fixed beams	2015

Data retrieved from the PTOGC website [7], last updated: February 2018.

** S/C/SC = Synchrotron (S) or Cyclotron (C) or SynchroCyclotron (SC);*
*** with pencil beam scanning;*
**** with spread beam and pencil beam scanning;*

Abbreviations: C-ion – carbon ion; MeV – Mega electron volt.

[1] ETOILLE aimed to become the national centre for light ion hadrontherapy in France [5], but some of their projects were abandoned in 2015 [6]. 1 ongoing randomised controlled trial with 250 enrolled patients at the ETOILLE was identified through hand-searching (NCT02838602).

[2] See https://www.france-hadron.fr/en/nodes/archade-caen.html (accessed on 15/02/2018).

Table 1-3: CIRT facilities under construction or in the planning stage [3, 4]

Country	CIRT Centre	Particle	Max Energy Accelerator type (S*)	Beam Directions	N of treatment rooms	Start of Treatment
China	HITFil, Lanzhou	C-ion	S 400/u	4 horiz, vertical, oblique,	4	2018
China	Heavy Ion Cancer Treatment Center, Wuwei, Gansu	C-ion	S 400/u	4 horiz, vertical, oblique, fixed beams	4	2018
Japan	Yamagata University Hospital, Yamagata	C-ion	S 430/u,	1 gantry, 1 horiz. & vertical fixed beam	2	2020
South Korea	KIRAMS, Busan	C-ion, p	S 430/u, 230	2 vertical and horiz. fixed beams, 1 horiz. fixed beam	3	2019
South Korea	Yonsei Univ. Hospital,Seoul	C-Ion	S 430/u,	2 gantries	2	2022

Data retrieved from the PTOGC website [7] (downloaded Oct 2017, last updated: January 2017),

S = Synchrotron (S);*

Abbreviations: C-ion – carbon ion; MeV – Mega electron volt.

1.2 MedAustron

Österreich – MedAustron: Strahlentherapie mit Protonen und mit C-Ionen

In Austria, MedAustron – planned approximately 2 decades ago – aimed at focusing on treating cancer patients with charged particles (using protons and C-ions) and on research [8, 9]. The centre started treating cancer patients with proton therapy a year ago, with approximately 30 treated patients as of September 2017, and has ambitious plans for the future: MedAustron aims at treating 1,000 patients per year with protons and carbon-ions by 2020 [8, 10].

MedAustron: 56 Indikationen für CIRT

In 2017, MedAustron issued a list of potential indications for CIRT (see Table 1-4): it consists of 56 different oncologic indications.

The 56 oncologic indications of the issued list were partly already structured by anatomical regions. The following further regions were added by the authors to structure those oncologic indications: lung region, bone and soft tissue region, kidney, nervous system, hematologic cancer, "other". In addition, orbital tumours was originally in the brain region on the provided list, but was changed to be in the ENT tumour region in this assessment.

Table 1-4: MedAustron list of potential indications for CIRT

Region	Indication
Skull base tumours	Skull base tumours
	Chordoma
	Chondrosarcoma
	Meningioma grade II/grade III
	Meningioma grade I (complex)
	Craniopharyngioma
	Pituitary adenoma (not suitable for stereotaxy)
	Acoustic neuroma
	Other neurinomas
	Glomus tumour
	Retinoblastoma
	Lacrimal gland tumours
	Sarcomas incl. Ewing's sarcoma
	Rhabdomyosarcomas of the skull base and orbit
Brain	Brain tumours
	Glioma grade II
	Glioma grade III
	Glioblastoma
	Ependymoma
	Medulloblastoma
	Other childhood brain tumours
Ear-Nose-Throat (ENT)	Ear-Nose-Throat (ENT)
	Orbital tumours
	Tumor of the nasal cavity and paranasal sinus
	Maxillary sinus carcinoma
	Nasopharyngeal carcinoma
	Oropharyngeal carcinoma
	Tonsil carcinoma
	Tongue base carcinoma
	Salivary gland carcinoma (pleomorphic)
	Salivary gland carcinoma (adenoid cystic)
	Sarcoma in the ENT area including Ewing's sarcoma
	Rhabdomyosarcoma
Lung	Non-small cell lung carcinomas
	Stage I and II
	Stage III
	Mediastinal tumours (including thymoma)
	Pleural mesothelioma

Region	Indication
Gastrointestinal tumours	Gastrointestinal tumours
	Esophageal carcinoma
	Pancreatic cancer
	Liver carcinoma
	Rectal carcinoma recurrence presacral
	Schwannomas/malignant schwannomas
	Ewing's sarcoma
Bone and soft tissue	Osteosarcoma
	Soft tissue sarcoma
	Chordoma WS/sacral
	Chondrosarcoma WS/sacral
	Spinal meningiomas
Prostate	Prostate cancer
	Low/intermediate risk
	high risk
	with metastases
Breast	Breast cancer
Kidney	Nephroblastoma
Nervous system	Neuroblastoma
Hematologic cancer	Non-Hodgkin's lymphoma (in exceptional cases)
	Hodgkin's lymphoma
Other	Solitary liver metastases in colorectal cancer
	Retroperitoneal metastases in controlled primary tumours
	Oligometastasis in controlled primary tumours in selected indications

1.3 Research question

This report aims at answering 2 research questions:

2 Forschungsfragen

1. For which tumour types is carbon ion radiotherapy (CIRT) currently in research (ongoing clinical trial)?

   The aim of this research question is to provide an overview of the main indications in both ongoing and published trials with CIRT and to give an estimation of the number of patients enrolled in those studies.

Indikationen in klinischen Studien und Anzahl der PatientInnen

2. What is the evidence that CIRT is more or equally effective, or safer than standard radiotherapy in selected oncologic indications?

   The aim of this research question is to provide an overview of the evidence regarding efficacy (mortality, morbidity, HRQOL) and safety of CIRT for selected indications.

Evidenz zu Wirksamkeit und Sicherheit von CIRT

2 Methodology

2.1 Scope

The EUnetHTA Core Model® for Rapid Relative Effectiveness Assessment was used for structuring this report. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment. However, due to its broad scope, the questions regarding the health burden of the specific indications are found in the chapter on efficacy and safety of CIRT.

flexible Nutzung des EUnetHTA Core Model®; Fragen zur Gesundheitslast im Kapitel Wirksamkeit/ Sicherheit

Description of the technology	
Element ID	**Research question**
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?
Clinical effectiveness	
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?
Safety	
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien
RQ1: alle prospektiven Studien
RQ2: nur prospektive Studien mit low/ moderate RoB

Inclusion criteria for relevant studies are summarised in Table 2-1.

For **research question 1** – overview of indications in research and number of patients in clinical trials – all prospective studies were analysed.

For **research question 2** – synthesis of evidence on efficacy and safety of CIRT in selected oncologic indications – only prospective studies published after 2005 and with at least moderate risk of bias were included.

Table 2-1: Inclusion criteria

Population	Patients with tumours as defined in Table 1-4 in the following areas: • Skull base • Eye • Brain • Ear-Nose-Throat (ENT) • Lung • Gastrointestinal (GI) • Bone and soft tissue • Prostate • Breast • Kidney • "Nervous system" • "Hematologic cancer"
Intervention	Carbon ion radiotherapy (CIRT)
Control	• Photon radiation therapy • Secondary: Proton radiotherapy, all other forms of radiotherapy, surgery
Outcomes	
Efficacy	• Overall Survival (OS) • Cause-Specific Survival (CSS)/Disease-Specific Survival (DSS) • Disease-Free Survival (DFS) • Recurrence-Free Survival (RFS) • Progression-Free Survival (PFS) • Local Control Rate (LCR) • Health-Related Quality of Life (HRQoL)
Safety	Toxicity: Acute and late radiation morbidity
Study design	
Efficacy	Randomised controlled trials Non-randomised controlled trials Prospective case series with more than 10 patients
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series with more than 10 patients
Publication period	
Language	German/English/French

2.3 Exclusion criteria

- Population: pathologies not listed in Table 1-1 (for RQ2)
- Intervention: other forms of radiotherapy, surgery
- Comparator: no restriction
- Outcomes: all other outcomes not depicted in Table 2-1
- Study design: retrospective case series, case reports, commentaries, prospective case series with less than, or equal to, 10 patients; studies only publicised as an abstract.
- Language: All languages other than German/English/French.

retrospektive Studien & Fallstudien, prospective Fallserien ≤ 10 Pts.

Sprache

In addition, studies were screened for overlapping samples in other, more recent publications by the same authors using the same endpoints: older studies with the same population were then excluded.

2.4 Systematic literature search

The systematic literature search was conducted between the 5th and 7th of September, 2017 in the following databases:

systematische Literatursuche in 4 Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

The systematic search was limited to randomised controlled trials and controlled trials as well as prospective case series and articles published in English, German or French. After deduplication, a total of 408 citations were included. The specific search strategy employed can be found in the Appendix (Section: Literature search strategies).

Suche in Referenzlisten von SR

The reference list of 5 systematic reviews on the use of hadron therapy (CIRT and PRT) [11-15] was also reviewed by hand search to identify potentially further eligible studies: 4 additional studies were identified. In addition, the websites of the cancer therapy centres currently offering CIRT were reviewed to identify further published studies. No further studies were hereby identified.

Suche nach laufenden Studien

Furthermore, a hand-search in 3 clinical trial registries [42 (ClinicalTrials.gov); 33 (WHO-ICTRP); 2 (EU Clinical Trials)] was conducted to identify ongoing and unpublished controlled studies on 19 September 2017, resulting in 77 relevant hits. An update of the search to identify ongoing studies was conducted on 8 February 2018 on the clinicaltrials.gov, EU Clinical trials and WHO-ICTRP websites: 5 further studies and 1 patient registry were identified.

insgesamt 802 Treffer: 414 Publikationen & 388 Treffer zu laufenden Studien identifiziert

In addition, a rigorous hand-search was conducted: on the Particle Therapy Co-Operative Group (PTCOG, https://www.ptcog.ch/) website and on the MedAustron website (https://www.medaustron.at/) to identify further ongoing and unpublished controlled studies, leading to further 305 potentially relevant hits. An additional hand-search on the National Cancer Institute (NCI) website complemented the searches.

Finally, the systematic search and the hand-search to identify published and ongoing studies resulted in 802 hits overall.

Informationen und Quellen zu onkologischen Indikationen

For information on the selected oncologic indications and for the description and epidemiology of the selected oncologic indications, a hand search on the websites of the following institutions:

- National Cancer Institute (NCI, https://www.cancer.gov/)
- Deximed (https://deximed.de/intro)
- UpToDate (https://www.uptodate.com/home)
- Surveillance, Epidemiology and End Results Program (SEER) (https://seer.cancer.gov)
- Statistics Austria (http://www.statistik.at/)

In addition, a radio-oncological expert reviewed the treatment modalities described in this assessment: The most common treatment for each indication in Austria was added in case those clinical treatment modalities differed to the ones identified according to the reviewed websites.

2.5 Flowchart of study selection

Literaturauswahl

Overall, 414 hits were identified. The references were screened by 2 independent researchers, and in case of disagreement, a third researcher was involved in solving the differences. The selection process is displayed in Figure 2-1.

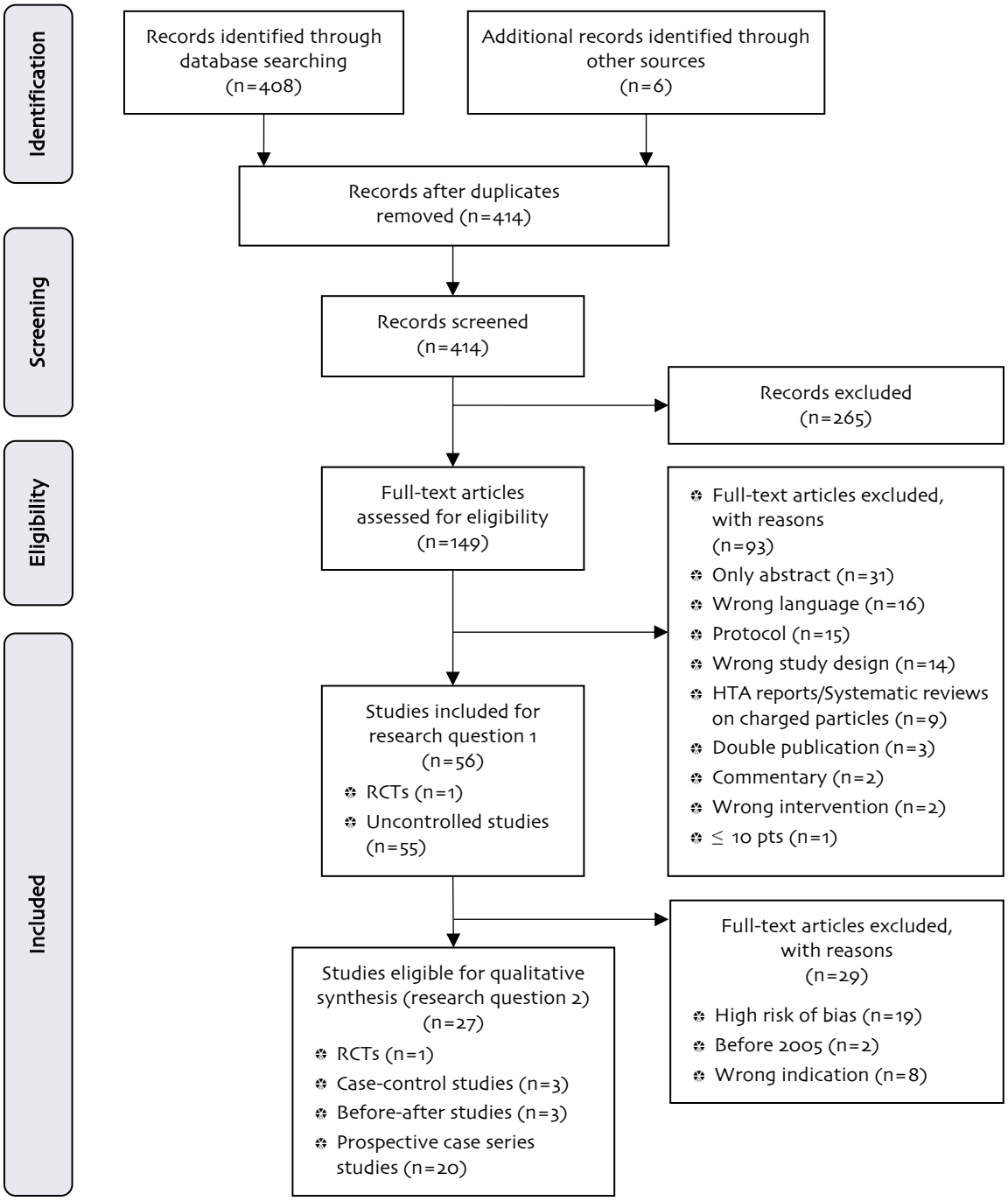

Figure 2-1: Flowchart of study selection (PRISMA Flow Diagram)

2.6 Analysis

Forschungsfrage 1: Zuordnung der identifizierten Studien nach Tumorentitäten

Kategorisierung nach Studienphasen

For **research question 1**, the identified (published) studies were screened and sorted by broad indication groups (regions). The studies were categorised by study design and were reviewed for reporting on patients in multiple indications. Those patients were then included in the samples of the respective indication. The indication list issued by MedAustron was then revised (reduced) to 54 (instead of 56) specific tumour entities: prostate and non-small cell lung cancer was judged as being 1 indication respectively. Choroid melanoma was also added to the potential indications.

Auflistung der Anzahl der PatientInnen in Studien

Data on the sample size and number of patients was extracted in order to assess which tumour indications CIRT is currently being studied for. The number of patients refers to the total number of enrolled patients. For specific tumour indications, data on the number of patients was additionally extracted alongside the issued revised MedAustron list including 54 potential CIRT indications. In case the same sample was published in multiple studies – for instance, if studies were judged to use the same sample but reported on different outcomes – the studies were not excluded, but those samples were only counted once in the analysis. The results of the Potential indications for the use of carbon ion radiotherapy (CIRT) according to clinical studiescan be found in the Appendix and in Section 4.1: CIRT indications in published clinical trials.

Forschungsfrage 2: RoB Beurteilung

Selektion von Studien mit moderate/low RoB

For **research question 2**, the internal validity of the included studies was assessed by 2 independent researchers (GG, MM) applying the EUnetHTA guidelines [16, 17]. For case series, the risk of bias (RoB) was assessed using the IHE-18 checklist (checklist and instructions: see Appendix Table A-9): a high score indicates a low risk of bias and a low score indicates a higher risk of bias (RoB). A cut-off for the inclusion of only those studies with low or moderate RoB was pre-defined. Thresholds used were:

Table 2-2: Cut-off criteria for the risk of bias (RoB) assessment

Criteria	Points
Low risk	14.5/18 to 18/18
Moderate	11/18 to 14/18
High risk	≤ 10.5/18

Table 2-3: RoB point system for the risk of bias (RoB) assessment

Answers to specific questions of the IHE-18 checklist	Points
No	0
Unclear	0.5
Partial	0.5
Yes	1

Data was then extracted from the included studies (low/moderate RoB) by 1 researcher (GG) and controlled by another researcher (MM). In the case of studies reporting about several different indications, these studies were only eligible if more than 10 patients, and at least 40% of the total sample, suffered from the specific indication.

2.7 Synthesis

Zusammenfassung der Evidenz in 12 Tumorentitäten (und 54 Sub-Indikationen)

Based on the MedAustron list of indications, the evidence was finally synthesised based on the data extraction tables (see Appendix Table A-1 to Table A-8) for both the 12 tumour "regions" and the 54 specific oncologic indications. In this assessment, prostate and non-small cell lung cancer was judged as being 1 indication respectively. The evidence for risk group-specific cancer forms for those diseases were not separated due to the broad scope of the assessment, leading to an evidence synthesis of CIRT for 54 oncologic indications. However, in the qualitative synthesis of those 2 indications, reference was made to the stage of the diseases.

In addition, 1 indication was added: choroid melanoma.

Some sub-indications (i.e., meningioma grade I and grade II-III, pleomorphic and adenoid cystic carcinomas) were also described in 1 section respectively for practical reasons. However, the synthesis was – if applicable – conducted independently for each of those sub-indications.

The evidence is reported systematically along the pre-defined crucial outcomes in Chapter 5.

2.8 Quality assurance

interner Review und externer Review

zur Qualitätssicherung

This report was reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence and amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What are carbon ion radiotherapy (CIRT) and photon radiotherapy?

Hadronen (u. a. Kohlenstoffionen) und Photonen werden in der Strahlentherapie eingesetzt

Both carbon ion radiotherapy and photon radiotherapy are forms of external beam radiation therapy methods. Radiation therapy is used to destroy cancer by damaging their DNA. If the DNA of the irradiated cancer cells is damaged, they either die or stop dividing [18]. A photon can be described as the basic unit of light and consists of either x-rays or gamma rays. Photon radiation therapy is the most common form of radiation therapy. The amount of energy to be used for irradiation varies, and the dosages are expressed in gray cobalt (Gy) [18].

Hadronen und Photonen unterscheiden sich in der Wirkweise

Hadronen: zielgerichtet, präzise

CIRT belongs – together with other charged particles such as protons, helium or neon – to the family of hadron therapy. Hadron therapy has several biological differences when compared to photon radiotherapy. Therefore, the irradiation dose cannot be expressed with Gy but with gray cobalt equivalents (GyE) [19]. Hadron therapy is characterised by a peak energy delivery (Bragg peak): a large fraction of the energy of hadron therapy is deposited at the target while being less invasive to surrounding tissues due to a low entrance dose affecting healthy tissues. The ionisation density and the relative biological effectiveness (RBE) increases with depth; that is when travelling deeper in the body [20].

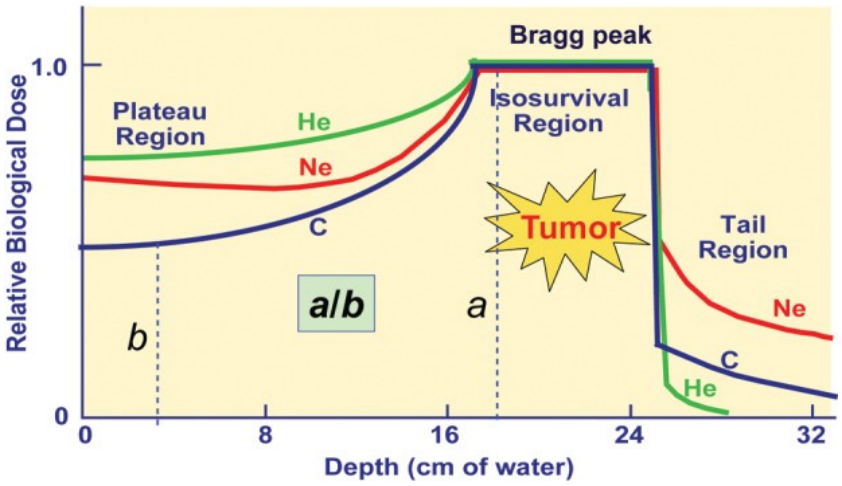

Figure 3-1: Illustration of the Bragg peak [20]

zerstört Tumorzellen effektiv

Hadron therapy enables a higher precision of irradiating tumours due to the ability of hadron therapy to adjust both the beam's energy and the intensity. The physical properties are different in hadron therapy: the cell killing is more efficient due to charged particles damaging a cell DNA differently than photons. As such, hadron therapy has a higher relative biological effectiveness (RBE) than photons. That is, proton irradiation leads, for instance, to approximately 10% more biological damage than photons (per unit) [19].

Unterschied CIRT zu Protonen (und Photonen): höhere Strahlungsdichte

The radiobiological properties of CIRT differ to the ones of protons as well, leading to higher RBE, a higher ionisation density and a considerably high linear energy transfer (LET) when compared to proton and photon radiotherapy [21]. Photons and protons can thus be described as forms of low-LET radiotherapies, while CIRT is a form of high LET radiation therapy [20].

B0002 – What is the claimed benefit of CIRT in relation to photon radiotherapy?

Annahme, dass CIRT effektiver den Tumor zerstört und umliegendes gesundes Gewebe – im Vergleich zur herkömmlichen Photonentherapie – geschont werden kann

Carbon ion radiotherapy (CIRT) is claimed to be both more effective and safer than conventional radiotherapy due to its physical dose distribution and its higher relative biological effectiveness (RBE). The physical distribution to be found in CIRT is promising due to its different radiobiological properties: the high ionisation density generates higher linear energy transfer (LET) and leads to an increase in radiobiological efficiency. CIRT is, therefore, expected to have a higher local control of a tumour than conventional radiotherapy while minimising the probability of damaging the surrounding healthy tissues [22].

C-ions are, therefore, considered to have the right balance between the physical dose distribution and the biological effect. That is, the peak-to-plateau ratio to be found in CIRT is considered to be superior when compared to other ion species [20].

theoretische Annahme zur Überlegenheit von CIRT kann auch Nachteile haben

Zerstörung von gesundem Gewebe

Within hadron therapy, a superiority of CIRT when compared to proton therapy is anticipated as well, due to its different biological properties. However, for soft tissue parameters, the biological advantage of CIRT may not be as stable [23]. That is to say, the higher ionisation density, resulting in high LET, can be described as a two-edged sword [24]: some of those differences may constitute advantages, while others may be disadvantages depending on the application. As such, CIRT could potentially also have its downside since a) the treated volume may not be limited to the volume of the gross tumour, thus, healthy tissues may be affected by high LET, as well as b) some substrates of the surrounding healthy tissues may be affected by a tumour, i.e., if a tumour is intertwined with, or embedded in healthy tissues [19].

B0003 – What is the phase of development and implementation of carbon ion radiotherapy (CIRT)?

MedAutron: PatientInnenbehandlungen seit Ende 2016 mit Protonen

In Austria, hadron therapy is a new form of cancer therapy. Patient treatment started at the end of 2016 using protons [8]. As of September 2017, approximately 30 patients were treated at the MedAustron, and radiation therapy using both proton and C-ions is currently being offered by the MedAustron [10].

CIRT keine neue Therapieform, aber neue Therapieanbote

CIRT is technically not a novel technique; cancer therapy centres started offering this therapy approximately 2 decades ago, and the first cancer therapy started experimenting with radiotherapy using heavy ion radiotherapy in 1975 [1]. Within the last decades, however, many cancer therapy centres started offering cancer therapy using C-ions in Europe and Asia. Historically speaking, some cancer therapy centres also stopped treating patients with CIRT and other types of heavy ion radiotherapy [2].

Administration, investments, personnel and tools required to use CIRT and photon radiotherapy

B0004 – Who administers CIRT and in what context and level of care is CIRT provided?

hochspezialisierte Einrichtungen

Carbon ion radiotherapy (CIRT) is provided in the tertiary, highly specialised level of care: in Austria, the treatment occurs in the outpatient setting at the MedAustron cancer therapy centre. The use of hadron therapy is to be approved by a chief physician [25].

B0008 – What kind of special premises are needed to use CIRT and standard radiotherapy? B0009 – What supplies are needed to use CIRT and photon radiotherapy?

für Strahlentherapie wird ein Linearbeschleuniger benötigt

A so-called linear accelerator (LINAC) can be used for the delivery of external beam radiation therapy. Electricity is used by the LINAC to form a stream of fast-moving subatomic particles. In so doing, high-energy radiation is created and can be used for cancer treatment. A LINAC is necessary for both photon radiotherapy and other more experimental, newer methods of radiation therapy, such as CIRT [18].

für CIRT kommt ein sog. Synchrotron bei MedAustron zum Einsatz

At the MedAustron [26], protons or carbon ions are generated by 3 ion sources: charged particles are first pre-accelerated in a LINAC on a straight line through alternating electric fields. Then, the ion beams are injected in a synchrotron – a circular accelerator with a circumference of approximately 80 metres. The synchrotron accelerates those particles to their final speed (approximately 200,000km/s). Lastly, the ion beam is led into 1 of the irradiation rooms through a so-called extraction line. A vacuum tube is used to hold particles in place using strong magnetic fields. In addition, there are 4 treatment rooms at MedAustron [27]: 1 gantry for proton radiotherapy (PRT) solely and 3 rooms in which both PRT and CIRT can be used. In the latter, 1 room uses a horizontal and vertical fixed beam, 1 room uses a horizontal fixed beam, and another treatment room is only for non-clinical research for PRT/CIRT using a horizontally fixed beam technique. In all of the latter 3 treatment rooms, C-ions can be accelerated to up to 120-400 MeV/n.

Regulatory and reimbursement status

A0021 – What is the reimbursement status of proton therapy and of CIRT?

Refundierung der Protonentherapie

Reimbursement for proton therapy was approved by the Main Association of the Austrian Social Security Institutions in June 2017 [8]. However, only selected oncologic indications are currently being reimbursed [28]:

ausgewählte Indikationsbereiche

basierend auf Evidenz

- Melanoma in the eye (if brachytherapy using iodine or ruthenium application is not suitable),
- Chordoma and chondrosarcoma of the skull base,
- Adenoid cystic salivary gland carcinoma (if inoperable or macroscopic disease residues after surgery are prevalent),
- Paediatric tumours in children younger than 16 years old,
- Meningioma (if they cause neurological symptoms and neurosurgical measures are likely to increase the risk of additional damage).

Entscheidung zur Refundierung von CIRT: noch ausständig

The decisions for the selection of the mentioned indications for protontherapy was based on the LBI-HTA report [9]. A decision on the reimbursement of CIRT indications is pending.

4 Current use of CIRT in published and ongoing clinical trials

In order to assess, for which indications carbon ion radiotherapy (CIRT) is currently being used in clinical trials – randomised clinical trials, non-randomised controlled trials and prospective case series –, published as well as ongoing studies were searched for and reviewed. This chapter will provide an overview of

Übersicht zu Indikationen aus

a. the main "regions" and specific indications on which trials have been conducted (and are published) and

publizierten klinischen Studien &

b. the specific indications on which clinical studies are currently being undertaken (ongoing controlled clinical studies).

laufenden klinischen Studien zu CIRT

The reader is reminded that all of the estimations calculated in this chapter are based on data retrieved from published studies and identified ongoing studies. Thus, the results must be interpreted with caution, since all the results depicted in this chapter might not reflect the true number of patients having been treated with CIRT, but only patients documented in published and ongoing clinical studies.

4.1 CIRT indications in published clinical trials

In this section, the identified studies for research question 1 are summarised using the MedAustron list of potential "regions". Of the 12 "regions" on the list, no publications were found for 4 tumour indications (breast, kidney, nervous system and hematologic cancer). However, the search was not limited to the list of the issued list of MedAustron in this chapter.

von 12 Indikationsbereichen keine Publikationen zu 4 Tumorbereichen

Overall, 56 studies elaborating on the efficacy and/or safety of CIRT have been identified: the majority of the studies chose samples with CIRT patients suffering from tumours in the brain and skull base, prostate and lung region, with 14, 11 and 9 identified studies in those regions respectively. Ear-nose-throat cancer was another significant cluster, consisting of 7 clinical studies. Less frequent clusters were in the gastrointestinal region (GI) and bone and soft tissue region, with 4 and 2 clinical studies assessing the efficacy and safety of CIRT in those regions respectively. In addition, 1 study was identified with choroid melanomas (eye), and 1 further study was identified with skin cancer patients, in their sample.

56 Studien identifiziert
14 Studien: Hirn- und Schädelbasis
11 Studien: Prostata
9 Studien: Lunge
7 Studien: HNO
4 Studien: GI Tumore;
2 Studien: Knochen- und Weichteiltumore
1 Studie: Auge
1 Studie: Hautkrebs

In addition, 8 further studies were found for 2 cancer regions not being on the issued list of the MedAustron were: 7 studies with gynecologic cancer types and 1 study with skin cancer were identified.

2 Regionen, die nicht auf der MedAustron Liste standen:
7 Studien: gynäkologische Tumore

Table 4-1 gives a broad overview of the 56 identified studies according to regions, phases of clinical research and numbers of enrolled patients in those clinical studies. It is noticeable that none of the studies were higher than in phase II and no controlled trial was undertaken, elaborating on the efficacy of CIRT for any of the regions. Only for safety parameters, 1 randomised controlled, pilot study, was identified.

keine einzige kontrollierte Vergleichsstudie zur Wirksamkeit

Doppelpublikationen?

However, the numbers of patients treated with CIRT in the published studies may be less since a) many of the included studies have an overlapping sample, and b) the number of patients suffering from specific tumour entities refer to the total number of enrolled patients and some studies enrolled (and reported) both CIRT and PRT patients.

Table 4-1: Published studies on CIRT in specific tumour regions: phase of clinical trial, number of studies and number of patients treated

Region of cancer		The phase of clinical research				n of studies identified	n of pts receiving CIRT in studies	n of pts in studies
		Ph 1/2[3]	Ph 2	Ph 3	NR			
Bone and soft tissue		2	0	0	0	2	74	74
Brain and skull base		5	0	0	9	14	543	763
Breast		0	0	0	0	0	0	0
Ear-Nose-Throat		2	2	0	3	7	489	523
Eye		1	0	0	0	1	59	59
Gastrointestinal (GI)	Oesophagus	1	0	0	0	1	31	31
	Liver	1	0	0	1	2	148	148
	Rectum	0	0	0	1	1	184	184
Gynaecologic		6	0	0	1	7	241	241
Hematologic cancer		0	0	0	0	0	0	0
Kidney		0	0	0	0	0	0	0
Lung		4	0	0	5	9	631	731
Nervous system		0	0	0	0	0	0	0
Prostate		2	2	0	7	11	3,206	3,253
Skin		1	0	0	0	1	45	45
Total		**25**	**4**	**0**	**27**	**56**	**5,651**	**6,052**

Abbreviations: ENT – Ear-Nose-Throat; NR – not reported; Ph – phase.

Hirn und Schädelbasis: 14 prospektive Studien

mit 763 StudienteilnehmerInnen

ca. 543 PatientInnen bekamen CIRT

For tumours in the **brain and skull base** region, 14 studies were identified, with approximately 763 enrolled patients, of which 543 patients received CIRT. 5 studies were in Phase 1/2 and 9 studies did not report on the clinical phase of their studies. No Phase 2 or Phase 3 studies have been identified for this region.

The most frequent **skull base** tumours of all enrolled patients were chordomas and chondrosarcomas, with 299 patients suffering from those diseases in all identified studies. In addition, 190 enrolled patients suffered from meningiomas. Craniopharyngiomas, pituitary adenomas and tumours of the lacrimal gland were less frequent skull base tumours in the identified studies, with 5, 14 and 21 patients with those diseases enrolled in all identified studies. For more information on the specific studies including skull base tumours, the reader is referred to Table A-19 in the Appendix.

In addition, 194 patients suffered from **brain** tumours, with 70, 45 and 79 patients suffering from WHO grade II gliomas, WHO grade III gliomas and glioblastomas respectively. For more information on the specific studies including brain tumours in their sample, the reader is referred to the Table A-20 in the Appendix.

[3] Phase 1 or a combination of Phase 1/2.

For **prostate** cancer (see Table A-21 in the Appendix), 11 studies were identified: 2 studies were in phase 1/2, and 2 other studies were phase 2 clinical studies. 7 of the identified studies did not report on the phase of the clinical research. Of those, 1 randomised controlled trial focusing on safety-related endpoints solely, and several case series and 3 before-after studies focusing on efficacy-related endpoints were identified: in total, the sum of the samples lead to 3,253 patients, of which 3,206 were treated with CIRT. However, it is assumed that a significant proportion of those patients were enrolled in multiple studies: 1 multi-institutional case series study (n=2,157) may have included many of patients from other identified studies in this assessment, leading to uncertainty of the true number of prostate cancer patients having been treated with CIRT according to those studies.

Prostata:
11 Studien mit ca. 3.253 Studienteilnehmern

ca. 3.206 PatientInnen bekamen CIRT

For **lung cancer**, 9 clinical studies were identified: 4 were phase 1/2 clinical studies, and 5 studies did not report on the phase of clinical research. Approximately 731 patients[4] were enrolled in those studies, and 631 patients have been treated with CIRT. 8 out of 9 identified studies had patients with non-small cell cancer (NSCLC) in their sample, and 1 study included 91 patients with oligo-recurrence in the lung. The reader is referred to Table A-22 in the Appendix for more information on the identified studies.

Lunge:
9 Studien mit 731 StudienteilnehmerInnen

ca. 631 PatientInnen bekamen CIRT

For the **Ear-Nose-Throat** region (see Table A-23 in the Appendix), 7 clinical studies were identified: 2 studies and 2 studies were phase 1/2 and phase 2 respectively. The other 3 clinical studies did not report on the phase of clinical research. Approximately 523 patients were enrolled. Of those, 489 patients received CIRT. From all enrolled patients, 215 patients had tumours in the nasal cavity and paranasal sinus, and 142 enrolled patients had adenoid cystic salivary gland tumours. Less frequent indications in those studies were pharynx carcinomas[5], sarcomas in the head and neck region, orbita tumours, and maxillary sinus carcinomas, with 34, 27, 20 and 13 patients with those indications included in the identified studies respectively. The rest of the enrolled patients had other ENT tumour types not within the list of the selected indications.

HNO-Bereich:
7 Studien mit 523 StudienteilnehmerInnen

ca. 489 bekamen CIRT

For **bone and soft tissue** tumours (see Table A-24 in the Appendix), 2 phase 1/2 studies with 74 enrolled patients receiving CIRT were identified. Of those, 29 patients had soft tissue sarcomas, and 18 had osteosarcomas. In addition, patients with sacral chordomas and sacral chondrosarcomas were enrolled in the identified studies, with 11 and 7 patients suffering from those cancer types respectively. The rest of the enrolled patients (n=9) had tumour types not within the list of the selected indications.

Knochen- und Weichteiltumore:
2 Studien mit 74 StudienteilnehmerInnen, alle bekamen CIRT

For **gastrointestinal tumours** (see Table A-25 in the Appendix), 4 studies were identified: 2 phase 1/2 studies and 2 further clinical studies did not report on the phase of clinical research. 363 patients were enrolled in those clinical studies, of which all patients received CIRT in different forms (e.g., dosages). Of all enrolled patients, cancer was prevalent in the following indications: rectum carcinoma, liver carcinoma and oesophagus carcinoma, with 184, 148 and 31 patients with those indications respectively.

GI Tumore:
4 Studien mit 363 StudienteilnehmerInnen, 184 PatientInnen bekamen CIRT

[4] 2 studies [29, 30] are assumed to have reported on the same 81 patients in their studies. It was found out considerably late in the assessment and both of the studies were excluded from the qualitative synthesis because of high risk of bias. Therefore, those patients were only counted once in the analysis (see Table A-22).

[5] In the studies [31-33], it was not specified whether the patients suffered from naso- or oropharyngeal cancer.

Auge: 1 Studie mit 59 StudienteilnehmerInnen, welche CIRT bekamen

gynäkologische Ca: 7 Studien mit 241 Pts. Hautkrebs: 1 Studie mit 45 Pts mit CIRT

In the **eye** region (see Table A-26 in the Appendix), only 1 study was identified, with 59 patients with choroid melanomas in their sample.

In addition, 2 further regions on which trials have been conducted were found (and are published): 7 case series studies with an estimated 241 patients, receiving CIRT, were found for **gynecologic cancer** types. 1 further study, with 45 CIRT patients suffering from cancer in the **skin** region, was also identified.

4.2 CIRT indications in ongoing studies

For the analysis of ongoing studies, studies were categorised by region, and phase of clinical research. Only controlled studies are described in this section (see Table A-17 in the Appendix). However, the phase of clinical research and the number of patients enrolled was extracted for all identified studies and are depicted in Table 4-2. It was noticeable during the hand-searches that numerous uncontrolled studies are currently being undertaken.

ca. 65 laufende Studien & 1 Patientenregister, wovon 10 kontrollierte Studien

8 laufende RCTs
2 laufende CTs

In total, the search for ongoing studies resulted in 382 hits [305 (PTCOG), 42 (ClinicalTrials.gov); 33 (WHO-ICTRP); 2 (EU Clinical Trials)]. After de-duplication and excluding those studies focusing on other forms of hadron therapy, 60 clinical studies remained, of which only 10 studies are controlled trials, evaluating the efficacy or safety of CIRT for 9 different indications. The update on 8 February 2018 of those registries led to the identification of further 5 uncontrolled studies and 1 patient registry from the MedAustron with 800 patients planned to be included in the next 10 years, receiving proton or C-ion therapy.

The following table gives an overview of the identified 65 ongoing studies for CIRT. The weighting of studies and enrolled patients according to regions may be different, but is still similar to the 1 of published studies to a certain extent: it appears that many studies (phase 1-2) are currently undertaken for tumours in the prostate, brain and skull base, and lung region.

Table 4-2: Ongoing clinical trials on CIRT in specific tumour regions: phase of clinical trial, number of patients enrolled

Region of cancer	The phase of clinical research					n of studies identified	n of pts in studies
	Ph 1	Ph 1/2	Ph 2	Ph 3	NR		
Bone & soft tissue tumour	1	3	3	0	1	8	391
Brain & skull base	0	2	3	2	0	7	1,219
Breast	0	1	0	0	0	1	20
ENT	1	3	4	0	1	9	612
GI tumours	7	1	6	0	2	16	861
Hematologic cancer	0	0	0	0	0	0	0
Kidney	0	2	0	0	0	2	20
Lung	1	0	3	0	1	5	860
Nervous system	0	0	0	0	0	0	0
Gynecologic	1	4	0	0	3	8	197
Prostate	0	2	5	0	2	9	1,858
Total	**11**	**18**	**24**	**2**	**10**	**65**	**6,038**

Abbreviations: ENT – Ear-Nose-Throat; NR – not reported; Ph – phase

Of the 10 controlled studies, 2 are phase 3 clinical trials, and 3 and 2 clinical trials are either phase 2 or a combination of phase 1 and phase 2 respectively. In addition, 1 clinical trial is in phase 1. 8 (of 10) studies are randomised trials and 2 studies did not report the phase of clinical research. The studies investigate the efficacy or safety of CIRT in 5 different regions and 9 different oncologic indications. Overall, 2,162 patients were enrolled in the identified ongoing clinical studies. However, the primary completion date of 4 studies has already passed, leading to approximately 1,129 patients currently enrolled in at least controlled clinical studies evaluating the efficacy or safety of CIRT.

(R)CTs:
insg. 2.162
StudienteilnehmerInnen
zu 9 onkologischen
Indikationen:

The following indications are investigated in the 10 ongoing controlled studies: tumours in bone and soft tissue (2 studies included patients with sacral chordomas); in the brain and skull base region, patients suffering from chordomas, meningiomas, chondrosarcoma, primary glioblastomas and recurrent gliomas are enrolled, with 1 study for each of those indications respectively; for tumours in the ENT region, patients with cystic carcinomas and sarcomas are enrolled in another study. 1 further study included patients with tumours in the gastrointestinal region (hepatocellular carcinoma), and 1 study included lung cancer patients (small-sized peripheral, non-small cell lung carcinoma).

2 Studien:
sakrale Chordome
Hirn- und Schädelbasis:
1 Studie: Chordome
1 Studie: Meningeom
1 Studie:
Chondrosarkom
1 Studie: Glioblastom
1 Studie: Gliom

The most frequent control interventions are other types of radiotherapy: 4 studies use proton radiotherapy (PRT) solely as a control intervention, and the following control interventions are being used in 1 study respectively: PRT in combination with CIRT, x-rays/protons, photon radiotherapy, and fractionated stereotactic radiotherapy (FSRT). In addition, surgery is also used as a control intervention in 2 studies: 1 study used surgery alone, and another study used surgery in combination with radiotherapy, as a control intervention.

HNO Bereich: 1 Studie:
adenoidzystisches
Karzinom und Sarkom;
GI: 1 Studie:
Leberzellkarzinom;
Lunge: 1 Studie:
Kleinzelliges
Lungenkarzinom

Surprisingly, the proportions of patients enrolled in the respective indication groups (clusters) for controlled, or randomised groups do not correspond with the distribution of the identified published and ongoing studies. That is to say, numerous uncontrolled studies were, and are currently being undertaken for many indications.

The reader is referred to Table A-17 in the Appendix for more information on the characteristics of the ongoing controlled studies identified through the hand-search.

5 Efficacy and safety of carbon ion radiotherapy (CIRT) for 54 indications

5.1 Outcomes

Wirksamkeit

To answer the question whether CIRT is more or equally effective as the standard irradiation, mortality, and mortality-related endpoints, as well as other patient-relevant endpoints, were used to evaluate the evidence regarding the efficacy of CIRT. For **efficacy**, the following outcomes were defined as *crucial* to derive a conclusion:

- Overall survival (OS)
- Cause-specific survival (CSS)/Disease-specific survival (DSS)
- Recurrence-free survival (RFS)
- Progression-free survival (PFS)
- Disease-free survival (DFS)
- Change in Health-Related Quality of Life (HRQoL)

Gesamtüberleben

Overall survival (OS) refers to the rate or probability of surviving a specified time period typically from a specified date (i.e., cancer diagnosis, start of cancer treatment) – to death. All causes, leading to death, are hereby included in the analysis [34, 35]. The endpoint is reported at 1, 2, 3, 4, 5 and 10 years.

Krankeitsfreies Überleben

Cause-specific survival (CSS)/Disease-specific survival (DSS) can be described as a "corrected" survival excluding deaths from other causes than the patient's disease. In so doing, several strengths can be observed: the ability to compare patient groups, inter alia, with different age distribution, increases. Moreover, the (excess) death rate being attributable to certain cancer may be shown with this endpoint [34]. The endpoint is reported at 1, 2, 3, 4, 5 and 10 years.

Tumorkontrolle

Disease-free survival (DFS) refers to the survival of patients until the date of recurrence (loco-regional or systemic) [36]. This endpoint is reported at 1, 2, 3, 4, 5 and 10 years.

Within the term **recurrence-free survival (RFS)**, related endpoints were judged as crucial and summed up within the endpoint RFS accordingly. RFS can be described as the period from therapy (e.g., CIRT) until a recurrent disease is detected. Typically, second, or other primary cancers are excluded in the analysis [36]. In this assessment, biochemical recurrence-free survival (BRFS) or biochemical relapse-free survival (BNED) were extracted and described within the endpoint RFS. The endpoint was seen as crucial at 1, 2, 3, 4, 5 and 10 years.

Progression-free survival (PFS) can be described as the "(…) time from randomisation to first radiological or clinical observation of disease progression or any-cause death" [9]. Disease progression can be measured using the Response Evaluation Criteria in Solid Tumours (RECIST) and includes recurrence (loco-regional or systemic), second malignancy, or any deaths from any cause. However, late deaths not attributable to cancer are typically excluded [36]. The endpoint is reported at 1, 2, 3, 4, 5 and 10 years.

In addition, the **local control rate (LCR)** was considered to be relevant and was seen as a surrogate endpoint in this assessment. Other forms of local

control, such as the loco-regional control (LRC), were also extracted within this endpoint. The endpoint is reported at 1, 2, 3, 4, 5 and 10 years.

Lebensqualität

Besides survival rates, improvements in **Health-Related Quality of Life (HRQoL)** was used as a crucial outcome since patient-reported outcomes (PRO) are important measures in oncology [37]. There are several instruments available to measure HRQoL and data was extracted pre- and post-interventional, short-term (<6 weeks), mid-term (>6weeks – ≤6 months) and longer-term (> 6 months). In this assessment, no restriction was set to specific questionnaires. 1 or more of the following questionnaires was used in 6 of the included studies: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ); the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire, including subscales and summary indexes such as the Trial Outcome Index (TOI); the Functional Assessment of Cancer Therapy-Prostate (FACT-P); the UCLA Prostate Cancer Index (UCLA-PCI); and the Japanese Version of the SF-8 questionnaire [38].

wesentliche Sicherheitsendpunkte

For **safety**, the following outcomes were defined as *crucial* to derive a recommendation:

- Acute radiation morbidities
- Late radiation morbidities

akute Strahlenbelastung

Acute radiation morbidities are analysed using the Radiation Therapy Oncology Group (RTOG) criteria or the Common Terminology Criteria for Adverse Events (CTCAE). Acute radiation morbidities are defined as those morbidities occurring between the start (day 1) of the therapy until 3 months (90 days) after the therapy was initiated by both the CTCAE [39] and RTOG [40] criteria.

späte Strahlenbelastung

Late radiation morbidities are analysed using the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Cancer (EORTC) and the CTCAE criteria. Late radiation morbidities are defined as radiation morbidities occurring 90 days after the start of the therapy by both the CTCAE [39] and RTOG [40] criteria.

5.2 Included studies

27 Studien erfüllten die Einschlusskriterien: prospektive Studien mit > 10 Pts und low/ moderate RoB, publiziert 2005-2017

In order to assess efficacy-, and safety-related outcomes of CIRT, all prospectively conducted studies with more than 10 patients, with low or moderate risk of bias (RoB) were eligible to answer the research question. Overall, 27 studies were identified and reviewed in this systematic review: of those 27 studies, only 1 randomised, open-label, pilot study focusing on toxicity/feasibility of CIRT for prostate cancer was identified. Moreover, 26 non-randomised, uncontrolled studies met the inclusion criteria. That is; 3 case-control studies and 23 case series studies reported on the efficacy and/or safety of CIRT in the following regions: prostate (n=7), lung (n=6), ear-nose-throat (n=5), skull base (n=3), brain (n=2), bone and soft tissue (n=1), gastrointestinal (n=2). Study characteristics and results of included studies are displayed in the Appendix (Table A-1 to Table A-8).

nur 1 RCT
3 Fall-Kontrollstudien
3 Vorher-Nachher Studien
20 Fallserien

The results will be reported separately for each of the 54 indications.

5.3 Results

efficacy and safety of CIRT

In the following section, the body of the evidence of the included studies focusing on efficacy and/or safety of carbon ion radiotherapy (CIRT) in 54 indications in 12 regions (according to the MedAustron list for potential indications) are reported. In addition, background information on the specific indications will be described and – if applicable – an evidence synthesis will be conducted.

5.3.1 Skull base tumours

Definition

13 Indikationen im Bereich „Schädelbasis"

"Skull base tumours" refers hereby to 13 different oncologic indications: skull base chordoma, skull base chondrosarcoma, meningioma (grade II-III), meningioma (grade I, complex), craniopharyngioma, pituitary adenoma, acoustic neuroma, other neurinomas, glomus tumours, retinoblastomas, lacrimal gland tumours, sarcomas (incl. Ewing's sarcoma), rhabdomyosarcomas of the skull base and orbit. In the medical literature, however, some of the sub-indications may be categorised differently. As such, meningiomas are, for instance, technically brain tumours [41], and many of the other tumours may be categorised as pediatric (e.g., rhabdomyosarcoma) and/or eye tumours (e.g., lacrimal gland tumours, retinoblastomas) [41][6].

Epidemiology, current treatment regimens and prognosis

Due to the broad variety of specific tumour entities to be found in this chapter, the reader is referred to each specific indication to gain more information on current treatment approaches and prognosis of the specific oncologic indications.

Included studies

3 Fallserien inkludiert
112 Pts,
48 GyE to 60,8 GyE

For skull base tumours, 3 case series studies from 2 cancer therapy centres, located in Germany and Japan, were included in this assessment. That is, 2 studies [42, 43] were conducted at the Heidelberg Ion Beam Therapy Centre (HIT) in Germany, and 1 study [44] was conducted at the Heavy Ion Medical Accelerator in Chiba (HIMAC) in Japan.

In total, 112 patients suffering from chordomas or chondrosarcomas of the skull base or paracervical spine were enrolled in the included studies. Of those, 53 and 59 patients suffered from chordomas and chondrosarcomas respectively. 79 patients received CIRT in a raster scanning technique; of those, 25 patients had recurrent tumours and were receiving CIRT as a re-irradiation. The total dose of CIRT ranged from 48 GyE to 60.8 GyE. Additional treatment – counting previous treatments – included, inter alia, photon irradiation, proton irradiation, CIRT, and surgery.

The reader is referred to the evidence synthesis for the specific indication and the data extraction table (see Table A-8) for more information on the included studies.

[6] The structure of the MedAustron list was not changed as conducting the evidence synthesis alongside the MedAustron list was judged to be more helpful in guiding the decision-making process

Conclusion: Efficacy and safety

Due to the heterogeneity of the different tumours (e.g., different prognosis) captured with the term "skull base tumours", the evidence synthesis for specific indications can be found in the respective sections.

keine Evidenz zu 11 Indikationen

unzureichende Evidenz zu Chordomen & Chondrosarkomen

For skull base tumours, 3 studies were included in this assessment: none of the studies were controlled for comparing CIRT to standard irradiation. Indirect comparisons were not conducted in any of the included studies. 13 oncologic "skull base" indications were assessed regarding superiority/inferiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity): no evidence was found for 11 oncologic skull base indications, and insufficient scientific evidence was found for 2 oncologic indications (chordomas and chondrosarcomas).

keine Schlussfolgerungen zu Überlegenheit/ Unterlegenheit bei Schädelbasistumoren möglich

Thus, neither superiority nor inferiority on the basis of the selected endpoints regarding efficacy or safety can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with skull base tumours.

In the following section results from specific skull base tumours are presented.

5.3.1.1 Chordoma in the skull base

Definition and epidemiology

Häufigkeit: 8,4 in 10 Mio

A skull base chordoma is a rare tumour occurring in the bone of the skull base, being locally invasive and an aggressive tumour type [45]. Epidemiologic data on the incidence and prevalence of chordomas of the skull base in Austria was not found. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (1973–2009) of patients suffering from skull base chordomas suggests that the overall incidence of intra- and extracranial skull base chordomas is 8.4 per 10 million persons [46]. The TNM system can be used to stage chordomas of the skull base even though the prognostic value may be limited [47].

Current treatment regimens and prognosis

Prognose: 5 Jahre: 65 % 10 Jahre: 32,3 %

The optimal treatment may not be fully clarified yet. However, combinations of surgery and radiation therapy using photons or charged particles are potential treatment modalities [47]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (1983-2009) including 416 patients suffering from skull base chordomas showed a relative survival at 5 and 10 years of 65% and 32.3% respectively [48].

Included studies

For skull base chordomas, 2 studies were included in this assessment: 1 dose-escalation case series, pilot study [44] at the Heavy Ion Medical Accelerator in Chiba (HIMAC) in Japan and 1 case series study [42] at the Heidelberg Ion Beam Therapy Centre (HIT) in Germany.

In total, 58 patients were enrolled in the included studies: 53 patients with chordomas of the skull base or paracervical spine and 5 patients with low-grade chondrosarcomas received CIRT. In the dose escalation, case series study [44], patients with chordomas of the skull base or paracervical spine (n=33) were irradiated with CIRT at a total dose ranging from 45 GyE/16 fr. to 60.8 GyE/16 fr. over 4 weeks. In the other included study [42], patients with chordomas and low-grade chondrosarcomas (n=25) received CIRT as a re-irradiation – after photon irradiation – in an active raster scanning technique at a total dose of 51 GyE (range: 45-50 GyE). Patients received surgery in both of the included studies before CIRT.

2 Fallserien:
58 Pts
47-50 Jahre

Dosis:
45 GyE – 60,8 GyE

The specific tumour stage was not reported by any of the studies [42, 44]. The median age of the patients was 47 years and 50 years in the included studies respectively. All patients were aged between 16 and 76 years at the start of the enrolment in the clinical trials [42, 44]. The loss to follow-up was not adequately reported in any of the included studies [42, 44].

Study characteristics, i.e., information on patient population, intervention, control and study design of the included studies, can be found in the Appendix (see Table A-8 in the Appendix).

Efficacy

Overall survival (OS)

Overall, 1 out of 2 included studies [44] measured overall survival (OS) at different time points. None of the included studies compared the OS of CIRT patients to the OS of patients undergoing conventional radiotherapy.

OS in 1 Studie, 33 Pts

5 Jahre OS: 87,7 %
10 Jahre OS: 67 %

1-year OS was not reported in any of the included studies.

2-year OS was not reported in any of the included studies.

3-year OS was not reported in any of the included studies.

4-year OS was not reported in any of the included studies.

5-year OS was reported in 1 study: the dose escalation study [44], including 34 cases of chordomas of the skull base and the paracervical spine in 33 patients undergoing CIRT at a total dose ranging from 48 GyE/16 fr. to 60.8 GyE/16 fr., observed an OS of 87.7% (95% CI: NR, SE: 7%) at 5 years.

10-year OS was reported in 1 study: the dose escalation study [44], including 34 cases of chordomas of the skull base and the paracervical spine in 33 patients undergoing CIRT at a total dose ranging from 48 GyE/16 fr. to 60.8 GyE/16 fr., observed an OS of 67% (95% CI: NR, SE: 14%) at 10 years.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by any of the included studies.

keine Daten:
CSS/DSS
DFS
RFS

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by any of the included studies.

Progression-free survival (PFS)

PFS 1 Studie, 25 Pts

2 Jahre PFS: 79,3 %

Overall, 1 out of 2 included studies [42] measured progression-free survival (PFS) 2 years after irradiation with photons and C-ions in an active raster scanning technique. None of the included studies compared the PFS of CIRT patients to the PFS of patients undergoing conventional radiotherapy.

1-year PFS was not reported in any of the included studies.

2-year PFS was reported in 1 study [42]: the 2-year-local progression-free survival (LPFS) was 79.3% (95 CI: NR) for 25 patients with recurrent chordomas or chondrosarcomas having been irradiated with a combined therapy of photon radiotherapy and CIRT in an active raster scanning technique.

3-year PFS was not reported in any of the included studies.

4-year PFS was not reported in any of the included studies.

5-year PFS was not reported in any of the included studies.

10-year PFS was not reported in any of the included studies.

Local control rate (LCR)

1 Studie LCR, 33 Pts

5 Jahre: 85,1 %
10 Jahre: 63,8 %

Overall, 1 out of 2 included studies [44] measured the local control rate (LCR) at different time points. None of the included studies compared the LCR of CIRT patients to the LCR of patients undergoing conventional radiotherapy.

1-year LCR was not reported in any of the included studies.

2-year LCR was not reported in any of the included studies.

3-year LCR was not reported in any of the included studies.

4-year LCR was not reported in any of the included studies.

5-year LCR was reported in 1 study: the dose escalation study [44], including 34 cases of chordomas of the skull base and the paracervical spine in 33 patients undergoing CIRT at a total dose ranging from 48 GyE/16 fr. to 60.8 GyE/16 fr., observed an LCR of 85.1% (95 CI: NR, SE: 8%) at 5 years.

10-year LCR was reported in 1 study: the dose escalation study [44], including 34 cases of chordomas of the skull base and the paracervical spine in 33 patients undergoing CIRT at a total dose ranging from 48 GyE/16 fr. to 60.8 GyE/16 fr., observed an LCR of 63.8% (95 CI: NR, SE: 19%) at 10 years.

Health-Related Quality of Life (HRQoL)

keine Daten: HRQoL

The endpoint Health-Related Quality of Life was not measured by any of the included studies.

Safety

All 2 included studies measured radiation morbidities [42, 44]: toxicities of CIRT occurred in the mucosa, skin and brain.

Acute radiation morbidity

akute Strahlenbelastung: 2 Studien

All 2 included studies measured acute radiation morbidities using the RTOG [44] or CTCAE [42]. No acute radiation morbidity higher than grade 3 occurred in any of the included studies. 1 study did not consistently and exhaustively report on acute radiation morbidities according to the severity (grades) [42].

Grade 1 acute radiation morbidities were reported in 2 studies [42, 44]: the dose escalation study [44] observed several grade 1 acute radiation morbidities in the mucosa and skin, occurring in 6 (17.6%) and 12 (35.3%) out of 33 cases of chordomas respectively. Another study [42] did not report on acute grade 1 morbidities in the skin or mucosa, but observed 5 out of 25 patients (20%) developing grade 1 asymptomatic temporal lobe reactions. The same study may have selectively reported on acute radiation morbidities since grade 1 acute radiation morbidities in the mucosa and skin were not reported.

Grad 1:
Mukosa: NR & 17,6 %
Haut: NR & 35,3 %

Grade 2 acute radiation morbidities were reported in both included studies [42, 44]: 1 study [44] observed several grade 2 acute radiation morbidities in the mucosa and skin, occurring in 6 (17.6%) and 1 (2.9%) out of 33 cases of chordomas respectively. Another study (n=25) [42] observed grade 2 mucositis and hypacasis, occurring in 1 patient (4%) and 3 patients (12%) respectively.

Grad 2:
Mukosa: 4-17,6 %
Haut: NR & 2,9 %

Grade 3 acute radiation morbidities were reported in both studies: 1 study (n=25) [42] observed 1 grade 3 osteoradionecrosis (4%) and another study [44] observed no grade 3 acute radiation morbidities.

Grad 3: 0-4 %

Grade 4 acute radiation morbidities were reported in both, and observed in none of the included studies [42, 44].

Grad 4: 0 %

Late radiation morbidity

Overall, 1 out of 2 included studies measured late radiation morbidities using the RTOG/EORTC criteria [44]. Another study [42] did not report on whether late radiation morbidities occurred.

späte Strahlenbelastung:
1 Studie

Grade 1 late radiation morbidities were reported in 1 study [44]: toxicities were observed in the mucosa, skin and brain, with 2 (5.9%), 2 (5.9%) and 5 (14.7%) cases developing grade 2 late radiation morbidities in those areas respectively.

Grad 1: Mukosa: 5,9
Haut: 5,9;
Hirn:14,7 %

Grade 2 late radiation morbidities were reported in 1 study [44]: 1 grade 2 radiation morbidity occurred in 1 out of 34 cases of chordomas (2.9%).

Grad 2: Hirn: 2,9 %

Grade 3 late radiation morbidities were reported in 1 study [44]: no grade 3 late radiation morbidity occurred in 34 cases of chordomas in this study.

Grad 3: 0 %

Grade 4 late radiation morbidities were reported in 1 study [44]: no grade 4 late radiation morbidity occurred in 34 cases of chordomas in this study.

Grad 4: 0 %

Conclusion

For chordomas of the skull base, 2 studies were included to assess the efficacy and safety of CIRT: none of the studies were controlled, comparing CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with chordomas of the skull base.

2 Studien ohne Vergleich, 58 Pts

unzureichende Evidenz

5.3.1.2 Chondrosarcoma of the skull base

Definition and epidemiology

seltener Tumor

Chondrosarcoma of the skull base is a rarely occurring malignant tumour [47]. Chondrosarcomas are the second most frequent malignant tumours and have a peak age of occurrence between 50 and 70 years [41]. Epidemiologic data on the incidence and prevalence of chordomas of the skull base in Austria was not found. The TNM system can be used to stage chondrosarcomas of the skull base, even though the prognostic value may be limited [47].

Current treatment regimens and prognosis

Prognose:
5 Jahre: 81,8 %
10 Jahre: 49,5 %

Current treatment modalities of chondrosarcomas include one of the following: radical compartmentalised resection or intensity-modulated stereotactic radiation therapy (IMSRT) [41]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (1983–2009) including 269 patients suffering from skull base chondrosarcomas showed a 5-year and 10-year relative survival of 81.8% and 49.5% respectively [48].

Included studies

1 Fallserie, 54 Pts
46 Jahre
60 CGE

For chondrosarcomas of the skull base, 1 clinical study [43] from the Heidelberg Ion Beam Therapy (HIT) Centre was included in this assessment. In total, 54 patients with low-grade and intermediate-grade chondrosarcomas of the skull base were enrolled in the included clinical study. The patients were treated with CIRT, after surgery, using a raster scan technique at a median dose of 60 Cobalt Gray Equivalents (CGE) in 7 fractions at 3.0 CGE per fraction.

Of the 54 tumours, 37 (68.5%) and 12 (22.2%) were staged as grade 1 and grade 2 tumours respectively. Also, 5 (9.3%) of the tumours were staged as grade 1 but had focal grade 2 areas. The median age of the patients was 46 years, and all patients were aged between 6 and 74 at the start of the enrolment. The median follow-up time was 33 months (range: 3–84) and loss to follow-up was not reported in the included study.

Study characteristics, i.e., information on patient population, intervention and study design of the included study, can be found in the Appendix (see Table A-8 in the Appendix).

Efficacy

Overall survival (OS)

OS in 1 Studie, 54 Pts

3 Jahre OS: 98,2 %
4 Jahre OS: 98,2 %

The included study measured overall survival (OS) of 54 patients with low-grade and intermediate-grade chondrosarcomas of the skull base having undergone carbon ion therapy (CIRT) at 3 and 4 years after CIRT [43]. No comparison between OS of CIRT patients and OS of patients undergoing conventional radiotherapy was undertaken.

1-year OS was not reported in the included study.

2-year OS was not reported in the included study.

3-year OS was reported in the included study [43]: the case series study observed a 3-year OS of 98.2% (95% CI: 94.6–100%) for 54 CIRT patients with chondrosarcomas having undergone CIRT in a raster scan technique at a median dose of 60 Cobalt Gray Equivalents (CGE) in 7 fractions.

4-year OS was reported in the included study [43]: the case series study observed a 4-year OS of 98.2% (95% CI: 94.6–100%) for 54 CIRT patients with chondrosarcomas having undergone CIRT in a raster scan technique at a median dose of 60 Cobalt Gray Equivalents (CGE) in 7 fractions.

5-year OS was not reported in the included study[7].

10-year OS was not reported in the included study.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included studies.

keine Daten:
CSS/DSS
DFS
RFS
PFS
HRQoL

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included study.

Progression-free survival (PFS)

The endpoint progression-free survival (PFS) was not measured by the included study.

Local control rate (LCR)

The included study [43] measured the local control rate (LCR) of 54 patients with low-grade and intermediate-grade chondrosarcomas of the skull base having undergone carbon ion therapy (CIRT) patients at 3 and 4 years.

LCR in 1 Studie:

3 Jahre LCR: 96,2 %
4 Jahre LCR: 89,8 %

1-year LCR was not reported in the included study.

2-year LCR was not reported in the included study.

3-year LCR was reported in the included study [43]: the case series study observed a 3-year cumulative local control rate of 96.2% (95% CI: 88.8–100%) for 54 CIRT patients with chondrosarcomas having undergone CIRT in a raster scan technique at a median dose of 60 Cobalt Gray Equivalents (CGE) in 7 fractions.

4-year LCR was reported in the included study [43]: the case series study observed a 4-year cumulative local control rate of 89.8% (95% CI, 75.6–100%) at 4 years for 54 CIRT patients with chondrosarcomas having undergone CIRT in a raster scan technique at a median dose of 60 Cobalt Gray Equivalents (CGE) in 7 fractions.

5-year LCR was not reported in the included study.

10-year LCR was not reported in the included study.

[7] The included study stated that in the abstract that the 5-year OS for 54 patients with chondrosarcomas was 98.2% (CI: NR). In the results section, this rate is referred to be for 3 and 4 years respectively. It is also stated that only 9 patients survived 5 years potentially without having calculated the respective 5-year OS.

Health-Related Quality of Life (HRQoL)

keine Daten: HRQoL

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included studies.

Safety

Acute radiation morbidity

akute Strahlenbelastung: 1 Studie

The included study [43] did report on acute radiation morbidities using the CTCAE v3.0 criteria[8]. No grade 4, and 1 grade 3, acute radiation morbidities occurred. Some grade 1-2 acute radiation morbidities were also observed.

Grad 1: 3,7 %

Grade 1 acute radiation morbidities were reported in the included study [43]: the case series study observed 2 patients (3.7%) developing grade 1 acute radiation morbidities in the mucosa.

Grad 2: NR

Grade 2 acute radiation morbidities were not reported in the included study.

Grad 3: 1,9 %

Grade 3 acute radiation morbidities were reported in the included study [43]: the case series study included 54 patients and observed 1 patient (1.9%) developing grade 3 mucositis.

Grad 4: 0 %

Grade 4 acute radiation morbidities were reported in the included study [43]: the case series study observed no grade 4 acute radiation morbidities.

1 weitere Stahlenbelastung: parotitis (Grad:NR)

Moreover, the same study observed parotitis (grade: NR) occurring in the acute phase in 1 (1.9%) out of 54 CIRT patients.

Late radiation morbidity

Späte Strahlenbelastung: 1 Studie

The included study [43] did report on late radiation morbidities using the RTOG/EORTC criteria[8].

Grad 1/2: 9,3 %

Grade 1 late radiation morbidities and **grade 2 late radiation morbidities** were reported in 1 study, but not separated from each other: the case series study [43] with 54 patients with chondrosarcomas observed 5 patients (9.3%) developing grade 1 or 2 late radiation morbidities.

Grad 3: 1,9 %

Grade 3 late radiation morbidities were reported in 1 study: the case series [43] of 54 patients with chondrosarcomas observed 1 grade 3 late radiation morbidity (1.9%).

Grad 4: 0 %

Grade 4 late radiation morbidities were reported in 1 study: the case series [43] of 54 patients with chondrosarcomas observed no grade 4 late radiation morbidities.

Conclusion

1 Studie ohne Vergleich, 54 Pts

unzureichende Evidenz

For chondrosarcoma of the skull base, 1 study [43] was included: the study was not controlled, comparing CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in chondrosarcoma of the skull base.

[8] However, the study did not consistently and exhaustively report on acute radiation morbidities according to the severity (grades).

5.3.1.3 Meningioma

Definition and epidemiology

WHO Grad I, II-III

In this section, the evidence regarding the use of CIRT for 2 indications according to the list of potential CIRT indications will be described: meningioma grade I and meningioma grade II-III. A meningioma is a tumour arising from the meninges of the brain or the spinal cord [41]. Epidemiologic data on the incidence and prevalence of meningioma of the skull base in Austria was not found.

Häufigkeit:
7,62 in 100.000 in USA

Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2004 and 2011) show that the average age-adjusted incidence rate of meningioma was 7.62 per 100,000 annually [49].

The World Health Organisation (WHO) scheme is used to classify meningioma. One can distinguish between the following grades of meningiomas: WHO grade I (benign meningiomas without a higher grade lesion to be elaborated using morphologic criteria), WHO grade II (e.g., atypical, choroid meningiomas) and WHO grade III (including anaplastic, rhabdoid as well as papillary meningiomas) [50].

Current treatment regimens and prognosis

The treatment of meningiomas depends on the WHO grade of the disease and may include watchful observation, neurosurgery and/or radiation therapy [41].

Prognose:
5 Jahre: 66 %-85,6 %

Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2004 and 2011) shows 5-year relative survival rates of benign, borderline malignant and malignant meningiomas of 85.6% 82.3% and 66.0% respectively [49].

Included studies, efficacy and safety

keine Studie inkludiert

For meningiomas, no study was eligible to be included in the qualitative synthesis. No evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority of CIRT regarding efficacy or safety for meningiomas. 5 case series studies were identified, but none of those studies met the inclusion criteria for the qualitative synthesis.

5.3.1.4 Craniopharyngioma

Definition and epidemiology

seltener Tumor

Craniopharyngiomas are rare tumours arising in the remnants of the so-called Rathke's pouch (on a line between the nasopharynx and the diencephalon). Usually, these tumours occur in the pituitary stalk – to be found in the suprasellar region – and adjacently located to the optic chiasm. However, a small proportion of craniopharyngiomas also occur in the optic system, third ventricle or the sella [51].

Epidemiologic data on the incidence and prevalence of craniopharyngioma in Austria was not found.

Häufigkeit: 1,7 in 1 Mio

A recent study [52] using data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2004 and 2008) calculated the age-adjusted incidence rate to be 1.7 cases per 1,000,000 persons. However, the study found a bimodal age distribution regarding the incidence rate of craniopharyngiomas. That is, peaks regarding the incidence rate were observed in children (aged 0-19 years) and adults (aged 40-79 years), with an incidence rate of 1.9 and 2.1 cases per 1,000,000 persons in those age groups respectively.

Current treatment regimens and prognosis

The treatment of craniopharyngiomas includes surgery (in almost all cases). Moreover, radiation therapy (RT) may be indicated if patients underwent partial surgical resection or if disease-recurrence occurred followed by a treatment aimed to be a gross total resection. The treatment modalities of RT include, inter alia, intensity-modulated radiation therapy (IMRT), stereotactic radiotherapy, and proton beam therapy [51].

Prognose: 1 Jahr: 91, % 3 Jahre: 86,2 %

A recent study [52] using data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2004 and 2008) calculated the 1- and 3-year overall survival of 644 patients with a craniopharyngioma-diagnosis, with an OS of 91.5% (95% CI, 88.9%–93.5%) and 86.2% (95% CI, 82.7%–89.0%) at 1 and 3 years respectively.

Included studies, efficacy and safety

keine Studie eingeschlossen

For craniopharyngioma, no study was eligible to be included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for craniopharyngioma.

5.3.1.5 Pituitary adenoma

Pituitary adenomas are intracranial neoplasms that constitute, besides carcinomas, the largest proportion of all pituitary neoplasms. Those tumours can be either benign or invasive [53]. Epidemiologic data on the incidence and prevalence of pituitary adenomas was not found.

Included studies, efficacy and safety

keine Studie eingeschlossen

For pituitary adenoma, no study was eligible to be included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for pituitary adenomas.

5.3.1.6 Acoustic neuroma

Definition and epidemiology

Acoustic neurinomas are Schwann cell-derived tumours arising in the cranial nerve [54]. Epidemiologic data on the incidence and prevalence of acoustic neurinomas was not found.

Current treatment regimens and prognosis

For acoustic neurinomas, one, or a combination of the following treatment options may be used: surgery, radiation therapy (RT), and observation [54]. Survival rates for acoustic neurinomas were not found.

Included studies, efficacy and safety

For acoustic neurinoma, no study was included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie eingeschlossen

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for acoustic neuroma.

keine Evidenz

5.3.1.7 Other neurinomas

Due to the lack of precision of this indication, no further information (i.e., epidemiological data) on "other neurinomas" is presented in this section.

Included studies, efficacy and safety

For "other neurinomas", no study was included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie eingeschlossen

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for "other neurinomas".

keine Evidenz

5.3.1.8 Glomus tumour

Definition and epidemiology

Glomus tumours are rare tumours arising from the "glomus body": there are solitary and multiple glomus tumours [55]. Epidemiologic data on the incidence and prevalence of glomus tumours was not found for Austria.

Current treatment regimens and prognosis

Resection can be described as a treatment modality for solitary glomus tumours [55]. No information regarding the prognosis of glomus tumours was found.

Included studies, efficacy and safety

For glomus tumours, no study was included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie eingeschlossen

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for glomus tumours.

5.3.1.9 Retinoblastoma

Definition and epidemiology

Häufigkeit: 1,5 in 1 Mio Kinder/Jugendliche

Retinoblastoma are relatively rare paediatric tumour arising in the retina [56]. In Austria, the age-adjusted incidence rate of retinoblastomas was 1.5 cases per 1,000,000 children and adolescents (0-19 years old) between 2002 and 2012 [57].

Current treatment regimens and prognosis

Prognose alle Kindertumore 5 Jahre: 84,3 % Kinder 83,8 % Jugendliche

The current treatment modalities may include one, or more of the following: radiation therapy, local treatment (i.e., cryotherapy, laser therapy, brachytherapy), and chemotherapy [56]. Epidemiologic data on the survival specifically for this tumour was neither found for Austria nor in the Surveillance Epidemiology and End Results (SEER) database. According to recent data from Statistics Austria, the 5-year survival of all paediatric tumour patients is 84.3% for children (0-14 years old) and 83.8% for adolescents (15-19 years old) [58].

Included studies, efficacy and safety

keine Studie eingeschlossen

For retinoblastomas, no study was included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for retinoblastomas.

5.3.1.10 Lacrimal gland tumours

Definition and epidemiology

Lacrimal gland tumours are rare types of eye tumours [59]. Epidemiological data regarding the incidence and prevalence specifically for lacrimal gland tumours was not found.

Current treatment regimens and prognosis

The treatment of lacrimal gland tumours is dependent on the tumour type [59]. Epidemiological data regarding the survival specifically for lacrimal gland tumours was not found.

Included studies, efficacy and safety

keine Studie eingeschlossen

For lacrimal gland tumours, no study was eligible to be included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for lacrimal gland tumours.

5.3.1.11 Sarcomas incl. Ewing's sarcoma in the skull base

Definition and epidemiology

Sarcomas in the head and neck area are rare tumours and include, inter alia, osteosarcomas, rhabdomyosarcomas, chondrosarcomas, and soft tissue sarcomas. Within sarcomas in the head and neck region, Ewing's sarcomas are less commonly occurring [60]. Epidemiologic data regarding the incidence and prevalence specifically of sarcomas in the ENT area in Austria was not found.

Current treatment regimens and prognosis

Treatment modalities may depend on the histologic subtype of a tumour and include one, or a combination of the following treatments: surgery, adjuvant radiotherapy or adjuvant chemotherapy [60]. Epidemiologic data regarding the prognosis of sarcomas in the ENT area in Austria was not found.

Included study, efficacy and safety

For skull base sarcomas, no study was included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie eingeschlossen

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for sarcomas of the skull base (incl. Ewing's sarcoma).

keine Evidenz

5.3.1.12 Rhabdomyosarcomas of the skull base and orbit

Definition and epidemiology

Rhabdomyosarcomas are rare, malignant and considered to be paediatric tumours [61]. Approximately 25% of all rhabdomyosarcomas occur in the head and neck region [62]. Epidemiologic data regarding the incidence and prevalence specifically for rhabdomyosarcomas in the skull base area in Austria was not found.

Tumor bei Kindern

Current treatment regimens and prognosis

Treatment modalities may include one, or a combination of the following treatments: surgery, radiation therapy, chemotherapy [62]. Epidemiologic data regarding survival specifically for rhabdomyosarcomas in the skull base area in Austria was not found.

Included study, efficacy and safety

For rhabdomyosarcoma of the skull base and orbit, no study was included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie eingeschlossen

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for rhabdomyosarcoma of the skull base and orbit.

keine Evidenz

5.3.2 Eye tumours

In this section, one will find an evidence synthesis for choroid melanoma. Evidence synthesises for other tumours near the eye may be found in Section 5.3.1 Skull base tumours.

5.3.2.1 Choroid melanoma

Definition and epidemiology

seltener Tumor
5,1 in 1 Mio (USA)

Choroid melanoma is a rare cancer type to be found in the choroidea of the uvea (middle eye skin) [63]. A study [64] using data from the Surveillance, Epidemiology and End Results (SEER) database measured the mean age-adjusted incidence of uveal melanoma to be 5.1 per 1,000,000 (95% CI: 4.2-6.1) based on 7,516 patients with uveal melanomas in the United States (1973–2012).

Current treatment regimens and prognosis

Prognose:
5 Jahre: 79,8 %

According to the National Cancer Institute [63] (NCI), the management of uveal melanomas depends on the histology: small choroid melanomas are, for instance, poorly understood, leading to doubt whether treatment of this disease has a preventive effect of metastases. Radiation therapy may be used to treat larger choroid melanomas: brachytherapy is most commonly used to treat intraocular melanomas, but newer forms of RT using charged particles can also be described as another current treatment form. In the past, eye removal (enucleation) was the standard treatment for primary choroid melanoma [63]. A study [64] using data from the Surveillance, Epidemiology and End Results (SEER) database measured the mean overall 5-year relative survival rate to be 79.8% (±5.8) (1973–2012).

Included study, efficacy and safety

keine Studie
eingeschlossen

For choroid melanoma, no study was eligible to be included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for choroid melanoma.

5.3.3 Brain tumours

Definition and epidemiology

6 Indikationen im
Bereich „Hirntumore"

The evidence regarding efficacy and safety of CIRT was assessed for the following 6 brain tumours: WHO grade II gliomas, WHO grade III glioma, glioblastoma (WHO grade IV), ependymoma, medulloblastoma, and "other childhood brain tumours"[9].

Typically, brain tumours are classified using the WHO Classification of Central Nervous System (CNS) tumours [65]. Brain tumours can be *localised*, *regional*, *distant* and *unstaged (unknown)*: localised cancer refers to the stage

[9] In the MedAustron list of oncologic indications orbita tumours are categorized as brain tumours. However, it is summarized within the tumours in the ENT region.

when the cancer is only found in the part of the body in which the cancer started. Cancer is regional if the cancer already spread to (an)other part(s) of the body and distant if cancer has metastasised as well [66].

Häufigkeit:
9 in 100.000 in Ö
6,4 in 100.000 in USA

Data from Statistics Austria, including all tumours in the brain and central nervous system (CNS) in Austria, shows an age-adjusted incidence rate of 9.0 per 100,000 persons in 2015. In addition, those tumours were prevalent in 1,948 men and 2,043 women in the same year [67]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2010-2014) calculated that 6.4 per 100,000 persons developed cancer within the brain and another nervous system [66].

Current treatment regimens and prognosis

Prognose:
5Jahre:
33,9 % in Ö
33,6 % in den USA

Epidemiologic data from Statistics Austria regarding relative survival (RS) of all tumours in the brain and nervous system between 2003 and 2007 shows a 1-, 3-, 5- and 10-year RS of 59.8%, 39.1%, 33.9% and 28.7% in Austria respectively [67]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2007–2013) shows a 5-year relative survival of 33.6%. Moreover, the 5-year RS for localised, regional, distant and unstaged brain and nervous system tumours was 36.5%, 21.4%, 33.9% and 25.7% respectively [66].

Included studies

2 Studien, 62 Pts,
16,8-55,2 GyE

For brain tumours, 2 studies [68, 69] conducted at the Heavy Ion Medical Accelerator in Chiba (HIMAC) in Japan were included in this assessment: 1 case series study and 1 dose-escalation, case series study.

In total, 62 patients suffered from low grade and high grade gliomas: 14 patients suffered from WHO grade II glioma (diffuse astrocytomas), and the other 48 patients suffered from high-grade brain tumours, with 16 and 32 patients suffering from anaplastic astrocytoma (WHO grade III) and glioblastoma multiforme (WHO grade IV) respectively. 48 patients received carbon ion boost after x-ray radiotherapy and 14 received CIRT as the main therapy. The dose ranged from 16.8 to 55.2 GyE. Additional treatment – before, during, or after the irradiation – included, inter alia, surgery, x-ray radiotherapy, and salvage treatment (e.g., chemotherapy).

The reader is referred to the evidence synthesis for the specific indication and the data extraction table in the Appendix (Table A-3) for more information on the included studies and the efficacy and safety for CIRT for the specific indications.

Conclusion, efficacy & safety

keine Evidenz zu
3 Indikationen

Due to the heterogeneity of the different tumours (e.g., different prognosis) captured with the term brain tumours, the evidence synthesis for specific indications can be found in the respective sections.

unzureichende Evidenz zu Glioma (Grad 1) Glioma (Grad 2) & Glioblastoma; keine Schlussfolgerungen zu Überlegenheit/ Unterlegenheit bei Hirntumore möglich

2 studies on brain tumours were included in this assessment. None of the studies were controlled, comparing CIRT to standard irradiation. In adddition, no indirect comparisons were conducted by any of the included studies. 6 oncologic indications were assessed regarding superiority/inferiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity): insufficient scientific evidence was found for WHO grade II gliomas, WHO grade III gliomas, and glioblastomas (WHO grade

IV gliomas). No scientific evidence was found for the remaining 3 indications (ependymoma, medulloblastoma, and "other childhood brain tumours").

Thus, neither superiority nor inferiority on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, that (randomised) controlled trials are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients.

In the following section results from specific brain tumours are presented.

5.3.3.1 Low-grade glioma (WHO grade II brain tumours)

Definition and epidemiology

A glioma is a primary brain tumour arising within the parenchyma of the brain. The histologic features of gliomas are similar to the ones of normal glial cells, such as – inter alia – astrocytes or oligodendrocytes [65]. The stage of gliomas can be classified along the WHO Classification of Central Nervous System tumours [65]. In this context, histopathologic appearance as well as "well-established molecular parameters" will be decisive for tumour stage grading [65]: one can distinguish between low-grade glioma (WHO grade II) [70] or high-grade glioma (WHO grade III-IV) [71].

Häufigkeit alle Hirntumore: 9,0 in 100.000 in Ö 6,4 in 100.000 in USA

Epidemiologic data regarding the incidence and prevalence of low-grade glioma was not found. However, data from Statistics Austria including all tumours in the brain and central nervous system in Austria shows an age-adjusted incidence rate of 9.0 per 100,000 persons in 2015. Those tumours were prevalent in 1,948 men and 2,043 women in the same year [67]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2010-2014) calculated that 6.4 per 100,000 persons developed cancer within the brain and another nervous system [66].

Current treatment regimens and prognosis

Generally speaking, the aim of treating low-grade gliomas is to prolong survival while minimising morbidities. Surgery, radiotherapy (RT) as well as chemotherapy may be treatment modalities even though controversies are existent when it comes to both the role/timing of certain therapies (i.e. RT, chemotherapy) and the treatment approach of surgeries (i.e. aggressive treatment vs. delayed intervention if disease is at an early stage with limited symptoms) [72].

Prognose (Gliom): keine Daten Prognose (alle Hirn- und ZNS-Tumore): 5 Jahre OS: 33,9 % in Ö

Epidemiologic data on survival rates specifically for gliomas was not found in Austria. However, epidemiologic data regarding relative survival (RS) of all tumours in the brain and nervous system between 2003 and 2007 shows a 1-, 3-, 5- and 10-year RS of 59.8%, 39.1%, 33.9% and 28.7% in Austria respectively [67]. No data was found on the prognosis specifically for gliomas. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2007–2013) shows a 5-year relative survival of 33.6% for all brain and nervous system tumours [66].

Included studies

1 Studie, 14 Pts, 46-55,2 GyE

For low-grade gliomas (WHO grade II), 1 study [69] was eligible to be included in this assessment: a phase I/II dose-escalation study at the Heavy Ion Medical Accelerator in Chiba (HIMAC). In total, 14 patients with diffuse astrocytoma (WHO grade II) were enrolled in the included study and treated with CIRT at a total dose, ranging from 46.2-55.2 GyE in 24 fractions (6 weeks). The patients received surgery before, and salvage treatment consisted of chemotherapy (n=2), operation (n=6) and RT (n=1).

The median age was 32.5 years, and all patients were aged between 18 and 66 years in the included clinical trial. The patients were followed for 62 months (range: 10-152), and loss to follow-up was not reported in the included study. Study characteristics, i.e. information on patient population, intervention, control and study design of the included studies, can be found in the Appendix (Table A-3).

Efficacy

Overall survival (OS)

OS in 1 Studie

5 Jahre: 43 %
10 Jahre: 36 %

The included study [69] reported on the overall survival (OS) of CIRT patients with WHO grade II gliomas at 5 and 10 years. No comparison between the OS of CIRT patients and the OS of patients undergoing conventional therapy was undertaken.

1-year OS was not reported in the included study.

2-year OS was not reported in the included study.

3-year OS was not reported in the included study.

4-year OS was not reported in the included study.

5-year OS was reported in the included study [69], and an OS of 43% (95% CI: NR; SEM: 13%) for 14 patients with WHO grade II gliomas, undergoing CIRT was observed at 5 years.

10-year OS was reported in the included study [69] and an OS of 36% (95% CI: NR, SEM: 13%) for 14 patients with WHO grade II gliomas, undergoing CIRT was observed at 5 years.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

keine Daten:
CSS/DSS
DFS
RFS
LCR
HRQoL

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included study.

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included study.

Progression-free survival (PFS)

PFS in 1 Studie:
5 Jahre: 36 %

The included study [69] reported on the progression-free survival (PFS) of CIRT patients with WHO grade II gliomas at 5 years. No comparison between the PFS of CIRT patients and the PFS of patients undergoing conventional therapy was undertaken.

1-year PFS was not reported in the included study.

2-year PFS was not reported in the included study.

3-year PFS was not reported in the included study.

4-year PFS was not reported in the included study.

5-year PFS was reported in the included study [69]: the dose-escalation study observed a PFS of 36% (95% CI: NR; SE: 13%) for 14 patients with WHO grade II gliomas at 5 years (low-dose group: 11%; high-dose group: 80%).[10]

10-year PFS was not reported in the included study.

Local control rate (LCR)

LCR, HRQoL: keine Daten

The endpoint local control rate (LCR) was not measured by the included study.

Health-Related Quality of Life (HRQoL)

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included study.

Safety

Acute radiation morbidity

akute Strahlenbelastung in 1 Studie

The included study [69] measured acute radiation morbidities using the RTOG criteria. Several grade 0-1 acute radiation morbidities and 2 grade 2 acute radiation morbidities occurred.

Grad 0-1: 86 %

Grade 1 acute radiation morbidities were measured by the included study [69]. However, it was summed up with grade 0 acute radiation morbidities and, thus, the exact data regarding grade 1 acute radiation morbidities could not be retrieved from the study. Grade 0-1 acute radiation morbidities occurred in 12 out of 14 patients (86%).

Grad 2: 14 %

Grade 2 acute radiation morbidities were measured by the included study [69]: 2 out of 14 patients (14%) developed grade 2 acute radiation morbidities in this dose-escalation study including patients with WHO grade II diffuse astrocytomas.

Grad 3: 0 %

Grade 3 acute radiation morbidities were measured by the included study [69]: no grade 3 acute radiation morbidities were observed in the 14 patients with diffuse astrocytomas (WHO grade II) having undergone CIRT.

Grad 4: 0 %

Grade 4 acute radiation morbidities were measured by the included study [69]: no grade 4 acute radiation morbidities were observed in the 14 patients with diffuse astrocytomas (WHO grade II) having undergone CIRT.

Late radiation morbidity

späte Strahlenbelastung in 1 Studie

The included study measured late radiation morbidities using the RTOG/EORTC criteria. Several grade 1 radiation morbidities occurred in the skin and brain, and 2 patients developed grade 2 late radiation morbidities in the brain.

[10] In addition, the same study [69] measured the median progression-free survival time (m-PFS) and observe an m-PFS of 33 months (low dose: 18; high dose: 91).

Grade 1 late radiation morbidities were measured by the included study [69]: grade 1 late radiation morbidities were observed in the skin and brain region, with 1 (7%) and 8 (66.7%) out of 12 CIRT patients with diffuse astrocytomas (WHO grade II) developing those radiation morbidities in those regions respectively.

Grad 1:
Haut: 8,3 %
Hirn: 66,7 %

Grade 2 late radiation morbidities was measured by the included study [69]: grade 2 late radiation morbidities were observed in the brain region, with 2 out of 12 CIRT patients (16.7%).

Grad 2: 16,7 %

Grade 3 late radiation morbidities were measured by the included study [69]: no grade 3 late radiation morbidities were observed.

Grad 3: 0 %

Grade 4 late radiation morbidities were measured by the included study [69]: no grade 4 late radiation morbidities were observed.

Grad 4: 0 %

Conclusion

For low-grade gliomas (WHO grade II), 1 study was eligible to be included in the assessment: the study was not controlled, comparing CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with low-grade gliomas.

1 Studie ohne Vergleich, 14 Pts
keine Schlussfolgerungen zu Überlegenheit/ Unterlegenheit bei WHO Grad 1 Glioma

5.3.3.2 High-grade glioma (WHO grade III-IV)

Definition and epidemiology

In this assessment, high-grade gliomas consist of all WHO grade III-IV brain and nervous system tumours: both gliomas (WHO grade III) and glioblastomas (WHO grade IV) [71]. A glioma is a primary brain tumour arising within the parenchyma of the brain. The histologic features of gliomas are similar to the ones of normal glial cells, such as – inter alia – astrocytes or oligodendrocytes [65].

hochgradige WHO-Hirntumore umfasst:
Glioma (Grad 3)
Glioblastoma (Grad 4)

The stage of gliomas can be classified along the WHO Classification of Central Nervous System tumours [65]. In this context, histopathologic appearance as well as "well-established molecular parameters" will be decisive for tumour stage grading [65]. Epidemiologic data regarding the incidence and prevalence of gliomas was not found. However, data from Statistics Austria including all tumours in the brain and central nervous system shows an age-adjusted incidence rate of 9.0 per 100,000 persons in Austria in 2015. Moreover, those tumours were prevalent in 1,948 men and 2,043 women in the same year [67]. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2010–2014) calculated that 6.4 per 100,000 persons developed cancer within the brain and other nervous system [66].

Häufigkeit alle Hirntumore:
9,0 in 100.000 in Ö
6,4 in 100.000 in USA

In addition, the high-grade gliomas can be *localised*, *regional*, *distant* and *unstaged (unknown)*: localised cancer refers to the stage when the cancer is only found in the part of the body in which the cancer started. Cancer is regional if cancer already spread to another part of the body and distant if cancer has metastasised as well. Two-thirds of all brain and nervous system cancer (77.1%) are diagnosed when the cancer is localised [66].

Current treatment regimens and prognosis

Prognose alle Hirn-/CNS Tumore: 5 Jahre: 33,9 % in Ö 33,6 in USA

The treatment of high-grade gliomas may include – depending on the tumour-subtype – the following modalities: surgical resection, adjuvant RT, intensity-modulated RT (other non-established therapies: interstitial brachytherapy, heavy particle RT) [71, 73]. Epidemiologic data on survival rates specifically for gliomas was not found in Austria. However, epidemiologic data regarding relative survival (RS) of all tumours in the brain and nervous system between 2003 and 2007 shows a 1-, 3-, 5- and 10-year RS of 59.8%, 39.1%, 33.9% and 28.7% in Austria respectively [67].

No data regarding the prognosis specifically for high-grade gliomas was found. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) of the United States (2007–2013) shows a 5-year relative survival of 33.6% for all brain and nervous system tumours [66].

Included studies

1 Fallserie, 48 Pts, 16,8-24,8 GyE

For high-grade gliomas (WHO grade III-IV), 1 case series study [68] from the Heavy Ion Medical Accelerator in Chiba (HIMAC) was identified and eligible to be included in this assessment. In total, 48 patients were enrolled in the included study and were treated with a combined treatment of x-ray radiotherapy (50 GyE in 25 fractions), chemotherapy (ACNU) and carbon ion radiotherapy (CIRT: 16.8-24.8 GyE in 8 fractions over 2 weeks). Of the 48 patients, patients had either glioblastomas multiforme (GBM) or anaplastic astrocytomas (AA), with 32 patients (67%) and 16 patients (33%) with those tumours respectively. The median age was 53 years, and all patients were aged between 18 and 78 years at the start of the clinical trial. The length of, and loss to follow-up was not reported in the included study. Study characteristics, i.e., information on patient population, intervention, control and study design of the included study, can be found in the Appendix (Table A-3).

Efficacy

keine Daten zu: OS CSS/DSS DFS RFS PFS LCR HRQoL

Overall survival (OS)

The included study [68] did not measure the overall survival (OS) rate at different time points[11].

Cause-specific survival (CSS)/Disease-specific survival (DSS)

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included study [68].

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was not measured by the included study [68].

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included study [68].

[11] However, the median survival time (MST) was measured: AA patients and GBM patients had an MST of 35 and 17 months respectively.

Progression-free survival (PFS)

The included study [68] did not measure the progression-free survival (PFS) rate[12].

Local control rate (LCR)

The endpoint local control rate (LCR) was not measured by the included study [68].

Health-Related Quality of Life (HRQoL)

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included study [68].

Safety

Acute radiation morbidity

akute Strahlenbelastung in 1 Studie

The included study [68] measured acute radiation morbidities using the RTOG criteria. Radiation morbidities were observed in the skin (≤grade 2), the white blood cells (≤grade 4), the platelet (≤grade 4) and the brain (≤ grade 1).

Grad 1: WBC: 13 %
Hirn: 13 %
Platelet: 15 %
Haut: 56 %

Grade 1 acute radiation morbidities were reported by the included study [68]: the case series study (n=48) observed 27 (56%), 6 (13%), 7 (15%) and 6 (13%) acute radiation morbidities in the skin, white blood cells (WBC), platelet and brain region respectively.

Grad 2: WBC: 23 %
Platelet: 35 %
Haut: 19 %

Grade 2 acute radiation morbidities were reported by the included study [68]: the case series study observed 9 (19%), 11 (23%), 17 (35%) acute radiation morbidities in the skin, white blood cells and platelet region respectively. No grade 2 acute radiation morbidities were observed in the brain.

Grad 3: WBC: 35 %
Platelet: 13 %

Grade 3 acute radiation morbidities were reported by the included study [68]: the case series study observed 17 (35%) and 6 (13%) acute radiation morbidities in the white blood cells and platelet region respectively. No grade 3 acute radiation morbidities were observed in the skin or brain.

Grad 4: WBC: 6 %
Platelet: 6 %

Grade 4 acute radiation morbidities were reported by the included study [68]: the case series study observed 3 (6%) and 3 (6%) acute radiation morbidities in the white blood cells and platelet region respectively. No grade 4 acute radiation morbidities were observed in the skin or brain.

Late radiation morbidity

späte Strahlenbelastung in 1 Studie

The included study measured late radiation morbidities using the RTOG/EORTC criteria. Late radiation morbidities were observed in the brain and skin.

Grad 1: Haut: 2 %
Hirn: 15 %

Grade 1 late radiation morbidities were reported by the included study [68]: the case series study (n=48) observed 1 (2%) and 7 (15%) grade 1 radiation morbidities in the skin and brain respectively.

Grad 2: Hirn: 8 %

Grade 2 late radiation morbidities were reported by the included study [68]: the case series study observed 4 patients (8%), developing late radiation morbidities in the brain. In the skin region, no grade 2 late radiation morbidities were observed in the same study.

[12] However, the median progression-free survival (m-PFS) was measured in months by 1 study [68]: AA patients and GBM patients had an m-PFS of 18 and 7 months respectively.

Grad 3: 0 %

Grade 3 late radiation morbidities were reported by the included study [68]: the case series study observed no grade 3 late radiation morbidities.

Grad 4: 0 %

Grade 4 late radiation morbidities were reported by the included study [68]: the case series study observed no grade 4 late radiation morbidities.

Moreover, the same study reported on late radiation morbidities using the LENT-SOMA criteria in the brain: the late radiation morbidities were identical except for grade 1 late radiation morbidities. 10 patients (21%) had brain late radiation morbidities according to the LENT-SOMA criteria, with slightly more grade 1 late radiation morbidities in the brain compared to the frequency elaborated with the RTOG/EORTC criteria.

Conclusion

1 Studie, 48 Pts

ohne Vergleich unzureichende Evidenz zu WHO Grad III-IV Tumore

For high-grade gliomas (WHO grade III-IV), 1 study [68] was eligible to be included in the assessment: the study was not controlled, comparing CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with high-grade gliomas (WHO grade III-IV).

5.3.3.3 Ependymoma

Definition and epidemiology

Häufigkeit: 2,8 in 1 Mio Kinder/ Jugendliche

Ependymoma is a paediatric tumour to be found in the brain and spinal cord [74]. Between 2002 and 2012, 53 cases of ependymoma and plexus-chorideus tumours in the central nervous system occurred in children and adolescents, with an age-adjusted incidence rate of 2.8 per 1,000,000 children and adolescents (0-19 years of age) in Austria [57].

Current treatment regimens and prognosis

Prognose: 5 Jahre: 90,6 %

According to the National Cancer Institute (NCI) of the United States, there are currently 4 standard treatment options: surgery, radiation therapy (RT), chemotherapy and observation [74]. Statistics Austria calculated the 5-year relative survival of ependymoma and plexus-chorideus tumours of the nervous system to be 90.6% (95% CI: 73.7-96.9) for children aged between 0 and 14 years based on 32 patients diagnosed with this disease in Austria between 2002 and 2009.

Included studies, efficacy and safety

keine Studie inkludiert

For ependymomas, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for ependymoma.

5.3.3.4 Medulloblastoma

Definition and epidemiology

A medulloblastoma is a malignant embryonal tumour in the brain (WHO grade IV). The incidence of medulloblastomas is approximately 1–5:1,000,000 [75]. Statistics Austria measured the incidence of all intracranial and intraspinal embryonal tumours to be 7.3 cases per 1,000,000 children (aged 0-14 years) [57].

Häufigkeit: 7,3 in 1 Mio Kindern

Current treatment regimens and prognosis

Current treatment of medulloblastomas includes surgery (exstirpation) and postoperative chemotherapy and/or radiation therapy. In addition, radiotherapy using a boost concept or adjuvant chemotherapy may be used in some circumstances. Additional therapies treating the symptoms may also be indicated (e.g., glucocorticoide) [75]. The prognosis of medulloblastomas is dependent on the localisation [75]. Statistics Austria measured the 5-year relative survival of all intracranial and intraspinal embryonal tumours to be 70% (95% CI: 58.7-78.8) based on data of 80 cases in Austria (2002-2009) [58].

Prognose: 5 Jahre: 70 %

Included studies, efficacy and safety

For medulloblastomas, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for medulloblastomas.

keine Evidenz

5.3.3.5 Other childhood brain tumours

Besides medulloblastomas and ependymomas, pilocytic astrocytomas and other embryonal tumours may be considered as “other childhood brain tumours” [76]. Due to the lack of precision of this indication, no epidemiological data on “other childhood brain tumours” is presented in this section.

Included studies, efficacy and safety

For “other childhood brain tumours”, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for “other childhood brain tumours”.

keine Evidenz

5.3.4 Tumours in the ear-nose-throat (ENT)

Definition and epidemiology

HNO oder Kopf-Hals Tumore

Tumours in the ear-nose-throat (ENT) region cover a variety of different tumours. In this assessment, the term "ENT tumours" is used interchangeably with "head and neck" tumours. The National Cancer Institute (NCI) uses the term "head and neck" cancer, including tumours in the oral cavity, pharynx, larynx the salivary gland as well as the paranasal sinuses and the nasal cavity [77]. Statistics Austria uses the term "head and neck" cancers as well, covering tumours of the pharynx, the lips and the oral cavity [78].

For tumour staging of head and neck tumours, the TNM classification, developed by the American Joint Committee on Cancer (AJCC) as well as the Union for International Cancer Control (UICC), is used: T indicates more details about a tumour (i.e., the extent of a primary tumour). N (nodes) indicates the node, and M (metastasis) whether distant metastasis occurred [79].

Tumours in the ENT region can be *localised*, *regional*, *distant* and *unstaged (unknown)*: localised cancer refers to the stage when the cancer is only found in the part of the body in which cancer started. Cancer is regional if cancer already spread to (an)other part(s) of the body and distant if cancer has metastasised as well [66].

Häufigkeit: 15 in 100.000 in Ö

According to Statistics Austria, the age-adjusted incidence of all head and neck tumours was 15 per 100,000 persons in Austria in 2015. In the same year, those head and neck cancers accounted for approximately 3% of all new cancers, with 1,283 Austrians developing cancers in this region in this year. Overall, 5,489 male and 2,341 female Austrians had a diagnosis of malignant head and neck tumours at the end of 2015 [80, 81].

Current treatment regimens and prognosis

Prognose: 5 Jahre: 47,6 % 10 Jahre: 35,6 %

The treatment of head and neck tumours may include surgical resection and chemotherapy and/or (chemo)radiation therapy differing according to the extent and histology of a specific tumour [79, 82, 83]. A combination of chemotherapy and RT represents the most common radio-oncological treatment. Background information on treatment modalities for specific indications can be found in the sections for the specific indications. Data from Statistics Austria shows a 5- and 10-year relative survival for all head and neck tumour patients of 47.6% and 35.6% respectively [84]. The patients included in the analysis were diagnosed with head and neck tumours within the time frame between 2003 and 2007.

Included studies

5 Studien, 415 Pts, 18-72 GyE

For tumours in the ENT region, 5 studies were included in this assessment: 4 case series [31, 33, 85, 86] and 1 case-control study [87] from 3 cancer therapy centres in Germany and Japan. That is to say, 2 studies [33, 86] were conducted at the Heavy Ion Medical Accelerator in Chiba (HIMAC), 1 study [31] was conducted at the Gunma University Heavy Ion Medical Centre (GHMC) and 2 studies [85, 87] were conducted at the Heidelberg Ion Beam Therapy Centre (HIT) in Germany.

In total, 415 patients were enrolled in the included studies. Of those, 381 received CIRT at a total dose ranging from 18 GyE-72 GyE. 54 of the included patients received CIRT in a raster scanned carbon ion boost method, and co-interventions included intensity-modulated RT in 54 patients and photon ir-

radiation in 29 patients receiving CIRT. Moreover, photon radiotherapy, surgery (prior and after CIRT), salvage therapy (re-irradiation), and post-chemotherapy were reported as further co-interventions by some of the included studies.

Studien umfassen Patientenpopulationen mit unterschiedlichen HNO Sub-Indikationen

1 study [86] included 27 patients, with unresectable bone and soft tissue sarcomas in the head and neck. Of those, 11 were to be found in the nasal cavity and paranasal sinus. In addition, 2 other studies [85, 87] included 83 patients receiving CIRT and suffering from salivary gland tumours; of those, 54 were malignant [85], and 29 [87] were locally advanced tumours. Lastly, 2 further case series studies [31, 33] included 271 enrolled patients suffering from carcinomas of the head and neck in different regions. Of those, 134 patients (49.5%) were located in the nasal cavity and paranasal sinus.

Several of those patients had cancer in the maxillary sinus, naso-/oropharynx, adenoid cystic salivary gland carcinomas, and orbital tumours, with 11 patients (4.1%), 27 patients (9.9%), 21 patients (7.7%) and 20 patients (7.4%) suffering from tumours in those regions respectively. The evidence regarding those indications could not be synthesised.

The reader is referred to the evidence synthesis for the specific indication and the data extraction table in the Appendix (see Table A-4) for more information on the included studies.

Conclusion: Efficacy and safety

Due to the heterogeneity of the different tumours (e.g., different prognosis) captured with the term "tumours in the ENT region", the evidence synthesis for specific indications can be found in the following sections.

1 Fall-Kontrollstudie & 4 Fallserien inkludiert

indirekte Vergleiche in 1 Studie (CIRT+Photon vs. Photon): kein Unterschied

keine Evidenz zu 8 Indikationen

unzureichende Evidenz zu Sarkome im ENT Bereich

Tumore der Nasenhöhlen und Nasennebenhöhlen & adenoidzystischem Speicheldrüßenkrebs

For tumours in the ENT region, 5 studies were included in this assessment: the studies were not controlled, comparing CIRT to standard irradiation. 11 oncologic[13] indications were assessed regarding superiority/inferiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity): no scientific evidence was found for 8 indications, and insufficient scientific evidence for superiority/inferiority of CIRT was found for 3 indications (sarcomas in the head and neck, tumours in the nasal cavity and paranasal sinus and adenoid cystic salivary gland carcinomas). Indirect comparisons were conducted in 1 study [87] for 2 indications: for adenoid cystic carcinoma of the salivary gland, 1 study found no statistically significant difference of OS, DFS and LRC between 29 patients receiving CIRT in combination with photon radiotherapy when compared to 34 patients receiving photon radiotherapy alone.

Neither superiority nor inferiority on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with tumours in the ENT-region.

In the following section results from specific ENT tumours are presented.

[13] The indications "tonsil carcinomas" and "tongue base carcinoma" were summarized in oropharyngeal carcinomas and the oncologic indications "pleomorphic and adenoid cystic carcinomas" can be found in the section salivary gland carcinoma.

5.3.4.1 Orbital tumours

Definition and epidemiology

Häufigkeit: keine Daten

Tumours in the orbit are rare and occur either in the tissue of the orbit or form of a metastasised/secondary tumour from tumours in neighbouring organs. Tumours to be found in the orbit cover many different forms of cancer: tumours can be benign, e.g., chondroma, osteoma, or malignant, e.g., rhabdomyosarcoma, osteosarcoma, rhabdomyosarcoma [41] [59]. Epidemiologic data on the incidence and prevalence of tumours specifically for orbital tumours was not found.

Current treatment regimens and prognosis

The treatment of orbital tumours is dependent on the type of a tumour. No data on the prognosis specifically for orbital tumours were found.

Included studies, efficacy and safety

keine Studie inkludiert

No study was included for the qualitative synthesis of orbital tumours. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence that CIRT is superior/inferior when compared to standard irradiation.

5.3.4.2 Tumour of the nasal cavity and paranasal sinus

Definition and epidemiology

umfasst viele Tumore

Häufigkeit: keine Daten aus Ö 11,3 in 100.000 in den USA

Tumours of the nasal cavity and paranasal sinus are rarely occurring tumours and include a great variety of different histologies (e.g., squamous cell carcinoma, but also adenocarcinomas, adenoid cystic carcinomas, etc.) [82]. In paranasal sinus cancers, frequently occurring tumours are adenocarcinomas and squamous cell carcinoma, e.g., of the maxillary sinus [83]. Epidemiologic data on the incidence and prevalence of tumours specifically for the nasal cavity and paranasal sinus in Austria was not found. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) shows that 11.3 per 100,000 persons developed, oral cavity and pharynx in 2014 in the United States (age-adjusted incidence rate) [88].

Current treatment regimens and prognosis

Prognose: keine Daten

The treatment of tumours in the nasal cavity and paranasal sinus may include surgical resection and chemotherapy and/or (chemo)radiation therapy differing according to the extent and histology of a specific tumour [89]. A combination of chemotherapy and RT represents the most common radio-oncological treatment. No data was found for the prognosis specifically for tumours in the nasal cavity and paranasal sinus.

Included studies

3 Fallserien, 298 Pts, davon 145 mit Tumore der Nasenhöhle und Nasennebenhöhle 57,6-70,4 GyE

For tumours in the nasal cavity and paranasal sinus, 3 case series studies from 2 cancer therapy centres in Japan were eligible to be included in this assessment: 2 case series studies [33, 86] were conducted at the Heavy Ion Medical Accelerator in Chiba (HIMAC), and 1 case series study [31] was conducted at the Gunma Heavy Ion Medical Centre (GHMC).

In total, 298 patients with head and neck tumours were enrolled in the included studies. Of those, 145 patients suffered from tumours in the nasal cavity and paranasal sinus. The tumours were diverse and included a variety of different carcinomas and sarcomas. All patients received CIRT at a total dose ranging from 57.6 GyE to 70.4 GYE in 16 fractions in the included studies. Only 1 study [33] reported on co-interventions, including operation and/or chemoradiotherapy. 2 studies [31, 33] reported on tumour stage using the TNM classification: the tumour stage of the patients ranged between T2/N0 to T4 N0. 1 study [86] used the histopathological grading according to the Union Internationale Contre le Cancer (UICC, 2002), with a histopathological tumour grade ranging from grade 1 to grade 4.

Age ranges were reported either as mean (with a mean age of 46.2 years) or as median (ranging from 56.5 to 59 years) with 1 study [86] and 2 studies [31, 33] using those measures respectively. All patients were aged between 16 and 80 years. The loss to follow-up was not reported by the included studies. Study characteristics, i.e., information on patient population, intervention, and study design of the included study, can be found in the Appendix (Table A-4).

Efficacy

Overall survival (OS)

OS in 2 Studien:

3 Jahre: 74,1 %-88 %
5 Jahre: 47,6 %-57,6 %

The included studies measured overall survival (OS) at 3 and 5 years. No comparison between the OS of CIRT patients in comparison to the OS of patients undergoing conventional radiotherapy was undertaken.

1-year OS was not reported in the included studies.

2-year OS was not reported in the included studies.

3-year OS was reported by 2 studies [31, 86], with all of the enrolled patients receiving CIRT: 1 case series study [86] with 27 patients with unresectable bone and soft tissue sarcomas in the head and neck[14] observed a 3-year OS of 74.1% (95% CI: 57.5–90.6%). Another study [31] observed an OS of 88% (95% CI: 77–99%) for 35 non-squamous cell carcinomas of the head and neck[15] at 3 years. In the same study, the overall survival specifically for patients with tumours in the nasal cavity and paranasal sinus was calculated: patients with tumours in the maxillary sinus/nasal cavity (n=18) had a 3-year OS of 88% (95% CI: NR).

4-year OS was not reported in the included studies.

5-year OS was reported by 2 studies [33, 86]: the case series [33] (n=236)[16] reported an OS of 47.6% (95% CI: NR, SE: 3.2%) for patients with head and neck tumours[16] at 5 years. Another study [86] observed an OS of 57.6% at 5 years for 27 patients with unresectable bone and soft tissue sarcomas in the head and neck[14].

10-year OS was not reported in the included studies.

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[14] Of those 27 patients, 11 patients were diagnosed with tumours in the nasal cavity and paranasal sinus [86].

[15] Of those 35 enrolled patients, 18 were diagnosed with tumours in the nasal cavity and paranasal sinus [31].

[16] Of those 236 patients, 116 patients were diagnosed with tumours in the nasal cavity and paranasal sinus [33].

Cause-specific survival (CSS)/Disease-specific survival (DSS)

keine Daten:
CSS/DSS
DFS
RFS

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included study.

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was not measured by the included studies.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included studies.

Progression-free survival (PFS)

PFS in 1 Studie, 35 Pts
3 Jahre: 71 %

One out of 3 included studies [31] measured the endpoint progression-free survival (PFS) at 3 years after CIRT. No comparison between the PFS of CIRT patients in comparison to the PFS of patients undergoing conventional radiotherapy was undertaken.

1-year PFS was not reported in the included studies.

2-year PFS was not reported in the included studies.

3-year PFS was reported in 1 included case series study [31]: The 3-year PFS was 71% (95% CI: 56–86%) at 3 years for 35 non-squamous cell carcinomas of the head and neck. Of those, 18 patients (51.5%) suffered from tumours in the nasal cavity and paranasal sinuses. The same study did not report on the 3-year PFS specifically for patients with tumours of the nasal cavity and paranasal sinus.

4-year PFS was not reported in the included studies.

5-year PFS was reported in the included studies.

10-year PFS was not reported in the included studies.

Local control rate (LCR)

LCR in 2 Studien
3 Jahre: 91,8 %-93 %

LCR in 1 Studie:
5 Jahre: 68 %

All of the included studies measured the local control rate (LCR) of head and neck tumour patients, undergoing CIRT at different time points. No comparison between the LCR of CIRT patients and the LCR of patients undergoing conventional radiotherapy was undertaken.

1-year LCR was not reported in the included studies.

2-year LCR was not reported in the included studies.

3-year LCR was reported in 2 included studies [31, 86] treating all of the enrolled patients with CIRT: 1 case series study [86] with 27 patients with unresectable bone and soft tissue sarcomas in the head and neck[17] observed a LCR of 91.8% (95% CI: 81.0–100%) at 3 years. Another study [31] observed a LCR of 93% (95% CI: 84–100%) at 3 years. In the same study, the 3-year LCR specifically for patients with tumours in the nasal cavity and paranasal sinus was calculated: patients with tumours in the maxillary sinus/ nasal cavity (n=18) had a 3-year LCR of 93% (95% CI: NR).

[17] Of those 27 patients, 11 patients (40.7%) were diagnosed with tumours in the nasal cavity and paranasal sinus [86].

4-year LCR was not reported in the included studies.

5-year LCR was reported in 1 included study [33]: the case series study reported a LCR of 68% (95% CI: NR, SE: 3.5%) at 5 years.

10-year LCR was not reported in the included studies.

Health-Related Quality of Life (HRQoL)

Veränderung HRQoL zu baseline in 1 Studie: MCS: stat. signifikante mittelfristige und längerfristige Verbesserung um ca. 8 Punkte nach 24 Monaten

PCS: keine stat. signifikanten Unterschiede im Zeitverlauf

The endpoint Health-Related Quality of Life (HRQoL) was measured by 1 out of 3 included studies [31]. HRQoL was measured for 35 patients, undergoing CIRT and suffering from non-squamous cell carcinomas of the head and neck[15]. The study used the Short-Form Health Survey (SF-8) questionnaire: physical component score (PCS) and mental component score (MCS) mean scores were measured before, at 1 month, at 3 months, at 6 months, 12 months and 24 months, and compared to baseline scores respectively. The study found a gradual mid-term and longer-term improvement of the MCS mean score after treatment, with statistically significantly higher mean scores at 6 months (MCS: 45.9±1.7), at 12 months (MCS: 47.3±1.4) and 24 months (MCS: 48.4 ±1.6) when compared to the baseline score (MCS: 40.8 ±1.8)[18] [31]. No statistically significantly short-term (< 6 weeks), mid-term (> 6 weeks ≤ 6 months) or longer-term (> 6 months) differences regarding the PCS mean scores were found.

Safety

Acute radiation morbidity

akute Strahlenbelastung in 3 Studien

Acute radiation morbidity was measured by all of the 3 included studies using the RTOG [33] or CTCAE v4.0 [31] and NCI-CTC v2.0 [86] criteria: acute radiation morbidities occurred as mucositis, dermatitis, conjunctivitis and dysgeusia.

Grad 1:
Mukosa: 29,6-41 %
Haut: 49-70,4 %

Grade 1 acute radiation morbidities were measured by 2 of the included studies [33, 86]: 1 study [33] (n=236)[16] observed 91 (41%)[19] and 115 (49%) acute radiation morbidities occurring in the mucosa and the skin respectively. Another study [86] observed 8 (29.6%) and 19 (70.4%) out of 27 patients with head and neck tumours[17], developing grade 1 acute radiation morbidities in the mucosa and skin respectively.

Grad 2:
Mukosa: 36-63 %
Haut: 22,2-38 %

Grade 2 acute radiation morbidities were measured by all 3 included studies [31, 33, 86]: In the mucosa, grade 2 radiation morbidities ranged from 81 out of 223 patients[16] [33] (36%) to 17 out of 27 patients[14] [86] (63%). In the skin region, grade 2 acute radiation morbidities ranged from 6 out of 27 patients[14] [86] (22.2%) to 90 out of 236 patients[16] [33] (38%). Furthermore, 1 study [31] reported 5 (14%) and 1 (3%) out of 35 patients[15] developing grade 2 acute radiation morbidities such as conjunctivitis and dysgeusia respectively.

[18] The author interpreted this difference by stating that the patients possibly had fear and anxiety due to the treatment before the therapy being improved after the therapy. No analysis including fear or anxiety as variables in their analysis was undertaken [31].

[19] The total number of patients analysed for acute and late radiation morbidities for mucosas was 223, since normal mucosa of "(…) 13 cases was out of irradiation field" [33]. In addition, 116 out of 236 enrolled patients were diagnosed with tumours in the nasal cavity and paranasal sinus [33].

Grad 3:
Mukosa: 3,7-23 %
Haut: 0-6 %

Grade 3 acute radiation morbidities were measured by all 3 included studies [31, 33, 86]: in the mucosa, grade 3 acute radiation morbidities ranged from 1 out of 27 patients[14] [86] (3.7%) to 8 out of 35 patients[15] [31] (23%). In the skin region, 2 studies observed no grade 3 acute radiation morbidities [31, 86] and 1 study [33] observed 15 out of 236 patients (6%) developing grade 3 skin acute radiation morbidities. No other grade 3 acute radiation morbidities were observed.

Grad 4: 0 %

Grade 4 acute radiation morbidities were measured by all 3 included studies [31, 33, 86]: no grade 4 acute radiation was observed by the included studies.

Late radiation morbidity

späte Strahlenbelastung in 3 Studien

Late radiation morbidities were measured by all of the included studies using the RTOG/EORTC [33, 86] or CTCAE [31] criteria.

Grad 1 in 2 Studien:
Mukosa:
19-34,6 %
Haut: 23-43 %

Grade 1 late radiation morbidities were measured by 2 out of 3 included studies [33, 86]: 1 study [33] (n=236)[16] observed 43 (19%)[19] and 101 (43%) grade 1 late radiation morbidities occurring in the mucosa and the skin respectively. Another study [86] observed 9 cases (34.6%) and 6 cases (23%) in 26 patients[14] acute grade 1 late radiation morbidities the mucosa and skin respectively. In the same study, 5 (19.2%) and 1 (3.8%) out of 26 patients had grade 1 late radiation morbidities in the brain and bone respectively.

Grad 2:
Mukosa: 0-31 %
Haut: 0-3 %

Grade 2 late radiation morbidities were measured by all 3 included studies [31, 33, 86]: In the mucosa, 1 study [86] did not observe any grade 2 late radiation morbidities and the other 2 studies observed grade 2 mucositis in 4 out of 223 patients [33] (2%) and 11 out of 35 patients [31] (31%) respectively. In the skin area, 1 study [33] observed grade 2 late radiation morbidities, with 7 cases (3%) occurring in this area. Moreover, 1 study [86] observed late radiation morbidities (grade 2) in the brain, eye, and bone, with 1 case (3.8%), 1 case (3.8%) and 1 case (3.8%) in these regions respectively. In another study [31] (n=35), further grade 2 late radiation morbidities were observed: 1 patient (3%), 2 (6%) patients and 2 (6%) patients developed grade 2 conjunctivitis, dysgeusia and brain necrosis respectively. In the same study, grade 2 visual impairment, trismus, otitis media and olfactory nerve disorder occurred, with 2 (6%), 3 (9%), 5 (14%) and 4 (11%) patients suffering from those radiation morbidities respectively.

Grad 3:
Mukosa: 0-3 %
Haut: 0 %

Grade 3 late radiation morbidities were measured by the all of the 3 included studies [31, 33, 86]: In the mucosa, 1 out of 3 studies [31] observed 1 grade 3 late mucositis (3%). In the skin region, no grade 3 late radiation morbidities were observed in any of the included studies. Also, 4 grade 3 bone late acute radiation morbidities (15.4%) were observed in 1 study [86]. In another study [31], 1 case of visual impairment (3%) and 2 cases of grade 3 cataract (6%) occurred.

Grad 4: Auge: 0-6 %

Grade 4 late radiation morbidities were measured by all of the included studies: in the mucosa and skin area, no grade 4 late radiation morbidities occurred. 2 studies [31, 86] observed grade 4 late radiation morbidities in the eye, with 1 out of 26 patients (3.8%) [86] and 2 out of 35 patients (6%) [31] respectively.

Conclusion

For tumours in the nasal cavity and paranasal sinus, 3 studies were eligible to be included in the assessment: none of the studies were controlled, comparing CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with tumours of the nasal cavity and paranasal sinus.

3 Fallserien, ohne Vergleich

keine Schlussfolgerungen zu Überlegenheit/ Unterlegenheit möglich

5.3.4.3 Maxillary sinus carcinoma

The maxillary sinus carcinoma is a type of paranasal sinus cancer [89]. The reader is referred to section tumours of the nasal cavity and paranasal sinus for information on the epidemiology, prognosis and treatment approaches of this cancer.

Included studies, efficacy and safety

For maxillary sinus carcinoma, no study was eligible to be included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for maxillary sinus carcinoma.

keine Evidenz

5.3.4.4 Nasopharyngeal carcinoma

Definition and epidemiology

Nasopharyngeal carcinomas are carcinomas to be found in the nasopharynx originating behind the nasal cavity [90]. Epidemiologic data on the incidence and prevalence of tumours specifically for nasopharyngeal carcinomas in Austria was not found. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) shows that 11.3 per 100,000 persons developed cancer in the oral cavity and pharynx in 2014 in the United States (age-adjusted incidence rate) [88].

Häufigkeit alle Oropharynx: 11,3 in 100.000

Current treatment regimens and prognosis

The treatment of nasopharyngeal carcinomas may include (chemo)radiation therapy (R[C]T), e.g., intensity-modulated radiotherapy (IMRT), chemotherapy. A combination of chemotherapy and RT represents the most common radio-oncological treatment. Surgery may not be used as a first-line treatment due to the nasopharynx being closely located to the neurovascular structure [91]. Treatments of all head and neck tumours differ according to the extent and histology of a specific tumour [79, 82, 83].

No data was found for the prognosis specifically for nasopharyngeal carcinomas. Statistics Austria shows a 5- and 10-year relative survival for all head and neck tumour patients of 47.6% and 35.6% respectively [84]. The patients included in the analysis were diagnosed with head and neck tumours within the time frame between 2003 and 2007.

Prognose fü alle Kopf-Hals Tumore:

5 Jahre: 47,6 %
10 Jahre: 35,6 %

Included studies, efficacy and safety

keine Studie inkludiert

For nasopharyngeal carcinomas, no study was included for the qualitative synthesis of the evidence regarding efficacy or safety of the use of CIRT. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for nasopharyngeal carcinoma.

5.3.4.5 Oropharyngeal carcinoma

Definition and epidemiology

Häufigkeit alle Oropharynx: 11,3 in 100.000

Oropharyngeal carcinoma can be found in the following parts of the oropharynx: the bottom of the tongue, the vallecula, the tonsillar region, the soft palate and the pharyngeal walls (posterior and lateral) [92]. Epidemiologic data on the incidence and prevalence of tumours specifically for oropharyngeal carcinomas in Austria was not found. Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) shows that 11.3 per 100,000 persons in 2014 developed, oral cavity and pharynx cancer in the United States (age-adjusted incidence rate) [88].

Current treatment regimens and prognosis

Prognose fü alle Kopf-Hals Tumore:

5 Jahre: 47,6 %
10 Jahre: 35,6 %

Treatment of oropharyngeal carcinomas may include one, or more of the following modalities: surgery, (chemo)radiation therapy, chemotherapy (concurrent or neoadjuvant) [92]. A combination of chemotherapy and RT represents the most common radio-oncological treatment. No data was found for the prognosis specifically for oropharyngeal carcinomas. Data from Statistics Austria shows a 5- and 10-year relative survival for all head and neck tumour patients of 47.6% and 35.6% respectively [84]. The patients included in the analysis were diagnosed with head and neck tumours within the time frame between 2003 and 2007.

Included studies

keine Studie inkludiert

For oropharyngeal carcinoma, no study was eligible to be included in the qualitative synthesis of the evidence regarding efficacy or safety of the use of CIRT to treat cancer in the oropharyngeal region. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for oropharyngeal carcinoma.

5.3.4.6 Salivary gland carcinoma

Definition and epidemiology

Speicheldrüßenkrebs: pleomorph oder adenoidzystisch

Salivary gland tumours are rarely occurring heterogeneous group of histologies. Tumours in this region can be benign or malignant: Pleomorphic adenomas are the most common type of benign salivary gland tumours. The most common type of malignant salivary gland tumours is, inter alia, adenoid cystic carcinomas [93]. Epidemiologic data regarding the incidence and prevalence specifically of salivary gland tumours in Austria was not found.

Häufigkeit: 1,2 in 100.000

Data of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) shows an age-adjusted incidence rate for salivary gland tumours of 1.2 cases per 100,000 persons in 2014 in the United States [88].

Current treatment regimens and prognosis

Treatment of salivary gland tumours differs according to the stage and histology of cancer: benign, low-grade salivary gland tumours may be treated with surgery alone. On the contrary, a combined treatment of surgery and postoperative radiotherapy may be indicated for patients with high-grade salivary gland carcinomas [79].

Prognose: 5 Jahre: 75,1 %

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) estimates the 5-year relative survival (RS) to be 75.1% based on calculations of patients having been diagnosed with salivary gland carcinomas in 2009 in the United States [66].

Included studies

Pleomorphe Tumore: keine Studie inkludiert

For pleomorphic salivary gland tumours, no study was identified.

For adenoid cystic salivary gland tumours 2 clinical studies, conducted at the Heidelberg Ion Beam Therapy Centre (HIT) in Germany, were eligible to be included in the assessment: 1 case-control study [87] and 1 phase 2, dose-escalation, case series study [85].

Adenoidzystische Tumore:
2 Studien,
117 Pts,
56-58 Jahre
18-24 GyE (CIRT)

In total, 117 patients were enrolled in the clinical studies, with 83 and 34 patients receiving, inter alia, carbon ion radiotherapy (CIRT)[20] and photon radiotherapy alone respectively. The irradiation dose of photon radiotherapy in combination with CIRT was a median dose of 72 GyE (54 Gy with photons and 18 GyE with C-ions) in 9 fractions for 29 patients. Another 54 patients received a carbon ion boost (CIB) at a dose of 24 GyE in 5-6 fractions followed by intensity-modulated radiotherapy (IMRT) at a total dose of 50 Gy in 5 fractions. The median irradiation dose of photon therapy for the 34 patients receiving photon RT in the case-control study [87] was 66 Gy (range: 54.0-70.4 Gy). Co-interventions included prior surgery and re-irradiation as a salvage treatment for some patients.

All 117 patients were diagnosed with malignant salivary gland tumours, of which 110 (94%) were adenoid cystic carcinomas. Tumour stages ranged from T1-T4, 13 patients had a positive lymph node status, and 12 patients had metastases. The age of the patients (median) ranged from 56 to 58 years. All patients were aged between 25 and 76 years. The median follow-up time of the included studies ranged from 16 to 42 months, and loss to follow-up was

[20] CIRT alone or as a carbon ion boost (CIB) in a raster scanned technique.

not reported. Study characteristics, i.e., information on patient population, intervention, control and study design of the included studies, can be found in the data extraction table in the Appendix (Table A-4).

Efficacy

Overall survival (OS)

Both 2 included studies [85, 87] measured overall survival (OS) at different time points.

1-year OS was not reported in any of the included studies.

OS 2 Jahre (in 1 Fall-Kontrollstudie): 86,6 % (CIRT+Photonen) vs. 77,9 % (nur Photonen), Diff. n. s.

2-year OS was reported in 1 study [87]: the case-control study included 63 patients with locally advanced adenoid cystic carcinomas of the salivary gland. The study observed an OS of 86.6% at 2 years for 29 patients receiving a combination of photon therapy and CIRT and an OS of 77.9% at 2 years for 34 patients receiving photon therapy alone. The difference in survival between the treatment groups was not statistically significant.

OS 3 Jahre (in 1 Fallserie): 78,4 %

3-year OS was reported in 1 study [85]: the dose-escalation study included 54 patients with malignant salivary gland tumours receiving a CIB before intensity-modulated RT and observed an OS of 78.4% (95% CI: NR) at 3 years.

OS 4 Jahre (in 1 Fall-Kontrollstudie): 75,8 % (CIRT+Photonen) vs. 77,9 % (nur Photonen), Diff n. s.

4-year OS was reported in 1 study [87]: the case-control study included 63 patients with locally advanced adenoid cystic carcinomas of the salivary gland. The study observed an OS of 75.8% at 4 years for 29 patients receiving a combination of photon therapy and CIRT and an OS of 77.9% at 4 years for 34 patients receiving photon therapy alone. The difference in OS between the treatment groups was not statistically significant.

5-year OS was not reported in any of the included studies.

10-year OS was not reported in any of the included studies.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

keine Daten: CSS/DSS RFS HRQoL

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included studies.

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was measured by 1 included study [87].

1-year DFS was not reported in any of the included studies.

DFS in 1 Fall-Kontrollstudie 2 Jahre: 71,5 % (CIRT+Photon) vs. 69,2 % (nur Photon), Diff. n. s.

2-year DFS was reported in 1 study [87]: the case-control study included 63 patients with locally advanced adenoid cystic carcinomas of the salivary gland. The study observed a DFS of 71.5% at 2 years for 29 patients receiving a combination of photon therapy and CIRT and a DFS of 69.2% at 2 years for 34 patients receiving photon therapy. The difference in DFS between the treatment groups was not statistically significant.

3-year DFS was not reported in any of the included studies.

4-year DFS was reported in 1 study [87]: the case-control study included 63 4 Jahre: 53 % (CIRT+Photon) vs. 23,6 % (nur Photon), Diff. n. s.

patients with locally advanced adenoid cystic carcinomas of the salivary gland. The study observed a DFS of 53% at 4 years for 29 patients receiving a combination of photon therapy and CIRT and a DFS of 23.6% at 4 years for 34 patients receiving photon therapy alone. The difference in DFS between the treatment groups was not statistically significant.

5-year DFS was not reported in any of the included studies.

10-year DFS was not reported in any of the included studies.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included studies.

Progression-free survival (PFS)

The endpoint progression-free survival (PFS) was measured by 1 included study [85] at 3 years.

PFS in 1 Fallserie:
3 Jahre: 57,9 %

1-year PFS was not reported in any of the included studies.

2-year PFS was not reported in any of the included studies.

3-year PFS was reported in 1 study [85]: the dose-escalation study included 54 patients with malignant salivary gland tumours receiving CIB in a raster scanned technique before intensity-modulated RT and observed and observed a PFS of 57.9% (95% CI: NR) at 3 years.

4-year PFS was not reported in any of the included studies.

5-year PFS was not reported in any of the included studies.

10-year PFS was not reported in any of the included studies.

Local control rate (LCR)

1-year LCR was not reported in any of the included studies.

LCR in 2 Studien:

2-year LCR was reported in 2 studies [85, 87]: the case-control study [87] included 63 patients with locally advanced adenoid cystic carcinomas of the salivary gland and observed an loco-regional control (LRC) of 77.5% at 2 years for 29 patients receiving a combination of photon therapy and CIRT and an LRC of 72.2% at 2 years for 34 patients receiving photon therapy alone. The difference in LRC between the treatment groups was not statistically significant. Another study [85] included 54 patients with malignant salivary gland tumours, receiving CIB in a raster scanned technique before intensity-modulated RT, and observed an LCR of 84.3% (95% CI: NR) at 2 years.

2 Jahre:
1 Fall-Kontrollstudie:
77,5 % (CIRT+Photon)
vs. 72,2 % (nur Photon),
Diff. n. s.
1 Fallserie: 84,3 %

3-year LCR was reported in 1 study [85]: the dose-escalation study included 54 patients with malignant salivary gland tumours receiving CIB in a raster scanned technique before intensity-modulated RT and observed an LCR of 81.9% (95% CI: NR) at 3 years.

3 Jahre in 1 Fallserie:
81,9 %

4-year LCR was reported in 1 study [87]: the case-control study included 63 patients with locally advanced adenoid cystic carcinomas of the salivary gland and observed an LRC of 77.5% at 4 years for 29 patients receiving a combination of photon therapy and CIRT and an LRC of 24.6% at 4 years for 34 patients receiving photon therapy. The difference in LRC between the treatment groups was not statistically significant.

LCR (4J.) in
1 Fall-Kontrollstudie:
77,5 % (CIRT+Photon)
vs. 24,6 % (nur Photon),
Diff. n. s.

5-year LCR was not reported in any of the included studies.

10-year LCR was not reported in any of the included studies.

Health-Related Quality of Life (HRQoL)

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included studies.

keine Daten: HRQoL

Safety

Acute radiation morbidity

akute Strahlenbelastung in 2 Studien

Acute radiation morbidities were measured in both 2 included studies [85, 87] using the CTCAE version 3 respectively.

Grad 1: Mukosa: 28 % & NR; Haut: 75 % & NR

Grade 1 acute radiation morbidities were reported in 1 study [85]: 15 cases (28%) of grade 1 mucositis, 40 cases (75%) of grade 1 dermatitis, 18 cases (34%) of grade 1 dysphagia and 28 cases (53%) of grade 1 xerostomia were observed in 1 dose escalation study at completion of CIRT with 53 patients[21] with malignant salivary gland tumours receiving CIB in a raster scanned technique before intensity-modulated RT. In addition, the study reported on several other morbidities without mentioning the respective grades; further toxicities occurred 6-8 weeks after CIRT and can be found in the data extraction table (Table A-4).

Grad 2: Mukosa: 40 % & NR Haut: 15 % & NR

Grade 2 acute radiation morbidities were reported in 1 study [85]: 21 cases (40%) of grade 2 mucositis, 8 cases (15%) of grade 2 dermatitis, 10 cases (19%) of grade 2 dysphagia and 6 cases (11%) of grade 2 xerostomia were observed at completion of CIRT in 1 dose escalation study with 53 patients with malignant salivary gland tumours, receiving CIB in a raster scanned technique before intensity-modulated RT. In addition, further toxicities occurred 6-8 weeks after CIRT and can be found in the data extraction table (Table A-4).

Grad 3 in 2 Studien: 1 Fallserie: Mukosa:26 %; Haut:6 % 1 Fall-Kontrollstudie: Mukosa: 6,5 % (CIRT+Photon) vs. 32,3 % (nur Photon)

Grade 3 acute radiation morbidities were reported in both included studies [85, 87]: 1 dose-escalation study [85] with 53 patients with malignant Salivary gland tumours, receiving CIB in a raster scanned technique before intensity-modulated RT, observed 14 cases (26%) of grade 3 mucositis and 3 cases (6%) of grade 3 dermatitis after completion of CIRT. In the same study, further toxicities occurred 6-8 weeks after CIRT and can be found in the data extraction table (Table A-4). Another study [87] reported on differences of grade 3 radiation morbidities in the mucosa between 1 group (n=29), receiving combined therapy (photon and CIRT) and another group (n=34), receiving photon therapy alone, with 2 out of 29 patients (6.5%) and 11 out of 34 patients (32.3%) developing grade 3 mucositis in those groups respectively.

Grad 4: 0 %

Grade 4 acute radiation morbidities were not reported in any of the included studies.

viele andere Strahlenbelastungen in 1 Fallserie

However, the frequencies of acute radiation morbidities must be seen with caution, since both studies [85, 87] reported on several other acute radiation morbidities without mentioning the grade of those radiation morbidities. The reader is referred to the data extraction table to see those further radiation morbidities with unreported respective grades (see Table A-4 in the Appendix).

Late radiation morbidity

späte Strahlenbelastung

Late radiation morbidities were measured by both included studies using the CTCAE v.3.0 criteria, but a stringently applied standardised reporting of those toxicities was absent in both studies[22].

[21] 54 patients were initially enrolled in the study and 1 person refused a follow-up. The calculations of acute and late radiation morbidities are based on the 53 patients included in the analysis.

[22] That is, 1 study [85] reported on numerous late radiation morbidities without including the grade of many of those, and another study [87] only reported on grade 3 late radiation morbidities.

Grade 1 late radiation morbidities were reported in 1 dose-escalation, case series study [85]: the dose escalation study with 53 patients with malignant salivary gland tumours, receiving CIB in a raster scanned technique before intensity-modulated RT, observed 26 cases (49%) of grade 1 xerostomia and another 3 cases (6%) of grade 1 blood-brain barrier changes (CNS necrosis).

Grad 1 in 1 Fallserie:
CNS necrosis: 6 %
Xerostomia: 49 %

Grade 2 late radiation morbidities were reported in 1 study [85]: the dose escalation study with 53 patients with malignant salivary gland tumours, receiving CIB in a raster scanned technique before intensity-modulated RT, observed 3 cases (6%) of grade 2 dysphagia and 1 case (2%) of grade 2 xerostomia.

Grad 2 in 1 Fallserie:
Dysphagia: 6 %;
Xerostomia: 2 %

Grade 3 late radiation morbidities were reported in 1 case-control study [87]: 1 patient developed grade 3 late radiation morbidities (not specified). It was not stated whether the grade 3 late radiation morbidity occurred in patients receiving a combined radiation treatment using photons and C-ions (n=29), or if it occurred in patients receiving photon radiotherapy alone (n=34).

Grad 3 in
1 Fall-Kontrollstudie:
1/63 (1,6 %),
jedoch unklar
in welcher Gruppe

Grade 4 late radiation morbidities were reported in 1 study [85]: 1 dose escalation study with 53 patients[21] with malignant salivary gland tumours receiving CIB in a raster scanned technique before intensity-modulated RT observed 1 case of grade 4 haemorrhage (2%).

Grad 4 in 1 Fallserie: 2 %

However, the frequencies of late radiation morbidities must be seen with caution, since 1 study [87] selectively reported on late radiation morbidities (only severe grade 3 late radiation morbidities were reported) and another study [85] did not report on the grades for numerous observed late radiation morbidities. The reader is referred to the data extraction table to see those further radiation morbidities with respective unreported grades (Table A-4 in the Appendix).

unvollständige
Berichterstattung
in beiden Studien

Conclusion

For pleomorphic salivary gland tumours, no study was included. That is to say, at present, there is no scientific evidence supporting or refuting the use of CIRT for pleomorphic salivary gland tumours.

pleomorpher
Speicheldrüßenkrebs:
keine Evidenz

For adenoid cystic salivary gland tumours, 2 studies were eligible to be included in this assessment [85, 87]: none of the studies were controlled, comparing CIRT to standard irradiation. Indirect comparisons were undertaken in 1 study [87] and showed no statistically significant 3-year OS, DFS and LRC when comparing combined treatment (photon and CIRT) to photon radiotherapy alone. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as, standard irradiation in patients with salivary gland tumours.

Adenoidzystischer
Speicheldrüßentumor:
unzureichende Evidenz

5.3.4.7 Sarcoma in the ENT area including Ewing's sarcoma

Definition and epidemiology

seltener Tumor

Sarcomas in the head and neck region are rare tumours and include, inter alia, osteosarcomas, rhabdomyosarcomas, chondrosarcomas, and soft tissue sarcomas. Within sarcomas in the head and neck region, Ewing's sarcomas are less commonly occurring [60]. Epidemiologic data regarding the incidence and prevalence specifically of sarcomas in the ENT area in Austria was not found.

Current treatment regimens and prognosis

Prognose alle Kopf-Hals-Tumore:

5 Jahre: 47,6 %
10 Jahre: 35,6 %

Treatment modalities may depend on the histologic subtype of a tumour and include one, or a combination of the following treatments: surgery, adjuvant radiotherapy or adjuvant chemotherapy [60]. Epidemiologic data regarding the prognosis of sarcomas in the ENT area in Austria was not found. Data from Statistics Austria shows a 5- and 10-year relative survival for all head and neck tumour patients of 47.6% and 35.6% respectively [84]. The patients included in the analysis were diagnosed with head and neck tumours within the time frame between 2003 and 2007.

Included studies

1 Fallserie,
27 Pts,
46,2 Jahre
70,4 GyE

For sarcoma in the ENT area (including Ewing's sarcoma), 1 study was included in this assessment: 1 prospective case series study [86] conducted at the Heavy Ion Medical Accelerator in Chiba (HIMAC). In total, 27 patients with unresectable soft tissue sarcoma of the head and neck were enrolled in the included study. The enrolled patients received carbon ion radiotherapy (CIRT) at a total dose of 70.4 GyE in 16 fractions. Of the 27 patients, 16 were classified as low grade (grade 1-2), and 10 were classified as high-grade (grade 3-4) using the histopathological grading system of the Union Internationale Contre le Cancer (UICC-2002). Moreover, 1 patient's histopathological grade was unknown. The median age was 46.2 years, and all patients were aged between 17 and 78 years at the enrolment in the clinical trial. The median follow up was 37 months (range: 4.1-73.0), and loss to follow-up was not reported. Study characteristics, i.e., information on patient population, intervention, control and study design of the included studies, can be found in Table A-4 in the Appendix.

Efficacy

Overall survival (OS)

OS in 1 Studie, 27 Pts

Overall survival (OS) of patients undergoing carbon ion radiotherapy (CIRT) was measured by the included study [86] at different time points.

3 jahre: 74,1 %
5 Jahre: 57,6 %

1-year OS was not reported in the included study.

2-year OS was not reported in the included study.

3-year OS was reported in the included study [86]: the case series study, with 27 patients with bone and soft tissue sarcoma of the head and neck receiving CIRT, observed an OS of 74.1% (95% CI: 57.5–90.6) at 3 years.

4-year OS was not reported in the included study.

5-year OS was reported in the included study [86]: the case series study, with 27 patients with bone and soft tissue sarcoma of the head and neck receiving CIRT, observed an OS of 57.6% (95% CI: 33.7–81.4) at 5 years.

10-year OS was not reported in the included study.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included study.

keine Daten:
CSS/DSS
DFS
RFS
PFS
HRQoL

Disease-free survival (DFS)

The endpoint disease-free durvival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included study.

Progression-free survival (PFS)

The endpoint progression-fyree survival (PFS) was not measured by the included study.

Local control rate (LCR)

The local control rate was measured by the included study [86] at 3 and 5 years after CIRT.

LCR in 1 Studie, 27 Pts

1-year LCR was not reported in the included study.

3 Jahre: 91,8 %
5 Jahre: 80,4 %

2-year LCR was not reported in the included study.

3-year LCR was reported in the included study: the case series study [86], with 27 patients with bone and soft tissue sarcoma of the head and neck, receiving CIRT at a total dose of 70.4 GyE, observed an LCR of 91.8% (95% CI = 81.0–100%) at 3 years.

4-year LCR was not reported in the included study.

5-year LCR was reported in the included study [86]: the case series study with 27 patients with bone and soft tissue sarcoma of the head and neck receiving CIRT observed an LCR of 80.4% (95% CI = 57.3–100%) at 5 years.

10-year LCR was not reported in the included study.

Health-Related Quality of Life (HRQoL)

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included study.

keine Daten: HRQoL

Safety

Acute radiation morbidity

Acute radiation morbidities were measured by the included study [86] using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) v.2.0. The study reported on all grade 1-4 acute radiation morbidities for 27 patients with bone and soft tissue sarcoma of the head and neck receiving CIRT.

akute Strahlenbelastung in 1 Studie, 27 Pts

Grade 1 acute radiation morbidities were observed by the included study [86], with 8 out of 27 patients (29.6%) and 19 out of 27 patients (70.4%), developing grade 1 acute radiation morbidities in the mucosa and skin respectively.

Grad 1: Mukosa: 29,6 %;
Haut: 70,4 %

Grade 2 acute radiation morbidities were observed by the included study [86], with 17 out of 27 patients (63%) and 6 out of 27 patients (22.2%) developing grade 2 acute radiation morbidities in the mucosa and skin respectively.

Grad 2: Mukosa: 63 %:
Haut: 22.2 %

Grad 3: Mukosa: 3.7 %; Haut: 0 %

Grade 3 acute radiation morbidities were observed by the included study [86], with 1 out of 27 patients (3.7%) developing grade 3 acute radiation morbidity in the mucosa.

Grad 4: 0 %

Grade 4 acute radiation morbidities were not observed by the included study.

Late radiation morbidity

späte Strahlenbelastung, in 1 Studie, 27 Pts

Late radiation morbidities were measured by the included study [86] using the RTOG/EORTC criteria. The study reported on all grade 1-4 late radiation morbidities for 27 patients with bone and soft tissue sarcoma of the head and neck receiving CIRT.

Grad 1: Mukosa: 34,6 %; Haut: 23 %; Hirn: 19,2 % Knochen: 3,8 %

Grade 1 late radiation morbidities were observed by the included study [86]: 9 patients (34.6%), 6 patients (23%), and 5 patients (19.2%) developed grade 1 radiation morbidities in the mucous membrane, skin and brain respectively. Also, 1 patient (3.8%) developed grade 1 late bone radiation morbidity.

Grad 2: 3,8 % (jew. in Hirn, Auge & Knochen)

Grade 2 late radiation morbidities were observed by the included study [86], with 1 patient (3.8%) developing grade 2 radiation morbidities in the brain, eye and bone respectively.

Grad 3: 15,4 % (Knochen)

Grade 3 late radiation morbidities were observed by the included study [86], with 4 patients (15.4%) developing grade 3 late radiation morbidities in the bone region.

Grad 4: 3,8 % (Auge)

Grade 4 late radiation morbidities were observed in 1 patient (3.8%) in the eye region.

Conclusion

1 Studie ohne Vergleich, 27 Pts

unzureichende Evidenz

For sarcomas in the ENT area, 1 study was included in this assessment: the study was not controlled, comparing CIRT to standard irradiation. No indirect statistical comparison between CIRT and standard radiotherapy was undertaken. Neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with sarcomas in the ENT area.

5.3.4.8 Rhabdomyosarcoma

Definition and epidemiology

seltener Tumor

Rhabdomyosarcomas are rare, malignant, and considered to be paediatric tumours [61]. Approximately 25% of all rhabdomyosarcomas occur in the head and neck region [62]. Epidemiologic data regarding the incidence and prevalence specifically for rhabdomyosarcomas in the head and neck area in Austria was not found.

Current treatment regimens and prognosis

Treatment modalities may include one, or a combination of the following: surgery, radiation therapy, chemotherapy [62]. Epidemiologic data regarding the survival specifically for rhabdomyosarcomas in the skull base area in Austria was not found.

Included studies, efficacy and safety

keine Studie inkludiert

For rhabdomyosarcomas in the ENT area, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for rhabdomyosarcoma in the ENT area.

5.3.5 Lung cancer

5.3.5.1 Non-small cell lung carcinomas

Definition and epidemiology

NSCLC häufigste Form

The non-small cell lung carcinoma (NSCLC) is the most frequent form of lung cancer and includes adenocarcinomas, squamous cell carcinomas and large cell carcinomas. The size of the cells in a tumour to be found under a microscope is decisive whether a lung tumour is classified as a non-small or small cell lung cancer [35, 94].

Häufigkeit:
57,9 in 100.000 in Ö

In 2014, 2,894 men and 1,822 women developed lung cancer in Austria. As such, lung cancer is one of the most frequently occurring malignant tumours, being the second and third most frequent cancer disease among men and women respectively. In 2015, the age-adjusted incidence rate of lung and bronchus cancer was 57.9 per 100,000 persons [95]. In 2016, deaths caused by NSCLC and small-cell, tracheal and bronchus cancer accounted for 4.72% (95% CI: 4.44-5.02) of all deaths in Austria [96].

Lung and bronchus cancer can be *localised*, *regional*, *distant* and *unstaged (unknown)*: localised lung and bronchus cancer refers to the stage when the cancer is only found in the part of the body in which cancer started. Lung and bronchus cancer is regional if cancer already spread to another part (s) of the body and distant if cancer has metastasised as well [66].

Current treatment regimens and prognosis

The treatment of patients suffering from NSCLC differs according to the patient's tumour stage, overall medical condition and the molecular characteristics of a tumour. For NSCLC patients within stages I-III, curative treatments are typically used: surgeries, chemotherapy, radiation therapy (RT) – or a combination of those therapies – are current treatment modalities. In case NSCLC is advanced (i.e., if metastatic), systemic therapy is indicated [94].

Prognose:
5 Jahre: 18,1 %

According to the Statistics from the Surveillance, Epidemiology, and End Results (SEER), the 5-year survival of all lung and bronchus cancer patients was 18.1% (2007–2013) in the United States (US). However, variations among the stages of cancer can be seen: patients with localised or regional lung and bronchus cancer have a higher chance of surviving 5 years after the diagnosis in comparison to patients suffering from distant lung and bronchus cancer, or patients with an unknown lung and bronchus stage, with a 5-year survival of 55.6%, 28.9%, 4.5% and 7.5% respectively [66].

Included studies

6 Studien inkludiert:
2 Fall-Kontrollstudien
4 Fallserien
559 Pts,
74-76 Jahre
Dosis: 52,8 to 76 GyE

For non-small cell lung carcinomas (NSCLC), 6 clinical studies [97-102] from 2 cancer therapy centres in Japan were included in this assessment. 4 studies conducted at the Heavy Ion Medical Accelerator in Chiba (HIMAC) and 2 studies conducted at the Hyogo Ion Beam Medical Center (HIBMC): 2 case-control studies [99, 100], 2 dose-escalation/non-randomised, open-label, single-centre, case series studies [97, 98] and 2 case series focusing on toxicity and local control [101, 102].

In total, 559 patients were enrolled in the included studies, with 459 and 100 patients receiving carbon ion radiotherapy (CIRT) and proton radiotherapy (PRT) respectively. The irradiation dose for CIRT and PRT patients between all included studies ranged from 52.8 to 76 GyE in 1-20 fractions and 60-80 GyE in 10-26 fractions respectively. In addition, 7 patients received co-interventions: 5 and 2 patients were treated with neoadjuvant therapy and salvage chemotherapy respectively. Of the 559 patients, the majority had stage IA and stage IB NSCLC, with 236 (42%) and 238 (43%) patients respectively. The rest of the patients suffered from Stage IIA, Stage IIB and Stage IIIA NSCLC, with 40 (7%), 22 (4%), and 23 (4%) patients in those tumour groups respectively.

Age ranges were reported either as mean (ranging from 74.1 to 74.8 years) or median (ranging from 75 to 76 years), with 2 [101, 102] and 4 [97-100] studies using those measures respectively. All patients were aged between 46 and 92 years at the start of the enrolment in the clinical trials. The loss to follow-up was not adequately reported in any of the included studies. 2 of the included studies may have overlapping patient populations: it is assumed, but not clearly stated, that the sample in Takahashi et al. 2015 [98] (n=62) is also included in Yamamoto et al. 2017 [97] (n=218). Study characteristics, i.e., information on patient population, intervention, control and study design of the included studies, can be found in Table A-6.

Efficacy

Overall survival (OS)

OS in 6 Studien
1 Jahr: 77,2 %
(stage II Pts)
2 Jahre: 51,9 %
(stage II Pts)
3 Jahre: 61 %-90 %
(stage IA-IB)
4 Jahre: 53-67 %
(stage IB-IIA)
5 Jahre: 25-62 %
(stage IA-IB)

All 6 included studies measured overall survival (OS) of carbon ion radiotherapy (CIRT) patients at different time points [97-102]. 2 included studies compared the OS to the OS of patients undergoing proton radiotherapy (PRT) and found no statistically significant differences between the survival rates of those therapy groups.

1-year OS was reported in 1 study [98] with 62 stage II NSCLC patients undergoing CIRT (17 Stage IIA, 22 Stage IIB, 23 Stage IIIA) with a 1-year OS of 77.2% (95% CI: 66.7%-87.7%).

2-year OS was reported in the same study [98] with an OS of 51.9% (95% CI: 39.2%-64.5%) at 2 years.

keine signifikanten Unterschiede hinsichtlich 3 und 4 Jahres OS zwischen CIRT und PRT Pts

3-year OS was reported in 2 studies: 1 study ([100], 80 patients: 23 and 57 undergoing CIRT and PRT respectively) reported on a 3-year OS of 75% (95% CI: 64%-86%; IA: 74%, IB: 76%). In the same study, OS of the therapy groups was reported: the OS for 23 patients undergoing CIRT was 86.6% (95% CI: NR). The OS for 20 and 37 patients undergoing PRT at different doses was 90% (95% CI: NR) and 61% (95% CI: NR) at 3 years respectively. There were no statistically significant differences between the results of the 3 treatment protocols [100]. The other identified study [97] reported on a 3-year OS of 68.3% (95% CI: NR) for 218 NSCLC (123 stage IA, 95 stage IB) patients, undergoing CIRT [97].

4-year OS was reported in 1 study [99] with 70 patients undergoing CIRT or PRT with a survival of 58% (95% CI: 46%–70%; IB: 53%; IIA: 67%) at 4 years. In the same study, it was stated that there were no statistically significant differences between the respective rates of PRT and CIRT patients. However, no survival rates of the therapy groups were reported.

5-year OS was reported in 3 studies [97, 101, 102]: 2 studies with 79 NSCLC patients [102] (42 IA and 37 IB NSCLC patients) and 50 NSCLC patients [101] (29 IA and 21 IB NSCLC patients) observed OS rates of 45% (95% CI: NR; T1 IA: 62%, T2 IB: 25%) and 50.0% (95% CI: NR; IA 55.2, IB: 42.9) respectively. The patients involved in those studies received CIRT. Another study reported on a 5-year OS of 49.4% (95% CI: NR) of 218 NSCLC patients (123 stage IA, 95 stage IB) undergoing CIRT [97].

10-year OS was not reported in the included studies.

Cause-specific survival (CSS)

CSS in 4 Studien

2 Jahre: 71,7 % (stage II)
3 Jahre: 86 % (stage IA-IB)
5 Jahre: 42-87 % (stage: IA-IB)

Overall, 4 out of 6 included studies measured cause-specific survival (CSS) of CIRT patients at different time points [98, 100-102]. None of the included studies compared the CSS to the CSS of patients undergoing conventional radiotherapy

1-year CSS was not reported in any of the included studies.

2-year CSS was reported in 1 study [98] with 62 stage II NSCLC patients (17 Stage IIA, 22 Stage IIB and 23 Stage IIIA) undergoing CIRT and was 71.7% (95% CI: NR).

3-year CSS was reported in 1 study [100] with 80 NSCLC patients undergoing CIRT (n=23) or PRT (n=57) with a CSS of 86% (95% CI: 77%-95%; IA: 84%; IB: 88%) at 3 years. CSS of the specific therapy groups was not reported in the study.

4-year CSS was not reported in any of the included studies.

5-year CSS was reported in 2 studies [101, 102]: 1 study reported on a CSS of 68% (95% CI: NR) for 79 NSCLC patients [102] (42 IA and 37 IB NSCLC pts). In the same study, CSS according to tumour stage was 87% (95% CI: NR) for IA patients and 42% (95% CI: NR) for IB patients at 5 years. Another study [101] reported on the 5-year CSS of 50 NSCLC patients (29IA and 21 IB NSCLC patients receiving CIRT: The 5-year CSS for all patients was 75.7% (95 CI: NR) at 5 years. The CSS according to tumour stage was 89.4 (95% CI: NR) for IA patients and 55.1 (95% CI: NR) for IB patients at 5 years.

10-year CSS was not reported in the included studies.

Disease-free survival (DFS)

DFS in 2 Studien

2 Jahre: 35,7 %
3 Jahre: 46-67 % (stage: IA-IB)

The endpoint disease-free survival (DFS) was measured by 2 [98, 100] out of 6 included studies.

1-year DFS was not reported in any of the included studies.

2-year DFS was reported in 1 study [98] with 62 stage II NSCLC patients (17 Stage IIA, 22 Stage IIB and 23 Stage IIIA) undergoing CIRT and was 35.7% (95% CI: NR).

3-year DFS was reported in 1 study [100] with 80 NSCLC patients undergoing CIRT (n=23) or PRT (n=57): The study observed a DFS of 54% (95% CI: 43%-68%; IA: 67%; IB: 46%) at 3 years.

4-year DFS was not reported in any of the included studies.

5-year DFS was not reported in any of the included studies.

10-year DFS was not reported in the included studies.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by any of the included studies.

Progression-free survival (PFS)

PFS in 1 Fall-Kontrollstudie 4 Jahre: 43-52 % (stage: IB-IIA) Diff. zwischen CIRT und PRT: n. s.

1 out of 6 included studies measured progression-free survival (PFS) of CIRT patients [99]: the progression-free survival of CIRT and PRT patients (n=70) was 46% (95% CI: 33%–59%; IB: 43%; IIA: 52%) at 4 years. The authors of this study stated that there were no statistically significant differences between the respective rates of PRT and CIRT patients. However, the PFS according to the groups was not reported in the study [99].

Local control rate (LCR)

LCR in 6 Studien:

All 6 included studies measured the local control rate (LCR) of CIRT patients at different time points [97-102]: 1 study compared the LCR of CIRT patients to the LCR of patients undergoing PRT and found no statistically significant differences regarding local control rates between therapy groups.

1 Jahr: 96 % (stage II)

1-year LCR was reported in 1 study [98] with 62 stage II NSCLC patients undergoing CIRT (17 Stage IIA, 22 Stage IIB, 23 Stage IIIA) with a 1-year LCR of 96.0% (95% CI: 90.5%-100.0).

2 Jahre: 93 % (stage: II)

2-year LCR was reported in the same study [98] with an LCR of 93.1% (95% CI: 85.4%-100.0) at 2 years.

3 Jahre: 77,9-86 % (stage: IA-IB)

3-year LCR was reported in 2 studies: 1 study [100] (80 patients, stage IA-IB: 23 and 57 undergoing CIRT and PRT respectively) reported on a 3-year LCR of 82% (95% CI: 72%-92%). In the same study, the LCR for each therapy group was reported: the LCR for 23 patients undergoing CIRT was 86% (95% CI: NR). The LCR for 20 and 37 patients undergoing PRT at different doses was 83% (95% CI: NR) and 81% (95% CI: NR) at 3 years respectively. There were no statistically significant differences between the results of the 3 treatment protocols [100]. The other identified study [97] reported on a 3-year LCR of 77.9% (95% CI: NR) for 218 NSCLC (123 stage IA, 95 stage IB) patients.

Diff. zwischen PRT und CIRT hinsichtlich 3 und 4 Jahre LCR n. s.

4 Jahre: 70-84 % (stage: IB-IIA)

4-year LCR was reported in 1 study [99] with 70 NSCLC patients (47 stage IB patients, 23 stage IIA patients) undergoing CIRT or PRT with a local control rate of 75% (95% CI: 63%–86%; IB: 70%; IIA: 84%) at 4 years. In the same study, it was stated that there were no statistically significant differences between the respective rates of PRT and CIRT patients. However, no LCR of the specific therapy groups were reported [99].

5 Jahre: 72,7-94,7 % (stage IA-IB)

5-year LCR was reported in 3 studies [97, 101, 102]: 2 studies with 79 NSCLC patients [102] (42 IA and 37 IB NSCLC pts) and 50 NSCLC patients [101] (29 IA and 21 IB NSCLC pts) observed LCR rates of 90% (95% CI: NR; T1 IA: 97%, T2 IB: 80%) and 94.7% (95% CI: NR)[23] respectively. Another study reported on a 5-year LCR of 72.7% (95% CI: NR) of 218 NSCLC patients (123 stage IA, 95 stage IB) [97].

10-year LCR was not reported in the included studies.

[23] The tumour-stage specific LCR was not reported.

Health-Related Quality of Life (HRQoL)

The endpoint Health-Related Quality of Life (HRQoL) was not measured by any of the included studies.

HRQoL: keine Daten

Safety

All of the included studies measured radiation morbidities: common toxicities within CIRT were in the lung (i.e., radiation pneumonitis) and skin (i.e., dermatitis). 4 studies [97, 98, 101, 102] distinguished acute and late radiation morbidities, while 2 studies [99, 100] did not clearly report when the observed radiation morbidities occurred.

Acute radiation morbidity

Overall, 4 out of 6 studies elaborated on acute radiation morbidities using the CTCAE [98], NCI-CTC [97] or the RTOG [101, 102] criteria: no grade 4, and 1 grade 3 acute radiation morbidity in the lung region were observed in 1 study [98]. Several grade 1-2 acute radiation morbidities were observed in the lung and skin region [97, 98, 101, 102].

akute Strahlenbelastung: 4 Studien

Grade 1 acute radiation morbidity (lung and skin) was reported in 3 studies [97, 101, 102]: in the lung area, 2 studies reported on none (0%) and 1 (1.9%) case of grade 1 acute radiation morbidity in 79 NSCLC patients with 80 primary lesions [102] and 50 NSCLC patients with 51 primary lesions [101] respectively. In the skin area, radiation morbidities were observed in 2 studies, with grade 1 radiation morbidities occurring in 75 out of 80 primary NSCLC lesions (93.8%) [102] and 50 out of 51 primary NSCLC lesions (98%) [101] respectively. 1 study did not specify the regions in detail and reported on 212 out of 218 NSCLC patients (97.2%) developing grade 1 acute radiation morbidities [97].

Grad 1:
97,2 % in 1 Studie,
Lunge in 2 Studien:
0-1,9 %
Haut in 2 Studien:
93,8 %-98 %

Grade 2 acute radiation morbidity (lung and skin) was reported in 4 studies: in the lung area, acute radiation morbidities ranged from 1 in 79 lesions (1.3%) [102] to 1 in 51 primary lesions (1.9%) [101]. In the skin area, acute radiation morbidities ranged from 1 in 51 primary lesions (1.9%) [101] to 5 in 62 NSCLC patients (8%) [98]. 1 study did not specify the regions in detail and reported on 3 out of 218 NSCLC patients (1.3%) developing grade 2 acute radiation morbidities [97]

Grad 2:
1,3 % in 1 Studie,
Lunge in 3 Studien:
1,3-1,9 %
Haut in 3 Studien:
1,9-8 %

Grade 3 acute radiation morbidities were reported in 4 studies: 1 study [98] observed 1 in 62 patients (1.6%) developing grade 3 radiation pneumonitis (lung region). The other studies did not observe grade 3 acute radiation morbidities in their samples [97, 101, 102].

Grad 3: 0-1,6 %

Grade 4 acute radiation morbidities were reported in all 4 studies [97, 98, 101, 102]: none of those studies observed any grade 4 acute radiation morbidities.

Grad 4: 0 %

Late radiation morbidity

Overall, 4 out of 6 studies reported on late radiation morbidities using the RTOG/EORTC [97, 98, 101, 102] criteria. In addition, 2 studies did not report on whether the radiation morbidities occurred in the acute or late period and used the CTCAE criteria to assess radiation morbidities: 2 grade 3 radiation morbidities and several grade 2 radiation morbidities were observed in those studies [99, 100].

späte Strahlenbelastung: 6 Studien

Grad 1: 97,6 % in 1 Studie Lunge in 2 Studien: 90,8 %-94 % Haut in 2 Studien: 96 %-98,7 %

Grade 1 (late) radiation morbidity (lung and skin) was reported in 3 studies [97, 101, 102]: in the lung area, 2 studies observed radiation morbidities in 69 out of 76 primary lesions (90.8%) [102] and in 48 out of 51 primary NSCLC lesions (94%) [101] respectively. In the skin area, radiation morbidities were observed in 2 studies, with grade 1 radiation morbidities occurring in 76 out of 77 NSCLC primary lesions (98.7%) [102] and 49 out of 51 NSCLC primary lesions (96%) [101] respectively. 1 study did not specify the regions in detail and observed 207 out of 212 NSCLC patients (97.6%) developing grade 1 late radiation morbidities [97].

Grad 2: 0,5 % in 1 Studie, Lunge in 3 Studien: 1,3-4,8 % Haut in 3 Studien: 1,3-1,9 %

Grade 2 late radiation morbidity (lung and skin) was reported in 4 studies: in the lung area, late radiation morbidities ranged from 1 in 76 primary lesions (1.3%) [102] to 3 in 62 NSCLC patients (4.8%) [98]. In the skin area, late radiation morbidities ranged from 1 out of 77 primary lesions (1.3%) [102] to 1 out of 51 primary lesions (1.9%) [101]. 1 study did not specify the regions in detail and reported on 1 out of 212 NSCLC patients (0.5%) developing grade 2 late radiation morbidities [97].

2 Fall-Kontrollstudien unklar, ob SB akut oder spät waren; kein statistischer Vergleich

In addition, grade 2 radiation morbidity (lung and skin) was reported in 2 further studies that did not specify whether the morbidities occurred in the acute or late period: 1 study [100] observed 2 out of 23 CIRT patients (8.7%) and 7 out of 57 PRT patients (12.3%) developing grade 2 radiation pneumonitis. In the same study, 2 in 23 CIRT patients (8.7%) and 8 in 57 PRT patients (14%) suffered from grade 2 dermatitis. No statistical comparison regarding the difference was conducted. In the same study, 23% and 5% of all patients had a grade 2 rib fracture and grade 2 soft tissue radiation morbidities respectively. In another study [99], 10 out of 70 patients (14.3%) receiving CIRT (n=27) or PRT (n=43) developed grade 2 radiation pneumonitis and dermatitis respectively[24].

Grad 3 in 4 Studien: 0-1,9 %

Grade 3 late radiation morbidities were reported in all 4 studies: 1 study (n=50) observed 1 grade 3 radiation morbidity in 51 lesions in the skin region (1.9) [101] and 1 other study observed 1 out of 62 NSCLC patients (1.6%) developing a grade 3 radiation morbidity in the oesophagus [98].

2 Fall-Kontrollstudien unklar, ob SB akut oder spät waren; kein statistischer Vergleich

Additionally, grade 3 radiation morbidity (lung and skin) was reported in both 2 studies not specifying whether the morbidities occurred in the acute or late period: 1 study [100] observed no radiation pneumonitis or dermatitis (0%) in the CIRT sample (n=23). In the same study, grade 3 radiation pneumonitis and dermatitis were observed in PRT patients (n=57), with 1 (1.8%) and 3 (5.3%) patients with those radiation morbidities respectively. No statistical comparison regarding the difference was conducted. In another study [99], 2 (2.9%) and 4 (5.7%) grade 3 late radiation morbidities occurred in the lung and skin respectively.

Grad 4: 0 % in 4 Studien

Grade 4 late radiation morbidities were reported in all 4 studies: no grade 4 late radiation morbidities were observed in any of the included studies.

2 Fall-Kontrollstudien: 0-1,4 %, wobei unklar ob in PRT oder CIRT PatientInnen

In addition, grade 4 radiation morbidity (lung and skin) was reported in both 2 studies not specifying whether the morbidities occurred in the acute or late period: 1 study [100] observed no grade 4 radiation morbidity and another

[24] Radiation morbidities of the therapy groups were not reported in this study [99]. However, tumour stage specific radiation morbidities were reported and can be found in the data extraction-table in the Appendix (see Table A-6).

study [99] observed 1 grade 4 dermatitis in 70 patients (1.4%) having been irradiated with CIRT (n=27) or PRT (n=43)[25].

Conclusion

For non-small cell lung cancer (NSCLC), 6 studies were identified: none of the eligible studies were controlled, comparing CIRT to standard irradiation. Indirect comparisons of overall survival (OS) and local control rate (LCR) and progression-free survival (PFS) show equal results when comparing CIRT to PRT (no statistically significant differences) [99, 100]. Neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as and safer than or as safe as standard irradiation in NSCLC patients.

2 Fall-Kontrollstudien
4 Fallserien
559 Pts
unzureichende Evidenz

5.3.5.2 Mediastinal tumours (including thymoma)

Definition and epidemiology

Mediastinal tumours are rare tumours that develop from structures within, or while passing through the mediastinum and are a set of various different tumours being benign or malignant [103, 104].

seltener Tumor

Current treatment regimens and prognosis

The current treatment of mediastinal tumours is dependent on the size and type of a tumour: therapy options may include a surgical approach, chemotherapy or radiation therapy [104].

Included studies, efficacy and safety

For mediastinal tumours, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for mediastinal tumours (including thymoma).

keine Evidenz

5.3.5.3 Pleural mesothelioma

Definition and epidemiology

Mesothelioma is a rare cancer arising from mesothelial surfaces to be found, inter alia, in the pleural cavity [105].

seltener Tumor

Current treatment regimens and prognosis

The treatment approach of pleural mesotheliomas depends on the extent of the tumour as well as on the patient's condition and may include, among others, one, or a combination of the following: chemotherapy (standard approach

[25] It is not clearly stated whether the grade 4 dermatitis occurred in the CIRT or PRT sample.

for malignant pleural mesotheliomas), resection, and radiation therapy (RT). However, malignant pleural mesotheliomas have a poor diagnosis, without further improvements through new therapeutic interventions. The benefits of surgery and RT are currently not derived from randomised trials, but rather from observational studies [105].

Included studies, efficacy and safety

keine Studie inkludiert

No studies for pleural mesotheliomas were included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for pleural mesotheliomas.

5.3.6 Gastrointestinal tumours

6 Indikationen im Bereich Gastrointestinale Tumore

In this section, the body of evidence of the included studies focusing on efficacy and/or safety of carbon ion radiotherapy (CIRT) for tumours in the gastrointestinal (GI) region will be assessed. That is, the evidence of CIRT for the following 6 indications will be assessed.

Included studies

2 Fallserien, 215 Pts

Overall, 2 studies [106, 107] with 215 patients enrolled patients were included in this assessment: 184 and 31 patients suffered from rectal cancer and esophageal cancer respectively.

Conclusion: Efficacy and safety

keine Evidenz zu 4 Indikationen, unzureichende Evidenz zu Ösophagus Ca & Rektum Ca,

keine Schlussfolgerungen zu Überlegenheit/ Unterlegenheit möglich

Due to the heterogeneity of the different tumours (e.g., different prognosis) captured with the term gastrointestinal tumours, the reader is referred to the results from specific gastrointestinal tumours. For gastrointestinal tumours, there is insufficient scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety for thoracic oesophageal squamous cell carcinoma and rectal cancer without distant metastases when compared to conventional radiotherapy (evidence base: 1 prospective case series respectively). No scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety when compared to standard irradiation was found for pancreatic cancer, liver carcinoma, schwannomas/malignant schwannomas, and Ewing's sarcomas.

In the following section results from specific gastrointestinal tumours are presented.

In the following section results from specific gastrointestinal tumours are presented.

5.3.6.1 Oesophageal carcinoma

Definition and epidemiology

squamous cell carcinomas (SCC) or adenocarcinomas

Most of the oesophagal cancers are either squamous cell carcinomas (SCC) or adenocarcinomas, accounting for approximately 95% of all malignant tumours occurring in the oesophagal area [108]. The tumor, node, metastasis (TNM) classification, developed by the American Joint Committee on Cancer (AJCC) as well as the Union Internationale Contre le Cancer (UICC), is used for oesophagal carcinomas. However, oesophagal SCC and adenocarcinomas starts to be differentiated when it comes to stage grouping, due to growing evidence suggesting that those oesophagal cancer types may be 2 different diseases due to heterogeneous features of those tumour types, i.e., regarding pathogenesis, epidemiology and tumour biology [108].

Häufigkeit:
5 in 100.000 in Ö

In Austria, the occurrence of oesophagal cancer was rare in 2015, with 418 new cases, accounting for 1% of all newly diagnosed cancer cases, in the same year. The age-adjusted incidence rate was 5 cases per 100,000 persons in the same year. In 2015, oesophagal cancer was prevalent in 920 and 271 men and women respectively [109].

Current treatment regimens and prognosis

The treatment of oesophagal cancer differs according to the tumour stage and may include 1 or more of the following therapies: surgery, preoperative chemoradiation therapy, preoperative chemotherapy, definitive chemoradiation, postoperative radiation therapy [110].

Prognose:
1 Jahr: 46 %
3 Jahre: 23,7 %

Data from Statistics Austria based on 1,744 patients diagnosed with oesophagal carcinomas within the time period of 2003 and 2007 shows a relative survival of 46% and 23.7% at 1 and 3 years respectively. The relative 5- and 10 year survival was 18.4% and 14.3% respectively [111].

Included studies

1 Fallserie inkludiert
31 Pts
28.8-36.8 GyE

For oesophagal carcinomas, 1 dose-escalation, case series study from the Heavy Ion Medical Accelerator in Chiba (HIMAC) [106] was eligible to be included in the assessment. In total, 31 patients were enrolled in the included studies and underwent neoadjuvant carbon ion radiotherapy (CIRT) at a dose ranging from 28.8 GyE to 36.8 GyE in 8 fractions over 2 weeks. All patients received surgery after CIRT.

All of the 31 patients were diagnosed with thoracic oesophagal squamous cell carcinoma (ESCC). Of those, the tumour stage ranged from 1-3 (T1: 12 patients, T2: 8 patients, T3: 11 patients). In 9 patients, the tumour spread to nearby lymph nodes (N1: 8, N2: 1). The study reported that 10, 14 and 7 patients were stage 1, stage 2, and stage 3 patients respectively. The mean age of the included patients was 65.4 (SD: 7.1). The range of the patients was further reported. The loss to follow-up was not reported in the included study.

Study characteristics, i.e., information on patient population, intervention, control and study design of the included studies, can be found in the Appendix (Table A-5).

Efficacy

Overall survival (OS)

OS in 1 Studie, 31 Pts (stage 1-3)

The included dose-escalation study [106] measured overall survival (OS) at different time points.

1 Jahr: 71-91 %
3 Jahre: 43-85 %
5 Jahre: 29-77 %

1-year OS was reported in the included study [106]: The OS was 91% (95% CI: NR), 100% (95% CI: NR) and 71% (95% CI: NR) for stage 1 patients (n=10), stage 2 patients (n=14) and stage 3 patients (n=7) at 1 year after surgery respectively. Overall survival of all patients was not reported.

2-year OS was not reported in the included study.

3-year OS was reported in the included study [106]: The OS was 81% (95% CI: NR), 85% (95% CI: NR) and 43% (95% CI: NR) for stage 1 patients (n=10), stage 2 patients (n=14) and stage 3 patients (n=7) at 1 year after surgery respectively. Overall survival of all patients was not reported.

4-year OS was not reported in the included study.

5-year OS was reported in the included study [106]: The OS was 61% (95% CI: NR), 77% (95% CI: NR) and 29% (95% CI: NR) for stage 1 patients (n=10), stage 2 patients (n=14) and stage 3 patients (n=7) at 1 year after surgery respectively. Overall survival of all patients was not reported.

10-year OS was not reported in the included study.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

CSS/DSS in 1 Studie, 31 Pts (stage 1-3)

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was measured at different time points by the included study [106].

1 Jahr: 83-100 %
3 Jahre: 50-90 %
5 Jahre: 33-90 %

1-year CSS was reported in the included study and observed a CSS of 97% (95% CI: NR) at 1 year (stage 1: 100%; stage 2: 100%; stage 3: 83%) for 31 ESCC patients.

2-year CSS was not reported in the included study.

3-year CSS was reported in the included study and observed a CSS of 79% (95% CI: NR) at 3 years (stage 1: 90%; stage 2: 85%; stage 3: 50%) for 31 ESCC patients.

4-year CSS was not reported in the included study.

5-year CSS was reported in the included study and observed a CSS of 71% (95% CI: NR) at 5 years (stage 1: 90%; stage 2: 77%; stage 3: 33%) for 31 ESCC patients.

10-year CSS was not reported in the included study.

Disease-free survival (DFS)

DFS: keine Daten

The endpoint disease-free survival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

RFS: 1 Studie, 31 Pts (stage 1-3)

The endpoint recurrence-free survival (RFS) was measured at different time points by the included study [106].

1 Jahr: 51-100 %

1-year RFS was reported in the included study and observed an RFS of 87% (95% CI: NR) at 1 year after surgery (stage 1: 100%; stage 2: 92%; stage 3: 51%) for 31 ESCC patients.

2-year RFS was not reported in the included study.

3-year RFS was reported in the included study and observed an RFS of 62% (95% CI: NR) at 3 years after surgery (stage 1: 80%; stage 2: 69%; stage 3: 17%) for 31 ESCC patients.

3 Jahre: 17-80 %

4-year RFS was not reported in the included study.

5-year RFS was reported in the included study and observed an RFS of 62% (95% CI: NR) at 5 years after surgery (stage 1: 80%; stage 2: 69%; stage 3: 17%) for 31 ESCC patients.

5 Jahre: 17-80 %

10-year RFS was not reported in the included study.

Progression-free survival (PFS)

The endpoint progression-free survival (PFS) was not measured by the included study [106].

keine Daten:
PFS
HRQoL

Local control rate (LCR)

The endpoint local control rate (LCR) was not measured by the included study [106].

Health-Related Quality of Life (HRQoL)

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included study [106].

Safety

Acute radiation morbidity

Acute radiation morbidity was measured by the included study [106] using the CTCAE v.3.0 criteria. Acute radiation morbidities were observed in the oesophagus, skin, respiratory organs and blood.

akute Strahlenbelastung:
1 Studie

Grade 1 acute radiation morbidities were reported in the included study [106] (with 31 ESCC patients) and were observed in the following regions: 19 in the oesophagus (61.3%), 27 cases in the skin (87.1%), 4 cases in the blood (12.9%). No grade 1 acute radiation morbidity was observed in respiratory organs.

Grad1:
Ösophagus: 61,3 %;
Haut: 87,1 %;
Blut: 12,9 %

Grade 2 acute radiation morbidities were reported in the included study [106]: the study observed 12 cases (38.7%) and 2 cases (6.4%) of grade 2 acute radiation morbidity in the esophagus and blood respectively. No grade 2 acute radiation morbidity was observed in respiratory organs or skin.

Grad 2:
Ösophagus: 38,7 %;
Blut: 6,4 %

Grade 3 acute radiation morbidities were reported in the included study [106]: the study observed 1 case (3.2%) of grade 3 acute radiation morbidity in respiratory organs.

Grad 3: 3,2 %
Atmungsorgane: 3,2 %

Grade 4 acute radiation morbidities were reported in the included study [106]: no grade 4 acute radiation morbidities occurred in any region.

Grad 4:0 %

Late radiation morbidity

Late radiation morbidities were measured by the included study [106] using the CTCAE v.3.0, but not reported in the included study[26].

späte Strahlenbelastung:
keine Daten

[26] It was only stated that no toxicities occurred.

Conclusion

1 Studie, ohne Vergleich, 31 Pts unzureichende Evidenz

For oesophagal cancer, 1 case series study [106] was eligible to be included in the assessment: the study was not controlled, comparing CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with oesophagal cancer.

5.3.6.2 Pancreatic cancer

Definition and epidemiology

Häufigkeit: 21 in 100.000 in Ö

Pancreatic cancer is the third most frequent gastrointestinal tumour, occurring more likely in older people [112]. In 2015, 1,757 persons developed pancreatic cancers in Austria; leading to an age-adjusted incidence of 21 cases per 100,000 persons. At the end of the same year, 1,178 men and 1,240 women were alive and diagnosed with pancreas carcinomas [113].

Current treatment regimens and prognosis

Prognose: 5 Jahre: 7 % 10 Jahre: 5,5 %

The treatment of pancreatic cancer depends on the stage and localisation of a tumour and may include surgery, systemic chemotherapy, and adjuvant radio-chemotherapy [112]. Data from Statistics Austria based on 5,888 patients diagnosed with pancreas carcinomas within the time period of 2003 and 2007 shows a relative survival of 28% and 10.2% at 1 and 3 years respectively. The relative 5- and 10-year survival was 7% and 5.5% respectively [114].

Included studies

keine Studie inkludiert

No studies for pancreatic cancer were included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for pancreatic cancer.

5.3.6.3 Liver carcinoma

Definition and epidemiology

aggressiver Tumor Häufigkeit: 11,2 in 100.000

Liver carcinomas (hepatocellular carcinoma) are aggressive tumours, frequently occurring when chronic liver diseases are existent [115]. In Austria, 941 malignant liver cancers were diagnosed in 2015, accounting for 2% of the annual cancer diseases in this year. The age-adjusted incidence rate is 11.2 cases per 100,000 men and women developing liver cancer in 2015 respectively. At the end of the same year, liver cancer was prevalent in 1,227 and 483 men and women respectively [116].

Current treatment regimens and prognosis

Surgical resection may be described as the mainstay of current treatment modalities. However, patients are frequently not eligible for surgical resection due to the extent of the tumour. Alternatively, other treatment modalities include, among others, tumour ablation using nonsurgical methods (radiofrequency ablation, transarterial chemoembolisation, radiation therapy, percutaneous ethanol injection) and systemic therapy [115]. Data from Statistics Austria based on 3,843 patients diagnosed with liver cancer within the time period of 2003, and 2007 shows a relative survival of 33.2% and 17.0% at 1 and 3 years respectively. The relative 5- and 10-year survival was 12.2% and 7.5% for the same population [117].

Prognose:
5 Jahre: 12,2 %
10 Jahre: 7,5 %

Included studies, efficacy and safety

For liver carcinoma, none of the identified studies met the inclusion criteria for the qualitative synthesis. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

None of studies for liver carcinoma were eligible to be included in the assessment. Thus, no evidence was found indicating superiority or inferiority of CIRT for liver carcinomas.

keine Evidenz

5.3.6.4 Rectal carcinoma

Definition and epidemiology

Rectal carcinoma is a type of cancer in the lower gastrointestinal tract (rectum). Rectal cancer may not be easily distinguishable from colon cancer when epidemiological data is concerned. That is, most epidemiological studies do not separate those 2 diseases and use the term colorectal cancer for their analysis [118]. Epidemiologic data on the incidence and prevalence of colorectal cancer in Austria shows an age-adjusted incidence rate of 51.9 cases per 100,000 people in Austria. In the same year, colorectal cancer was diagnosed more often in men than in women, with 68 and 39.9 new cases per 100,000 people respectively [119].

Häufigkeit:
51,9 in 100.000

The tumor, node, metastasis (TNM) classification, developed by the American Joint Committee on Cancer (AJCC) as well as the Union Internationale Contre le Cancer (UICC), is usually used to stage rectal carcinomas [118]. Colorectal cancer can be *localised*, *regional*, *distant* and *unstaged (unknown)*: localised colorectal cancer refers to the stage when the cancer is only found in the part of the body in which cancer started. Colorectal cancer is regional if cancer already spread to another part of the body and distant if cancer has metastasised as well. In the United States, 39.2% of colorectal cancer patients are diagnosed when a tumour is in the local stage [66].

Current treatment regimens and prognosis

The standard treatment modalities of rectal cancer depend on the stage of a tumour and may include one, or more of the following: polypectomy or surgery, pre- or postoperative chemoradiation therapy [118]. Data from Statistics Austria based on 24,205 patients diagnosed with colorectal cancer within

Prognose:
5 Jahre 61 %
10 Jahre 55,6 %

the time period of 2003 and 2007 shows a relative survival of 79.8 and 67.2 at 1 and 3 years respectively. The relative 5- and 10-year relative survival was 61% and 55.6% for the same population [120].

According to the Statistics from the Surveillance, Epidemiology and End Results (SEER), the 5-year survival of all colorectal cancer patients was 64.9% (2007–2013) in the United States. However, variations among the stages of cancer can be seen: patients with localised or regional colorectal cancer have higher relative survival after the diagnosis in comparison to patients suffering from distant or unstaged colorectal cancer, with a 5-year relative survival of 89.9%, 71.3%, 13.9% and 35.4% respectively [66].

Included studies

1 Fallserie, 184 Pts mit rezidivierendem Rektumkarzinom

61,3 Jahre
67,2-73,6 GyE

For rectal cancer, 1 study [107] was identified and eligible for the qualitative synthesis: the study consisted of 1 dose-escalation (phase 1/2) and 1 non-randomised, single-arm study part (phase 2). In total, 184 patients with locally recurrent rectal cancer were included in the study and were treated with carbon ion radiotherapy (CIRT) at a dose ranging from 67.2 to 73.6 GyE in the dose escalation part (phase 1/2) of the study (n=38) and 70.4 to 73.6 GyE for the patients in the phase 2 part of the study (n=146).

Of the 184 patients, all patients had locally recurrent rectal cancer. Tumour stage using the TNM classification was not reported in the study. However, the average tumour size of the patients was 3.4 cm (SD: 1.4) and ranged from 1.0 to 14.0 cm. The median age of the patients enrolled in the included study was 61.3, and all patients were aged between 37 and 79 years. The median follow-up time was 42 months (range: 7-131). 4 patients were excluded from the analysis and the loss to follow-up was not further reported in the included study.

Study characteristics, i.e., information on patient population, intervention, control and study design of the included study, can be found in the Appendix (Table A-5).

Efficacy

Overall survival (OS)

OS in 1 Studie, 184 Pts

2 Jahre: 91 %
3 Jahre: 72 %
5 Jahre: 53 %

The endpoint overall survival (OS) was measured by the included study [107] at 3 and 5 years after carbon ion radiotherapy.

1-year OS was not reported in the included study.

2-year OS was not reported for all patients in the included study. However, the 2-year OS in phase 2 [107] for 139 patients was 91% (95 %CI: NR).

3-year OS was reported in the included study [107] with 184 enrolled patients: the study observed a 3-year OS of 72% (95 %CI: 66%-79%).

4-year OS was not reported in the included study.

5-year OS was reported in the included study [107] with 184 enrolled patients: the study observed a 5-year OS of 53% (95% CI: 45%-62%).

10-year OS was not reported in the included study.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included study.

keine Daten:
CSS/DSS
DFS
RFS
PFS

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included study.

Progression-free survival (PFS)

The endpoint progression-free survival (PFS) was not measured by the included study.

Local control rate (LCR)

The endpoint local control rate (LCR) was measured at 5 years for different dose groups by the included study.

LCR in 1 Studie, 184 Pts

5 Jahre: 35 %-88 %

1-year LCR was not reported in the included study.

2-year LCR was not reported in the included study.

3-year LCR was not reported in the included study.

4-year LCR was not reported in the included study.

5-year LCR was reported in the included study [107]: the study observed a dose-dependent 5-year LCR ranging from 35% (95% CI: 2-76) to 88% (95% CI: 80-93).

10-year LCR was not reported in the included study.

Health-Related Quality of Life (HRQoL)

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included study.

HRQoL: keine Daten

Safety

Acute radiation morbidity

Acute radiation morbidities were measured by the included study using the NCI-CTC criteria.

akute Strahlenbelastung

Grade 1 acute radiation morbidities were reported in the included study [107]: In the phase 2 part of the study (n=143), 112 (78.3%) skin radiation morbidities occurred. Within the dose-escalation part of the study (n=37), 20 cases (54%) of grade 1 acute skin radiation morbidities occurred. No grade 1 GI or urinary radiation morbidities occurred.

Grad 1:
78,3 % in Ph 2
54 % in Ph 1/2

Grade 2 acute radiation morbidities were reported in the included study [107]: In the phase 2 part of the study (n=143), 5 (3.5%) and 3 (2.1%) grade 2 acute radiation morbidities occurred in the skin and gastrointestinal (GI) region respectively. Within the dose-escalation part of the study (n=37), 2 (5.4%) and 1 (2.7%) grade 2 acute radiation morbidities occurred in the skin and GI tract respectively. No urinary grade 2 acute radiation morbidities occurred.

Grad 2:
Skin: 3,5 % in Ph 2,
5,4 % in Ph 1/2
GI: 2,1 % in Ph 2,
2,7 % in Ph 1/2

Grad 3: 0 %

Grade 3 acute radiation morbidities were reported in the included study [107]: no grade 3 acute radiation morbidities were observed in 180 patients.

Grad 4: 0 %

Grade 4 acute radiation morbidities were reported in the included study [107]: no grade 4 acute radiation morbidities were observed in 180 patients.

Late radiation morbidity

späte Strahlenbelastung: 1 Studie

Late radiation morbidities were measured by the included study using the RTOG/EORTC criteria.

Grad 1: Haut: 44,8 %; GI: 0,6 %; Urinaltrakt: 0,6 % in Ph 2 37,8 % für Ph.1/2 Pts

Grade 1 late radiation morbidities were reported in the included study [107]: In the phase 2 part of the study (n=143), 64 (44.8%), 1 (0.6%) and 1 (0.6%) case of grade 1 late radiation morbidities were observed in the skin, GI tract and urinary system respectively. Within the dose-escalation part of the study (n=37), 14 (37.8%) grade 1 late radiation morbidities were observed in the skin region and no GI or urinary grade 1 radiation morbidities occurred.

Grad 2: 0,6 % (jeweils in GI und Urinaltrakt) in Ph 2 2,7 % für Ph. 1/2

Grade 2 late radiation morbidities were reported in the included study [107]: In the phase 2 part of the study (n=143), 1 (0.6%) and 1 (0.6%) case of grade 2 late radiation morbidity occurred in the GI and urinary system respectively and no grade 2 radiation morbidity occurred in the skin. Within the dose-escalation part of the study (n=37), 1 (2.7%) and 1 (2.7%) case of grade 2 late radiation morbidity were observed in the skin and GI tract respectively.

Grad 3: Haut: 1,4 %; GI: 0,6 % in Ph 2 0 % in Phase 1/2

Grade 3 late radiation morbidities were reported in the included study [107]: In the phase 2 part of the study (n=143), 2 (1.4%) cases and 1 (0.6%) case of grade 3 late radiation morbidities were observed in the skin and GI tract respectively. Within the dose-escalation part of the study (n=37), no grade 3 late radiation morbidity was observed.

Grad 4: 0 %

Grade 4 late radiation morbidities were reported in the included study [107]: No grade 4 late radiation morbidities were observed in the included study.

Conclusion

1 Studie, ohne Vergleich

unzureichende Evidenz

For rectal carcinoma, 1 study [107] was included in the assessment: a dose-escalation, phase 2 case series study. The study was not controlled and did not compare CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled studies are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with rectal carcinomas.

5.3.6.5 Gastrointestinal schwannomas/malignant schwannomas

Definition and epidemiology

seltener Tumor

A gastrointestinal schwannoma is an utterly rare, mesenchymal tumour [121]. Epidemiologic data regarding the incidence and prevalence for gastrointestinal schwannomas was not found.

Current treatment regimens and prognosis

No information was found to answer current treatment and prognosis specifically for gastrointestinal schwannomas.

Included studies, efficacy and safety

For gastrointestinal schwannomas, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for gastrointestinal schwannomas.

keine Evidenz

5.3.6.6 Gastrointestinal Ewing's sarcoma

Definition and epidemiology

Ewing's sarcomas are rare cancers to be found in bones (e.g., legs, arms, feet, pelvis, skull) or soft tissues (e.g., abdominal cavity, arms, head and neck) [122]. No epidemiological data regarding the incidence and prevalence of gastrointestinal Ewing's sarcomas in Austria was found.

seltener Tumor

Current treatment regimens and prognosis

According to the National Cancer Institute (NCI) of the United States, there are 5 types of standard treatments currently used for Ewing's sarcomas: chemotherapy, radiation therapy (RT), surgery, targeted therapy and high-dose chemotherapy in combination with stem cell rescue [122]. No epidemiological data regarding survival rates of gastrointestinal Ewing's sarcomas in Austria was found.

Included studies, efficacy and safety

For gastrointestinal Ewing's sarcomas, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for gastrointestinal Ewing's sarcomas.

keine Evidenz

5.3.7 Bone and soft tissue tumours

Definition and epidemiology

In this section, the body of the evidence of the included studies focusing on efficacy and/or safety of carbon ion radiotherapy (CIRT) for bone and soft tissue sarcomas will be assessed. An evidence synthesis will be conducted for 5 specific indications. Available evidence for bone and soft tissue tumours in the skull base can be found in a previous section (Skull base tumours). The Surveillance, Epidemiology, and End Results Program (SEER) calculated the age-adjusted incidence of bone and joint cancers to be 0.9 cases per 100,000 persons per year (based on data in the time period of 2010 and 2014) [66].

5 Indikationen im Bereich Knochen- und Weichteiltumore

Häufigkeit: 0,9 in 100.000

Current treatment regimens and prognosis

Prognose: 5 Jahre: 67,7 %

Treatment modalities differ according to the tumour type. The specific treatment modalities for bone and soft tissue tumours can be found in the following sections. The Surveillance, Epidemiology, and End Results Program (SEER) calculated the 5-year survival of patients with bone and joint cancer to be 67.7% based on data from the SEER in the time period of 2007 and 2014 in the United States [66].

Included studies

1 Studie, 17 Pts mit Sarkomen in den Extremitäten

Overall, 1 study was included for bone and soft tissue tumours including 17 patients with localised primary sarcoma of the extremities (medically inoperable or declined surgery).

Conclusion: Efficacy and safety

keine Evidenz zu 4 Indikationen unzureichende Evidenz zu Weichteilsarkome

For bone and soft tissue tumours, insufficient scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety was found for soft tissue sarcoma (localised primary sarcoma of the extremities) when compared to conventional radiotherapy (evidence base: 1 prospective case series study). No scientific evidence indicating superiority/inferiority of CIRT regarding efficacy or safety when compared to standard irradiation was found for osteosarcoma, sacral chordoma, sacral chondrosarcoma and spinal meningioma.

In the following section results from specific bone and soft tissue tumours are presented.

5.3.7.1 Osteosarcoma

Definition and epidemiology

Häufigkeit alle Knochen- und Weichteiltumore: 0,9 in 100.000

Osteosarcomas are uncommonly occurring malignant tumours in the bone [123]. Epidemiologic data regarding the incidence and prevalence of osteosarcomas in Austria was not found. However, the Surveillance, Epidemiology, and End Results Program (SEER) calculated the age-adjusted incidence of bone and joint cancers to be 0.9 cases per 100,000 persons per year (based on data in the time period of 2010 and 2014) [66].

Current treatment regimens and prognosis

Prognose alle Knochen- und Weichteiltumore: 5 Jahre: 67,7 %

According to the National Cancer Institute (NCI) of the United States, there are 5 types of standard treatments for osteosarcomas: surgery, chemotherapy, radiation therapy and targeted therapy [123]. Epidemiologic data regarding survival rates of osteosarcomas in Austria was not found. However, the Surveillance, Epidemiology, and End Results Program (SEER) calculated the 5-year survival of patients with bone and joint cancer to be 67.7% based on data from the SEER in the time period of 2007 and 2014 in the United States [66].

Included studies, efficacy and safety

keine Studie inkludiert

For osteosarcoma, no study was included. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding efficacy or safety of the use of carbon ion radiotherapy (CIRT) for osteosarcoma.

5.3.7.2 Soft tissue sarcoma

Definition and epidemiology

seltener Tumor

Soft tissue sarcoma is a rare cancer and forms a heterogeneous group of tumours. That is, there are more than 100 distinct histopathologic subtypes of this cancer [124]. Soft tissue sarcomas could potentially occur anywhere in soft tissues of the body, but there are common regions for the occurrence of soft tissue sarcomas (e.g., head and neck, arms, and legs) [125]. Epidemiologic data regarding the incidence and prevalence of soft tissue sarcoma in Austria was not found.

keine Daten zur Häufigkeit

For tumour staging of nasopharyngeal carcinoma, the TNM classification, developed by the American Joint Committee on Cancer (AJCC) as well as the Union Internationale Contre le Cancer (UICC), is often used. However, different tier systems were developed to increase the prognostic value. A three-tiered system is also incorporated in the AJCC's TNM classification of soft tissue sarcomas and includes the following: well differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3) [124].

Current treatment regimens and prognosis

According to the National Cancer Institute (NCI) of the United States, the standard treatment of soft tissue sarcoma may include one, or a combination of the following: surgery, radiation therapy and chemotherapy [125]. Epidemiologic data regarding survival rates in Austria was not found.

Included studies

1 Fallserie, 17 Pts
53 Jahre

Dosis:
52,8-70,4 GyE

For soft tissue sarcoma, 1 case series study [126] from the Heavy Ion Medical Accelerator in Chiba (HIMAC) was eligible to be included in the qualitative synthesis. In total, 17 patients with localised primary sarcomas of the extremities, being either medically inoperable or surgery declined, were enrolled in the clinical study. Of those, the majority of the patients had soft tissue sarcomas, with 13 out of 17 (76.5%) suffering from this disease. The other patients had either osteosarcomas (n=3) or chondrosarcomas (n=1).

Patients were irradiated with CIRT at a total dose, ranging from 52.8-70.4 GyE. The median age of the patients in the included study was 53, and all patients were aged between 14 and 87 years. The median follow-up time was 37 months (range: 11-97) and loss to follow-up was not reported by the included study.

Study characteristics, i.e., information on patient population, intervention, control and study design of the included study, can be found in Table A-2.

Efficacy

Overall survival (OS)

OS in 1 Studie, 17 Pts

The included study measured the endpoint overall survival at 3 and 5 years.

1-year OS was not reported by the included study [126].

3 Jahre: 68 %
5 Jahre: 56 %

2-year OS was not reported by the included study [126].

3-year OS was reported by the included study [126] and observed a 3-year OS of 68% (95% CI: 42-86).

4-year OS was not reported by the included study [126].

5-year OS was reported by the included study [126] and observed a 5-year OS of 56% (95% CI: 29-80%).

10-year OS was not reported by the included study [126].

Cause-specific survival (CSS)/Disease-specific survival (DSS)

keine Daten: CSS/DSS

The endpoint cause-specific survival (CSS)/disease-specific survival (DSS) was not measured by the included study.

DFS
RFS
PFS
HRQoL

Disease-free survival (DFS)

The endpoint disease-free survival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

The endpoint recurrence-free survival (RFS) was not measured by the included study [126].

Progression-free survival (PFS)

The endpoint progression-free survival (PFS) was not measured by the included study [126].

Local control rate (LCR)

LCR in 1 Studie, 17 Pts

Local control rate (LCR) was measured at 3 and 5 years by the included study [126].

3 Jahre: 76 %
5 Jahre: 76 %

1-year LCR was not reported by the included study [126].

2-year LCR was not reported by the included study [126].

3-year LCR was reported by the included study [126] and observed a 3-year LCR of 76% (95% CI: 51-93).

4-year LCR was not reported by the included study [126].

5-year LCR was reported by the included study [126] and observed a 3-year LCR of 76% (95% CI: 51-93).

10-year LCR was not reported by the included study [126].

Health-Related Quality of Life (HRQoL)

keine Daten: HRQoL

The endpoint Health-Related Quality of Life (HRQoL) was not measured by the included study [126].

Safety

Acute radiation morbidity

akute Strahlenbelastung, 1 Studie, 17 Pts

The included study measured acute radiation morbidity with the CTCAE v.3.0 criteria.

Grad 1: 94,1 %

Grade 1 acute radiation morbidities were measured by the included study [126]: 16 out of 17 (94.1%) developed grade 1 acute radiation morbidities.

Grad 2: 0 %

Grade 2 acute radiation morbidities were measured by the included study [126]: no grade 2 acute radiation morbidities were observed.

Grad 3: 0 %

Grade 3 acute radiation morbidities were measured by the included study [126]: no grade 3 acute radiation morbidities were observed.

Grad 4: 0 %

Grade 4 acute radiation morbidities were measured by the included study [126]: no grade 3 acute radiation morbidities were observed.

Late radiation morbidity

The included study [126] measured late radiation morbidities using the CTCAE v.3.0 criteria.

späte Strahlenbelastung, 1 Studie, 17 Pts

Grade 1 late radiation morbidities were not reported in the included study.

Grad 1: NR

Grade 2 late radiation morbidities were reported by the included study [126]: 1 out of 17 patients (5.9%) developed grade 2 skin toxicities, and 4 patients (23.5%) developed grade 2 neurological toxicities.

Grad 2:skin: 5,9 neurological toxicities: 23,5 %

Grade 3 late radiation morbidities were reported by the included study [126]: 1 out of 17 patients (5.9%) developed a grade 3 femoral fracture.

Grad 3: 5,9 %

Grade 4 late radiation morbidities were not reported by the included study.

Grad 4: NR

In addition, the same study [126] reported on 3 and 1 patient, developing a lower limb tumour and an upper limb tumour respectively.

zusätzliche Tumore entwickelten sich in 4 PatientInnen

Conclusion

For soft tissue sarcomas, 1 study was eligible to be included in the assessment: the study was not controlled, comparing CIRT to standard irradiation. Thus, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, (randomised) controlled trials are needed to clarify whether CIRT is more effective than or as effective as, or safer than or as safe as standard irradiation in patients with soft tissue sarcomas.

1 Studie ohne Vergleich, 17 Pts

unzureichende Evidenz

5.3.7.3 Sacral chordoma

Definition and epidemiology

Chordomas are rare types of bone tumours to be found in the skull base or in the lower spine [127, 128]. Epidemiologic data on the incidence and prevalence of sacral chordomas in Austria was not found. However, the Surveillance, Epidemiology, and End Results Program (SEER) calculated the age-adjusted incidence of bone and joint cancers to be 0.9 cases per 100,000 persons per year (based on data in the time period of 2010 and 2014) [66]

seltener Tumor

Current treatment regimens and prognosis

For chordomas in the spinal cord, surgery and postoperative radiation therapy (RT) may be used [129]. Epidemiologic data on the survival of sacral chordomas in Austria was not found. However, the Surveillance, Epidemiology, and End Results Program (SEER) calculated the 5-year survival of patients with bone and joint cancer to be 67.7% based on data from the SEER in the time period of 2007 and 2014 in the United States [66].

Included studies, efficacy and safety

For sacral chordomas, none of the identified studies met the inclusion criteria for the qualitative synthesis.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for sacral chordomas.

keine Evidenz

5.3.7.4 Sacral chondrosarcoma

Definition and epidemiology

seltener Tumor

Chondrosarcomas are malignant tumours of the cartilage. Most of the chondrosarcomas occur in the pelvis and relatively infrequent in the sacrum, with approximately 5% of chondrosarcomas occurring in the spine [127, 129]. Epidemiologic data on the incidence and prevalence of sacral chondrosarcomas was not found. However, the Surveillance, Epidemiology, and End Results Program (SEER) calculated the age-adjusted incidence of bone and joint cancers to be 0.9 cases per 100,000 persons per year (based on data in the time period of 2010 and 2014) [66].

Current treatment regimens and prognosis

Treatment of chondrosarcomas depends on the stage of the disease and consists of surgery. In addition, radiation therapy is only indicated in some circumstances (i.e., after incomplete resection) since chondrosarcomas are relatively radioresistant. Chemotherapy is not used for the treatment of chondrosarcomas [130]. Epidemiologic data on the survival of sacral chondrosarcoma in Austria was not found. However, the Surveillance, Epidemiology, and End Results Program (SEER) calculated the 5-year survival of patients with bone and joint cancer to be 67.7% based on data from the SEER in the time period of 2007 and 2014 in the United States [66].

Included studies, efficacy and safety

keine Studie inkludiert

For chondrosarcomas, none of the identified studies were eligible to be included in the qualitative synthesis: No evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for the treatment of sacral chondrosarcoma.

5.3.7.5 Spinal meningiomas

Definition and epidemiology

Häufigkeit CNS Tumore:
9 in 100.000

Spinal meningiomas are invasive lesions commonly occurring in the thoracic spine. [129]. No epidemiologic data regarding the incidence and prevalence of spinal meningiomas in Austria was found. However, data from Statistics Austria including all tumours in the brain and central nervous system in Austria shows an age-adjusted incidence rate of 9.0 per 100,000 persons in 2015. In addition, those tumours were prevalent in 1,948 men and 2,043 women in the same year [67].

Current treatment regimens and prognosis

Prognose:
5 Jahre: 33,9 %
10 Jahre; 28,7 %

The current treatment modality of spinal meningiomas is typically complete resection. Symptomatic recurrence may be treated by using surgery, radiation therapy (RT) or radiosurgery [129]. No epidemiological data regarding the prognosis of spinal meningiomas in Austria was found. However, epidemiologic data regarding relative survival (RS) of all tumours in the brain and nervous system between 2003 and 2007 shows a 1-, 3-, 5-and 10-year RS of 59.8%, 39.1%, 33.9% and 28.7% in Austria respectively [67].

Included studies, efficacy and safety

keine Studie inkludiert

For spinal meningioma, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for spinal meningioma.

5.3.8 Prostate cancer

Definition and epidemiology

Häufigkeit 64 in 100.000 Männern in Ö

Prostate cancer occurs in a gland in tissues of the male reproductive system to be found between the rectum and bladder [66]. In Austria, prostate cancer is the most frequent cancer occurring in men: 4,532 men developed, and 1,116 died due to, prostate cancer in 2012. After age-standardisation, the incidence of prostate cancer was 64 in 100,000 men developing prostate cancer in 2012, and the respective mortality rate was 14 in 100,000 men in the same year [95].

Prostate cancer can be *localised*, *regional*, *distant* and *unstaged (unknown)*: localised prostate cancer refers to the stage when the cancer is only found in the part of the body in which cancer started. Prostate cancer is regional if the prostate cancer already spread to another part(s) of the body and distant if cancer has metastasised as well. The majority of prostate cancer patients (79.2%) are diagnosed when the cancer is still localised [66].

Stages: 1-4 (PSA, GS)

In addition, prostate cancer may be defined according to tumour stages: stage 1 refers to the localised prostate cancer, and stage 2-4 differs according to the prostate-specific antigen (PSA) level and the Gleason score, as well as to the extent of a tumour spreading out to other body parts (for a more precise description, see [131]).

Current treatment regimens and prognosis

viele Therapieoptionen

According to the National Cancer Institute (NCI) of the US, treatment regimens differ depending on the stage of a tumour: For stage 1 and stage 2 prostate cancer watchful waiting/active surveillance (monitoring), radical prostatectomy, external beam radiation therapy (EBRT) and interstitial implantation of radioisotopes may be used as treatment modalities. For prostate cancers higher or equal to grade 2, EBRT may or may not be combined with hormonal therapy [131].

In addition, hormonal manipulations with or without radiation therapy, radical prostatectomy with or without EBRT, watchful waiting under certain circumstances can be described as treatment modalities for stage 3 prostate cancer. For stage 4 prostate cancer, hormonal manipulations, bisphosphonates, palliative radiation therapy, palliative surgery with transurethral resection of the prostate (TURP) and watchful waiting/active surveillance (monitoring) may be used as treatment modalities [131].

Prognose:
5 Jahre: 98,6 %

According to statistics from the Surveillance, Epidemiology, and End Results (SEER), the 5-year survival of all prostate cancer patients was 98.6% (2007–2013) in the United States (USA). However, variations among the stages of cancer can be seen: patients with localised or regional prostate cancer have a relatively high chance of surviving 5 years after the diagnosis in com-

parison to patients suffering from distant prostate cancer or patients with an unknown prostate stage, with a 5-year survival of 100%, 100%, 29.8% and 81.2% respectively [66].

Included studies

8 Studien, ca. 2.715 Studienteilnehmer 66-70 Jahre

For prostate cancer, 8 studies were included in this assessment: 1 randomised, paralelly assigned, open-label, pilot study focusing on toxicity [132], 3 before-after studies measuring primarily Health-Related Quality of Life (HRQoL) [133-135], and 4 case series (1 interim report of acute side effects [136], 1 dose-escalation study [137], 1 multi-institutional study [138], 1 phase 2 case series focusing on efficacy and feasibility of CIRT [139]).

51,6-72,0 GyE

Overall, the sum of the samples in the included studies resulted in approximately 2,715 prostate-enrolled patients[27]. Of those, 2,668 received CIRT. The tumour stage ranged from T1a-T3b. The patients were irradiated with CIRT at a total dose ranging from 51.6-72.0 GyE and fractions ranging from 12-20. However, 14 patients, enrolled in 1 study [136] received intensity-modulated radiotherapy (IMRT) and carbon ion boost (CIB), using 60 Gy in 5 fractions and 18 GyE in 6 fractions respectively. Co-interventions included hormonal therapy and neoadjuvant hormonal depending on the risk group of prostate cancer patients.

Kategoriserung von Risikogruppen (PSA, GS): in Studien nicht standardisiert

Most of the studies defined risk groups and measured differences between those risk groups according to tumour stage, prostate-specific antigen (PSA) level and Gleason score (GS). The definitions of the risk groups were not standardised and, therefore, differed between each respective study primarily according to PSA level and GS. All of the patients were between 45 and 92 years old at the start of enrolment in the clinical trials.

mehrfach publizierte Patientendaten wahrscheinlich

Berichterstattung unterschiedlicher Endpunkte

The median follow-up time ranged from 28-60 months. 2 studies did not report on the follow-up time [135, 137], and no included study explicitly reported on loss to follow-up. 5 of the included studies may have an overlapping patient population: it is assumed that some patients included in the Ishikawa et al. 2006 (n=175) [139] and the Wakatsuki et al. 2008 (n=194) [135] studies are included in the case series study of Tsuji et al. 2005 (n=201) using 3 prospective protocols [137]. In addition, it may be assumed that some patients of Maruyama et al. 2017 (n=417) [134] and Ishikawa et al. 2015 (n=76) [133] are included in the multi-institutional case series study of Nomiya et al. 2016 (n=2,157) [138]. None of the studies were excluded from this analysis since they provided data on different endpoints: Wakatsuki et al. 2008 [135] conducted a health-related quality of life (HRQoL) assessment and Ishikawa et al. 2006 [139] provided more nuanced data regarding risk group-specific survival rates. Additionally, Maruyama et al. 2017 (n=417) [134] and Ishikawa et al. 2015 (n=76) [133] reported on HRQoL, while the multi-institutional observational study of Nomiya et al. 2016 (n=2,157) [138] did not use this endpoint in their analysis.

Study characteristics, i.e., precise information on patient population, intervention, control and study design of the included studies, can be found in the Appendix (Table A-7).

[27] 2 included studies [134, 135] assessed the quality of life for 611 patients already included in other studies. Thus, those patients were not included in the calculation. There may be significant overlapping samples in further studies. The reader is referred to the data extraction table (Table A-7) for more information.

Efficacy

Overall survival (OS)

OS in 5 Studien
3 Jahre (actuarial): 100 %

4 Jahre: 91-97,4 %
5 Jahre: 89,2-100 %
10 Jahre: 78-96 %

Overall, 5 out of the 8 included studies measured overall survival (OS) of CIRT patients at different time points [133, 136-139]. None of the included studies compared the OS with the OS of patients undergoing conventional radiotherapy.

1-year OS was not reported in any of the included studies.

2-year OS was not reported in any of the included studies.

3-year OS was not reported in any of the included studies. However, 1 study calculated an actuarial 3-year OS of 100% (95% CI: NR) for intermediate-risk prostate cancer patients [136].

4-year OS was reported in 2 studies [133, 139]: 1 study (n=76)[133] observed a 4-year OS of 97.4% (95% CI: 93.8-100.0%) for low-, intermediate-, and high-risk prostate cancer patients, with 3, 29 and 40 prostate cancer patients[28] in those groups respectively. Another study (n=175) [139] observed a 4-year OS of 91% (95% CI: 87–96%), with a 4-year OS of 94% (95% CI: 90–98%) and 91% (95% CI: 85–96%) for the low and high-risk group respectively (with 33 and 142 low-risk and high-risk prostate cancer patients respectively).

5-year OS was reported in 2 studies [137, 138]: 1 multi-institutional study (n=2.157) reported on the 5-year OS for low-, intermediate-, and high-risk prostate cancer patients, with an OS of 100% (95% CI: NR), 99% (95% CI: NR) and 96% (95% CI: NR) at 5 years respectively. Another study [137] observed a 5-year OS of 89.2% (95% CI: NR) for 201 prostate cancer patients.

10-year OS was reported in 1 study [138]: The multi-institutional study (n= 2,157) reported a 10-year OS for low-, intermediate-, and high-risk prostate cancer patients, with an OS of 96% (95% CI: NR), 78% (95% CI: NR) and 88% (95% CI: NR) in those risk groups respectively. The number of patients in each risk group were 263 (12%), 679 (31%) and 1,215 (56%) in the low-, intermediate-, and high-risk group respectively.

Cause-specific survival (CSS)/Disease-specific survival (DSS)

CSS/DSS in 3 Studien

4 Jahre: 97-100 %
5 Jahre: 92,2-100 %
10 Jahre: 88-100 %

Overall, 3 out of the 8 included studies measured cause-specific survival (CSS) of CIRT patients at different time points [137-139]. None of the included studies compared the CSS to the CSS of patients undergoing conventional radiotherapy.

1-year CSS was not reported in any of the included studies.

2-year CSS was not reported in any of the included studies.

3-year CSS was not reported in any of the included studies.

4-year CSS was reported in 1 study [139]: the study (n=175) observed a cause-specific survival (CSS) of 97% (95% CI: 95–100%) at 4 years. The CSS within the risk groups at 4 years was 100% (95% CI: NR) and 97% (95% CI: 95–98%) in the low- and high-risk group respectively (with 33 and 142 low-risk and high-risk prostate cancer patients respectively).

[28] The sample included 4 castration resistant patients who were not included in any of those risk groups.

5-year CSS was reported in 2 studies [137, 138]: 1 multi-institutional study (n=2,157)[138] reported on the 5-year CSS for low-, intermediate-, and high-risk prostate cancer patients, with a CSS of 100% (95% CI: NR), 100% (95% CI: NR) and 99% (95% CI: NR) at 5 years in those risk groups respectively. Another study [137] reported on the 5-year disease-specific survival (DSS) of 201 t1-t2a, t2b and t3 prostate cancer patients with 81, 39 and 81 in those groups respectively. The 5-year DSS was 92.2% (95% CI: NR) for the included patients.

10-year CSS was reported in 1 study [138]: the multi-institutional study (n= 2,157) reported a 10-year CSS for low-, intermediate-, and high-risk prostate cancer patients, with a CSS of 100% (95% CI: NR), 88% (95% CI: NR), and 98% (95% CI: NR) in those risk groups respectively. The number of patients in each risk group were 263 (12%), 679 (31%) and 1,215 (56%) in the low-, intermediate-, and high-risk group respectively [138].

Disease-free survival (DFS)

DFS: keine Daten

The endpoint disease-free survival (DFS) was not measured by the included study.

Recurrence-free survival (RFS)

RFS in 5 Studien

Overall, 5 out of 8 included studies measured recurrence-free survival (RFS) of CIRT patients at different time points [133, 136-139]. None of the included studies compared the observed RFS to the RFS of patients undergoing conventional radiotherapy.

1 Jahr: keine Daten

1-year RFS was not reported in any of the included studies.

2-year RFS was not reported in any of the included studies.

3 Jahre in 1 Studie: 86 % (actuarial)

3-year RFS was not reported in any of the included studies. 1 study [136] (n=14) including prostate patients at an intermediate risk reported on an actuarial 3-year biochemical relapse-free survival of 86% (95% CI: NR).

4 Jahre in 2 Studien: 87-94,6 %

4-year RFS was reported in 2 studies [133, 139]: 1 study [133] observed a 4-year biochemical recurrence-free (BRF) rate of 94.6% (95% CI: 89.4-99.8%) for low-, intermediate-, and high-risk prostate cancer patients, with 3, 29 and 40 prostate cancer patients[28] in those groups respectively. Another study [139] observed a 4-year biochemical relapse-free survival (bNED) of 88% (95% CI: 83–93%). The bNED for each risk group at 4 years was 87% (95% CI: 77–98%) and 88% (95% CI: 82–94%) for the low-, and high-risk group respectively.

5 Jahre in 2 Studien: 83,2-100 %

5-year RFS was reported in 2 studies [137, 138]: 1 multi-institutional study (n=2,157) [138] reported on the 5-year BRFS for low-, intermediate-, and high-risk prostate cancer patients, with a BRFS of 92% (95% CI: NR), 89% (95% CI: NR) and 92% (95% CI: NR) at 5 years in those risk groups respectively. Another study [137] observed a 5-year bNED of 83.2% (95% CI: NR). Data of the risk groups[29] showed a bNED of 100% (95% CI: NR) and 80.5% (95% CI: NR) for patients in the low- and high-risk groups respectively.

[29] bNED was the only outcome for which risk-group related data was reported. The bNED rates refer to 37 and 164 prostate cancer patients in the low-risk and high-risk group respectively.

10-year RFS was reported in 1 study [138]: 1 multi-institutional study (n= 2,157) [138] reported on the 10-year BRFS for low-, intermediate-, and high-risk prostate cancer patients, with a BRFS of 77% (95% CI: NR), 70% (95% CI: NR) and 79% (95% CI: NR) in those risk groups respectively. The number of patients in each risk group were 263 (12%), 679 (31%) and 1,215 (56%) in the low-, intermediate-, and high-risk group respectively.

10 Jahre in 1 Studie: 70-79 %

Progression-free survival (PFS)

The endpoint progression-free survival (PFS) was not measured by any of the included studies.

PFS: keine Daten

Health-Related Quality of Life (HRQoL)

Overall, 5 out of 8 included studies used health-related quality of life (HRQoL) as an endpoint at different time points. No study compared HRQoL in CIRT patients to HRQoL of patients undergoing conventional therapy.

HRQoL in 5 Studien

1 study [132] measured HRQoL, using the QLQC30 and PR25 questionnaire, in CIRT (n=45) and PRT (n=46) patients before, at the end of, 6 weeks, and 6 months after CIRT/PRT. For both groups, a significant worsening of quality of life was seen during RT, and several improvements in QLQC30 and the QLQPR25 scores during follow-up were observed. It is stated that urinary symptoms, as well as pain and fatigue, were reduced both during and 6 weeks after CIRT. Differences in HRQoL between treatment arms were only found in some subscales: it was stated that urinary and bowel symptoms scores were statistically significantly lower for CIRT patients when compared to PRT patients at different time points after treatment. However, it was not stated in their analysis for which time point the reported significant p-values for the differences between treatment groups apply. In addition, it was not stated whether the difference refers to the time point or changes over time of the 2 groups under comparison. Scores of urinary and bowel symptoms and precise changes of all of the subscales of those tools can be found in Table A-7. The study concluded that CIRT and PRT patients have comparable HRQoL parameters.

1 Studie: Vergleich: 45 CIRT vs. 46 PRT Pts

s. s. geringere Harn- und Darmsymptome in CIRT Patienten

keine anderen s. s. Unterschiede bei Verwendung des QLQC30 und PR25 Fragebogen

The other 4 studies [133-135, 139] did not compare HRQoL of CIRT patients with HRQoL of patients undergoing other forms of radiotherapy and measured and compared HRQoL before and up to 1 year after CIRT: in 1 study [133], no short-term or mid-term statistical differences and a slight and statistically significant longer-term decrease of the physical component summary (PCS) score [baseline vs. 12 months: 51.14 (±1.85) vs. 47.71 (±1.84)] of CIRT, using the Japanese version of the SF-8 ($p<0.05$), were found. There were no statistically significant short-term, mid-term or longer-term changes in the mental component summary (MCS) score before and after 12 months of CIRT in this study.

4 weitere Studien ohne Vergleichsgruppe

In 1 study [134], the FACT-G, FACT-P and TOI mean scores before CIRT were 84.2 (±12.6), 119.5 (±16.9) and 81.8 (±12.0) respectively. The study found statistically significant short-term changes (at 1 month) in FACT-P and TOI (with 116.2 and 77.8 respectively) and no short-term statistical difference in FACT-G score (83.7). In addition, longer-term differences in HRQoL were found: FACT-G and FACT-P long-term differences were statistically significantly lower, and no statistical difference in TOI scores was observed. The study found, for instance, statistically significantly lower FACT-G and FACT-P, and no statistically significant changes in TOI mean scores at 60 months after CIRT when compared to the corresponding scores before CIRT

was initiated, with mean scores of 82.7 (±15.0), 117.6 (±20.2), 81.4 (±14.6) respectively. The reader is referred to the data extraction table for more information on the detailed changes at the respective long-term time points (Table A-7).

Another study [135] measured the HRQoL of CIRT alone (n=25) and CIRT in combination with adjuvant therapy (n=125) before, post-interventional and longer-term (at 12 months): in the 25 patients receiving CIRT alone, there were no significant differences between the mean scores before, just after, and 12 months after CIRT alone, using the FACT-G and FACT-P questionnaire, with a mean score of 88.4 (±13.2) and 122.6 (±19.8) before and 89.1 (±13.6) and 123.8 (±20.3) at 12 months after CIRT respectively. On the contrary, there were significant mean score differences in the CIRT+ADT group, with statistically significantly lower mean scores at 12 months after CIRT in comparison to the respective baseline scores. That is, the FACT-G and FACT-P scores in this group were 86.1 (±19.4) and 120.0 (±26.1) before CIRT and 83.9 (±21.7) and 116.7 (±29.1) at 12 months after CIRT (s. s. to baseline score).

Another study [139], including 175 prostate cancer patients, found no longer-term statistically significant changes in health-related quality of life (HRQoL) when comparing the mean FACT-G and FACT-P scores before and 1 year after CIRT, with a difference of 1.8±1.1 (89.1 vs. 87.3; p=0.1) and 2.6±1.4 (123.1 vs. 120.4; p=0.07) using those tools respectively.

Safety

Acute radiation morbidity

akute Strahlenbelastung in 5 Studien

From the included studies, 5 out of 8 studies measured acute radiation morbidities using the CTCAE [132, 133, 136, 138] or the RTOG [139] criteria: none of the studies observed severe radiation morbidities (Grade ≥3), except for 1 study [138], in which 1 out of 2,157 patients developed grade 3 genitourinary (GU) toxicities. Several grade 1-2 acute radiation morbidities were observed in the genitourinary (GU) and gastrointestinal (GI) region. In addition, 1 study compared toxicity profiles of CIRT patients and PRT patients.

Grad 1:
GU: 33-57 % in 3 Studien
GI: 1 %-35 % % in 3 Studien

Grad 0-1 in 1 Studie:
GU: 94,4 %
GI: 100 %

1 Studie mit Vergleich:
45 CIRT pts: proctitis: 11 %, diarrhoea: 55,6 %, cystitis 28,9 %
46 PRT pts: proctitis: 13 %, diarrhoea: 60,9 %, cystitis: 39,1 %

Grade 1 acute radiation morbidity (genitourinary and gastrointestinal) was reported in all 5 studies [132, 133, 136, 138, 139]: in the GU region, grade 1 acute radiation morbidities ranged from 57 out of 175 (33%) [139] to 43 out of 76 (57%) [133] prostate cancer patients in 3 of the included studies [133, 136, 139]. In the GI region, the incidence of grade 1 acute radiation morbidities ranged from 1 out of 76 patients (1%) [133] to 5 out of 14 patients (35%) [136] in 3 of the included studies [133, 136, 139]. In addition, 1 study [138] did not specify whether grade 1 or grade 0 acute radiation morbidities occurred and observed 2,037 (94.4%) and 2,157 (100%) grade 0-1 acute radiation morbidities in the GU and GI region respectively. Moreover, 1 study [132] reported on grade 1 radiation morbidities in 45 CIRT patients with localised prostate cancer: proctitis, diarrhoea and cystitis were observed with 5 (11%), 25 (55.6%) and 13 (28.9%) patients suffering from those toxicities respectively. In the PRT group in this study, those radiation morbidities occurred in 6 patients (13%), 28 patients (60.9%) and 18 patients (39.1%) respectively.

Grade 2 acute radiation morbidity (genitourinary and gastrointestinal) was reported in all 5 studies [132, 133, 136, 138, 139]: in the GU region, 3 studies [133, 136, 138] observed grade 2 acute radiation morbidities, ranging from 119 out of 2,157 prostate cancer patients (5.5%) [138] to 5 out of 14 prostate cancer patients (35.7%) [136]. In the GI region, 4 studies [133, 136, 138, 139] did not observe any grade 2 radiation morbidities. In addition, 1 study observed grade 2 proctitis, diarrhea and cystitis in 45 CIRT patients and 46 patients undergoing PRT: In the CIRT group, 1 patient (2.2%), no patients (0%) and 6 patients (13.3%) developed those diseases respectively. In the PRT treatment group, 4 patients (8.7%), 4 patients (8.7%) and 10 patients (21.7%) developed the aforementioned grade 2 morbidities respectively.

Grad 2:
GU: 0-35,7 % in 4 Studien
GI: 0 % in 4 Studien

1 Studie mit Vergleich:
45 CIRT pts: proctitis: 2,2 %; diarrhoea: 0 %; cystitis: 13,3 %
46 PRT pts: proctitis: 8,7 %; diarrhoea: 8,7 %; cystitis: 21,7 %

Grade 3 acute radiation morbidity (genitourinary and gastrointestinal) was reported in all 5 studies [132, 133, 136, 138, 139]: in the GU region, 1 study observed 1 incidence of acute grade 3 radiation morbidities in 2,037 (0%) prostate cancer patients. In the GI region, 1 study [132] observed no grade 3 acute radiation morbidities in the CIRT group of their study (n=45) and 2 patients (4.3%) in the PRT group (n=46) developing grade 3 proctitis (rectum fistula). No other grade 3 acute radiation morbidities occurred in the included studies.

Grad 3: 0 % in 4 Studien

1 Studie mit Vergleich:
45 CIRT pts: 0 %
46 PRT pts: 4,3 %

Grade 4 acute radiation morbidity (genitourinary and gastrointestinal) was reported in all 5 studies [132, 133, 136, 138, 139]: grade 4 acute radiation morbidities were neither observed in the GU nor in the GI region.

Grad 4: 0 %

One of the included studies [132] compared toxicity profiles of 45 CIRT patients to the toxicity profiles of 46 PRT profiles and found no statistically significant differences between those arms.

1 Studie: keine stat. signifikanten Unterschiede hinsichtlich Toxizitätsprofilen zwischen CIRT und PRT

Late radiation morbidity

From the included studies, 5 out of 8 studies measured late radiation morbidities using the CTCAE [133, 138] or the RTOG/EORTC [134, 137, 139] criteria: none of the studies reported on severe radiation morbidities (grade ≥ 3), except for 2 studies, in which grade 3 genitourinary (GU) toxicities were observed, with 1 out of 1,929[30] patients [138] and 1 out of 417 patients [134] developing grade 3 GU toxicities occured. Several grade 1-2 late radiation morbidities were observed in the genitourinary (GU) and gastrointestinal (GI) region.

späte Strahlenbelastung in 5 Studien

Grade 1 late radiation morbidity (genitourinary and gastrointestinal) was reported in 5 studies [133, 134, 137-139]: in the GU region, several grade 1 late radiation occurred in 4 studies [133, 134, 137, 139], ranging from 66 out of 394 (16.8%) [134] to 108 out of 175 (62%) [139] prostate cancer patients developing grade 1 late morbidities in this region. In the GI region, grade 1 late radiation morbidities were observed less frequently in the same studies, ranging from 7 out of 201 prostate cancer patients (3.5%) [137] to 23 out of 175 prostate cancer patients (13%) [139] developing grade 1 late morbidities in the rectum. Additionally, 1 study [138] did not specify whether grade 1 or grade 0 late radiation morbidities occurred and observed 1,840 (95.4%) and 1,921 (99.6%) out of 1,929 prostate cancer patients (95.4%) with grade 0-1 late radiation morbidities in the GU and GI region respectively.

Grad 1:
GU: 16,3 %-62 % in 4 Studien
GI: 3,5 %-13 % in 4 Studien

Grad 0-1 in 1 Studie:
GU: 95,4 %
GI: 99,6 %

[30] The study stated that patients with a follow-up <6 months were excluded from the analysis.

Grad 2 in 5 Studien: GU: 2,5 %-7 % GI: 0,4-2 %

Grade 2 late radiation morbidity was reported in 5 studies [133, 134, 137-139]: in the GU region, late radiation morbidities were observed in all studies, ranging from 10 out of 394 prostate cancer patients (2.5%) [134] to 5 out of 76 prostate cancer patients (7%) [133], developing late radiation morbidities in the bladder/urethra. In the GI region, late radiation morbidities ranged from 0.4-2%.

Grad 3 in 5 Studien: GU: 0-0,3 % GI: 0 %

Grade 3 late radiation morbidity was reported in 5 studies [133, 134, 137-139]: in the GU region, 2 studies observed grade 3 late radiation morbidities in the bladder/urethra, with 1 out of 1,921 (0%) [138] and 1 out of 394 (0.3%) [134] prostate cancer patients developing grade 3 GU late radiation morbidities in those studies respectively. In the GI region, none of the studies reported on CIRT patients with prostate cancer developing any grade 3 GI late radiation morbidities [133, 134, 137-139].

Grad 4in 5 Studien: 0 %

Grade 4 late radiation morbidity (genitourinary and gastrointestinal) was reported in all 5 studies [133, 134, 137-139]: grade 4 late radiation morbidities were neither observed in the GU nor in the GI region.

Conclusion

8 Studien, ca. 2.715 Studienteilnehmer 1 RCT nur zu Safety-Parameter

unzureichende Evidenz

For prostate cancer, 8 studies were identified: for efficacy-related endpoints, none of the eligible studies were controlled, comparing CIRT to standard irradiation. 1 randomised, parallel assigned, open-label, pilot study was identified comparing toxicities between CIRT and PRT and found no statistically significantly different toxicity profiles between both experimental arms [132]. However, neither inferiority nor superiority of CIRT on the basis of the selected endpoints regarding efficacy (OS, CSS, DFS, RFS, PFS, LCR, HRQoL) or safety (acute radiation morbidity, late radiation morbidity) can be concluded from the evidence. That is to say, further (randomised) controlled trials are needed to clarify whether CIRT is more effective than, or as effective as, or safer than, or as safe as conventional irradiation in prostate patients.

5.3.9 Breast cancer

Definition and epidemiology

häufiger Tumor: 116,7 in 100.000 Frauen hier: nur junge Patientinnen

Breast cancer occurs in the tissues of the breast caused by malignant cancerous cells [140]. Breast cancer is the most frequent cancer occurring in women, constituting 30% of all cancers in women in 2014. In 2015, the age-adjusted incidence rate for breast cancer was 116.7 cases per 100,000 women, and 2.4 cases per 100,000 men. At the end of the same year, 647 men and 74,170 women were alive with a breast cancer diagnosis [141].

Current treatment regimens and prognosis

Prognose: 5 Jahre: 84,4 % 10 Jahre: 77,9 %

There are 5 types of standard treatment currently used: surgery, radiation therapy (RT), chemotherapy, hormone therapy, and targeted therapy [140]. According to Statistics Austria, the relative survival of breast cancer patients was 94.6% and 88.9% at 1 and 3 years after their diagnosis respectively. The 5-, and 10-year relative survival for the same population was 84.4% and 77.9% respectively. The analysis was based on 24,767 patients (267 men and 24,500 women) diagnosed with breast cancer in the time period of 2003 and 2007 [142].

Included studies, efficacy and safety

For breast cancer, no clinical study was identified in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no evidence indicating superiority/inferiority of CIRT for breast cancer when compared to standard irradiation.

keine Evidenz

5.3.10 Kidney

For renal cancer, evidence was only assessed for 1 renal paediatric cancer (nephroblastoma).

5.3.1.1 Nephroblastoma

Definition and epidemiology

Nephroblastoma (Wilms tumour) is a paediatric renal cancer accounting for approximately 7% of all paediatric cancers [143]. In Austria, the age-adjusted incidence rate was 8.2 per 1,000,000 children (0-14 years old) diagnosed with nephroblastomata between 2002 and 2012 [57].

pädiatrischer Tumor
8,2 in 1 Mio Kindern

Current treatment regimens and prognosis

The treatment approach is typically multimodal and usually all of the patients suffering from this tumour should be considered to be enrolled in clinical trials, since Wilms tumours are rarel cancers. Current treatment of nephroblastomata depends on the stage of the disease and may consist of the following: surgery, chemotherapy, and radiation therapy (RT) in some circumstances [143]. Treatment approaches may differ according to the clinical groups. For instance, the National Wilms Tumor Study (NWTS) group established standard treatment for this disease consisting of nephrectomy (if feasible) and postoperative chemotherapy and RT (in some circumstances), while trials from the European consortium typically provide chemotherapy before a surgical operation (definitive resection) [143].

Prognose:
5 Jahre: 93,6 %

According to Statistics Austria, the 5-year survival of patients suffering from nephroblastomata is measured to be 93.6% (95% CI: 85.3-97.3) based on analysis including 78 children (0-14 years old) diagnosed with this disease between 2002 and 2009 [58].

Included studies, efficacy and safety

No studies elaborating on the efficacy or safety of carbon ion radiotherapy (CIRT) for patients with this specific indication were identified. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for nephroblastomata when compared to standard irradiation.

keine Evidenz

5.3.11 Central nervous system (CNS)

For tumours in the nervous system, evidence was assessed for neuroblastoma.

5.3.11.1 Neuroblastoma

Definition and epidemiology

pädiatrischer Tumor
11,9 in 1 Mio Kindern

Neuroblastomas are paediatric, malignant and extracranial solid tumours [144]. In Austria, the age-adjusted incidence rate of neuroblastomas and other tumours occurring in other peripheral nerves was 11.9 cases per 1,000,000 children (0-14 years old) in the time period of 2002 and 2012. [57].

Current treatment regimens and prognosis

Prognose:
5 Jahre: 79,8 %

Treatment modalities are dependent on the risk group of neuroblastomas and may include one, or a combination of the following: observation, surgery, chemotherapy, radiation therapy, isotretinoin, immunotherapy, myeloablative therapy and stem cell transplantation [58]. According to Statistics Austria, the 5-year survival of patients suffering from neuroblastomas or other peripheral nerve tumours is 79.8% (95% CI: 71-86.2) based on analysis including 109 children (0-14 years old) diagnosed with this disease between 2002 and 2009 [58].

Included studies, efficacy and safety

keine Studie inkludiert

No studies elaborating on the efficacy or safety of carbon ion radiotherapy (CIRT) for patients with this specific indication were identified. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) for neuroblastomas.

5.3.12 Hematologic cancer

For hematologic cancer types, evidence was assessed for Non-Hodgkin's lymphoma and Hodgkin's lymphoma.

Included studies, efficacy and safety

keine Studie inkludiert

No study was included for hematologic cancer: no scientific evidence indicating superiority/inferiority regarding efficacy or safety of CIRT when compared to conventional radiotherapy for Non-Hodgkin's lymphoma and Hodgkin's lymphoma.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT).

5.3.12.1 Non-Hodgkin's lymphoma

Definition and epidemiology

Non-Hodgkin's lymphomas are tumours originating in lymphoid tissues [145]. In Austria, the age-adjusted incidence of NHL was 15.5 cases per 100,000 persons in 2015. At the end of the same year, 6,131 men and 5,668 women were diagnosed with non-Hodgkin's lymphomas [146].

Häufigkeit:
15,5 in 100.000

Current treatment regimens and prognosis

Treatment options for NHL may include, inter alia, one, or a combination of the following: radiation therapy, chemotherapy, drug therapy (e.g., rituximab, lenalidomide) [145]. Statistics Austria data based on 5,519 patients diagnosed with non-Hodgkin's lymphomas within the time period of 2003, and 2007 shows a relative survival of 77.2% and 68% at 1 and 3 years respectively. The relative 5- and 10-year survival was 64.1 and 57.4% for the same population [147].

Prognose:
5 Jahre: 64,1 %
10 Jahre: 57,4 %

Included studies, efficacy and safety

For non-Hodgkin's lymphoma, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for non-Hodgkin's lymphoma.

keine Evidenz

5.3.12.2 Hodgkin's Lymphoma

Definition and epidemiology

Hodgkin's lymphomas (Morbus Hodgkin) are malignant tumours of the lymphatic system. In Austria, the age-adjusted incidence of Hodgkin's lymphomas was 1.7 cases per 100,000 persons in 2015. At the end of the same year, 1,832 men and 1,723 women were diagnosed with Morbus Hodgkin [148].

Häufigkeit:
1,7 in 100.000 Personen

Current treatment regimens and prognosis

Treatment modalities of Hodgkin's lymphomas may include, among others, one, or a combination of the following: radiation therapy, chemotherapy and drug therapy [145]. Data of Statistics Austria based on 908 patients diagnosed with Morbus Hodgkin within the time period of 2003, and 2007 shows a relative survival of 91.7% and 87.4% at 1 and 3 years respectively. The relative 5- and 10-year relative survival was 84.1% and 80% for the same population [149].

Prognose:
5 Jahre: 84,1 %
10 Jahre: 80 %

Included studies

For Hodgkin's lymphomas, no studies were included in this assessment. Thus, no evidence was found to answer the research question.

keine Studie inkludiert

Conclusion: Efficacy and safety

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for Hodgkin's lymphomas.

keine Evidenz

5.3.13 Other oncologic indications

In this section, one will find the assessed evidence for "other oncologic indications" according to the MedAustron list of potential CIRT indications. That is, solitary liver metastases in colorectal cancer, retroperitoneal metastases in controlled primary tumours, as well as oligometastases in controlled primary tumours in selected indications.

Included studies, efficacy and safety

keine Studie inkludiert
keine Evidenz

No study was included for any of those indications: no scientific evidence indicating superiority/inferiority regarding efficacy or safety of CIRT when compared to conventional radiotherapy for solitary liver metastases in colorectal cancer, retroperitoneal metastases in controlled primary tumours, and oligo-metastasis in controlled primary tumours in selected indications.

5.3.13.1 Solitary liver metastases in colorectal cancer

Included studies, efficacy and safety

keine Studie inkludiert

No evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for solitary liver metastases in colorectal cancer.

5.3.13.2 Retroperitoneal metastases in controlled primary tumours

Included studies, efficacy and safety

keine Evidenz

No evidence was found to answer the research question.

Conclusion

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for retroperitoneal metastases in controlled primary tumours.

5.3.13.3 Oligometastases in controlled primary tumours in selected indications

Included studies, efficacy and safety

keine Studie inkludiert

No study was included in the analysis. Thus, no evidence was found to answer the research question.

Conclusion

keine Evidenz

At present, there is no scientific evidence indicating superiority or inferiority regarding the use of carbon ion radiotherapy (CIRT) in comparison to standard irradiation for oligometastases in controlled primary tumours in selected indications.

6 Discussion

Until 2016, approximately 21,580 patients were recorded to have been treated with CIRT [2] internationally. In this assessment, 56 clinical studies were identified to assess for which cancer indications CIRT is currently used: the majority of the studies included cancer in the brain & skull base region, prostate and lung, with 14, 11 and 9 identified studies respectively. In addition, 7 clinical studies were identified for the tumours in the ENT region and 4 studies were identified for gastrointestinal tumours. Less frequently identified studies enrolled patients with bone and soft tissue and eye tumours, with 2 and 1 identified study respectively. Furthermore, 2 tumour regions not on the MedAustron list were identified on the basis of the identified studies: 7 studies had gynecologic tumour patients in their sample and 1 further study had skin cancer patients included in the sample. The number of patients in those published clinical trials resulted in an estimated 6,052 patients (5,651 patients receiving CIRT). However, 1 multi-institutional study [138] was included with more than 2,000 included patients. Those patients are possibly also included in other studies (overlap in enrolment time), and thus the number of patients included in the identified studies may be significantly lower.

bis Ende 2016:
21.580 PatientInnen weltweit dokumentiert mit CIRT behandelt

in diesem Bericht
56 Studien:

ca 5.651 dokumentierte CIRT PatientInnen in prospektiven Studien

The search for **ongoing studies** revealed that the great majority of currently undertaken studies are uncontrolled: 65 studies were identified of which 10 are controlled, enrolling patients suffering from tumours in the following regions: brain and skull base, bone and soft tissue, gastrointestinal, and ENT as well as lung. Interestingly, no randomised controlled trials were found in the prostate or lung region, and only 1 controlled trial enrolled lung cancer patients in their study.

65 laufende Studien, davon 10 (R)CTs

In addition, results from (randomised) controlled trials are expected to arise in the following years, since the primary completion date of 4 of the ongoing RCTs has already passed (region brain and skull base:studies include: 319 patients with chordomas, 80 patients with meningioma, 150 patients with primary glioblastomas and 436 patients with recurrent gliomas in 1 study respectively, see: “List of ongoing randomised and non-randomised clinical trials“). The primary completion date of the other controlled and randomised controlled trials is in the next 4 years (bone & soft tissue: 2 studies, with 100 patients respectively; chondrosarcoma: 1 phase 3 RCT, with 154 patients; adenoid cystic carcinoma and sarcoma: 1 RCT, with 250 patients; hepatocellular cancer: 1 CT, with 48 patients; lung cancer: 1 CT, with 525 patients, see “List of ongoing randomised and non-randomised clinical trials“).

4 bereits abgeschlossene Studien, aber ohne Publikation
Weitere Ergebnisse in den nächsten Jahren zu erwarten

Of those published 56 studies, 27 clinical studies were eligible for the qualitative synthesis of the efficacy and safety of CIRT when compared to standard irradiation: 1 randomised controlled trial focusing on toxicity and feasibility of CIRT/PRT with a high risk of bias and 26 were either prospective case series or – less frequently – case-control studies or single-arm before-after studies focusing on HRQoL. No other controlled study was found. When assessing the superiority/inferiority of CIRT in comparison to standard irradiation regarding efficacy and safety on the basis of the selected oncologic endpoints, no scientific evidence was found for 41 indications, and insufficient scientific evidence was found for 13 indications in 7 regions (**Skull base**: chordomas, chondrosarcomas; **brain**: glioma grade II, glioma grade III; glioblastoma; **ear-nose-throat**: sarcomas in the head and neck, tumours in the nasal cavity and paranasal sinus, adenoid cystic salivary gland carcinoma;

von 56 publizierten Studien nur 27 mit moderatem RoB

gar keine Evidenz in 41 (von 54) Indikationen, unzureichende in 13 (von 54)

bone and soft tissue: soft tissue sarcoma; **lung:** non-small cell lung carcinoma; **prostate:** prostate carcinoma; **gastrointestinal:** oesophageal carcinoma, rectum carcinoma) (see Table 6-1, Table 6-2, Table 6-3).

Limitationen: Ausschluss von retrospektiven Studien und mit hohem RoB daher wurde nicht der gesamte verfügbare Evidenzstand miteinbezogen

Limitations of this systematic review are as follows: although the literature was selected independently by 2 researchers, as was the Risk of Bias Assessment (RoB) done, the data was extracted by 1 researcher and controlled by the second, there is always the risk of error or of overseeing data, though this risk is small. The exclusion criteria also applied, i.e., to exclude studies with high RoB and retrospective case series may have led to not capturing the whole available body of evidence. That is, retrospective studies or low-quality studies (with a high risk of bias) were not included within this systematic review. In case of lack of explicit description of the retrospective or prostpective study design and data collection, the authors tended to take a 'liberal' inclusion strategy and to include the respective study.

Einbettung in bestehendes Wissen:

SR (2013) empfiehlt CIRT als experimentelle Behandlung anzusehen

The results found in this assessment are in accordance with existing knowledge from other systematic reviews to some extent: 1 recent systematic review [15] on charged particle therapy for hepatocellular carcinoma identified 4 CIRT studies, but did not compare any of the results to standard irradiation. Another systematic review [14] conducted in 2013 found no randomised controlled trial and concluded that CIRT should be considered as an experimental treatment, and comparisons (by using RCTs) of CIRT and photon as well as proton therapy are necessary.

andere SRs und HTA-Reporte beinhalten wenige Primärstudien zu CIRT zu Einzelindikationen

keine vergleichenden Studien

3 other less recent systematic reviews compared CIRT to conventional RT and other newer forms of RT on the basis of observational studies: 1 systematic review [13] conducted an evidence synthesis and meta-analysis of the results of 86 observational and comparative in-silico studies. The review identified 5 studies in which CIRT was used and found statistically significantly higher 5-year survival in mucosal malignant melanoma patients after CIRT in comparison to photon therapy (44% vs. 25%; p=0.007). While those results sound promising and may indicate that CIRT could potentially be superior in this indication, it must be stated that a) the evidence base of the meta-analysis are observational studies and b) the percentage of patients having undergone operation was not included in those observational studies and, thus, a potentially significant confounder was not statistically tested.

indirekte Vergleiche

Another meta-analysis [12] conducted in 2010 included 3 studies comparing the efficacy of different radiotherapy treatment modalities for non-small cell lung cancer and found statistically significantly higher survival rates of CIRT when compared to conventional photon radiotherapy and no statistically significant survival rates when compared to stereotactic radiotherapy or proton radiotherapy. Another less recent systematic review on particle therapy from the same author group was identified with similar conclusions: "promising results" with a lack of evidence to suffice particle therapy replacing the standard treatment. In addition, a conflict of interest is existent in this study [11].

SR von Mitarbeitern von Hadronzentren: Interessenskonflikte

However, it must be stated that many of the identified systematic reviews and meta-analyses have been undertaken by researchers working for hadron therapy centres, and were sometimes even funded by manufacturers [11, 12]. Thus, a conflict of interest may exist.

KCE HTA-Bericht: Überzeugung von PRT und CIRT verhindert Studien

A previous report by the Belgian Health Care Knowledge Centre KCE [19] on the use of proton beam therapy PBT found that no randomised controlled trials were available for paediatric cancer indications and pointed out that 1 factor may be that many clinicians are highly convinced that proton beam

therapy is superior to conventional radiotherapy, leading to a high degree of reluctance to randomise patients. For CIRT, a similar scenario may be true, potentially explaining the lack of controlled and randomised controlled trials proving superiority or inferiority of CIRT.

ethische Barrieren gegen die Durchführung von RCTs nicht akzeptabel,

In the same report [19], it is argued that **ethical reasons**, legitimating not conducting controlled or randomised controlled trials due to the better physical properties of hadron therapy, may not be convincing except for some indications in which physical or anatomical reasons against using photons are prevalent.

weil es sehr viele andere neue Therapien gibt,

die vielversprechend sind

However, and even if ethical reasons were evident hindering conducting randomised controlled trials for proton therapy for some indications, the same logic may not necessarily apply to the difference of carbon ion radiotherapy when compared to other treatment modalities: the advantage of carbon ion radiotherapy is – to the knowledge of the authors – even theoretically speaking not known extensively. The reviewed medical literature describes CIRT as a two-edged sword [24]: some of the radiobiological differences are advantages, and some may be disadvantageous [19, 150]. At the same time, many new and potentially promising techniques in radiation therapy, such as intensity-modulated radiation therapy (IMRT), CyberKnife and PRT, coexist alongside with CIRT [151], leading to a necessity to conduct more comprehensive evaluations.

Verstärkung der Kooperation innerhalb der EU wichtig, um den Evidenzstand zu verbessern

Furthermore, there may be other significant boundaries and structural factors hindering the generation of sound scientific evidence: a lack of collaboration between the cancer therapy centres [19] exists within the European Union (EU). The member states of the EU are asked to establish an environment in which collaboration and evidence generation is promoted, and a "medical arms race" [152] between cancer therapy centres is hindered in order to reach more patient-relevant outcomes (PRO) for cancer patients within the EU.

Fragen zur adäquaten Ressourcenallokation und Versorgungs-forschung von Krebstherapien wichtig

In this context, cooperation cannot be limited to generating clinical evidence solely: questions regarding the adequate allocation of resources [153] within the Austrian health care system, but also more broadly in the EU arise: more scientific health service research evaluations [154], and economic evaluations [155] – including societal parameters – may help to reach a scientific basis for decisions in the EU, leading to the greatest PROs for cancer patients.

Ziel muss es sein, die Evidenzbasis für CIRT zu stärken
CIRT: derzeit experimentell

In conclusion, the evidence regarding superiority/inferiority of CIRT regarding efficacy or safety can as of today only be called an experimental therapy: more research (prospective controlled and randomised studies) is necessary to reach a sophisticated evidence base for the evaluation of CIRT for cancer therapy.

Table 6-1: Summary of the included studies for the skull base and brain and ENT region

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Skull base (3 studies)								
Mizoe et al. 2009 [44]	Chordoma of the skull base and the paracervical spine	Prospective; Pilot study, dose-escalation study, enrolment: 1995-2007; n=33; age: 47 (median, range: 16-76)	53 (median, range: 8-29)	Variable[31] (incl. surgery)	-	**OS (5yr):** 87.7% (95% CI: NR, SE: 7%) at 5 years **OS (10yr):** 67% (95% CI: NR, SE: 14%) at 10 years **LCR (5yr):** 85.1% (95% CI: NR, SE: 8%) at 5 years **LCR (10yr):** 63.8% (95% CI: NR, SE: 19%) at 10 years	**Acute:** Mucosa: 12/34 [6 (17.6)/ 6 (17.6)/0(0)/0(0)]; skin: 13/34 [12 (35.3)/1 (2.9)/0 (0)/0 (0)] **Late:** Mucosa: 2/34 [2 (5.9)/0 (0)/ 0 (0)/0 (0)]; skin: 2/34 [2 (5.9)/0 (0)/ 0 (0)/0 (0)]; brain: 6/34 [5 (14.7)/1 (2.9)/0 (0)/0 (0)]	At present insufficient scientific evidence indicating superiority/ inferiority of CIRT for skull base tumours
Schulz-Ertner et al. 2007 [43]	Low-grade and intermediate-grade chondro-sarcomas of the skull base	Prospective; case series; enrolment: 1998-2005; n=54; age: 46 (median, range: 6–74)	33 (median, range: 3–84)	Variable[31] (incl. surgery)	-	**OS (3yr):** 98.2% (95% CI: 94.6–100%) **OS (4yr):** 98.2% (95% CI: 94.6–100%) **LCR (3yr):** 96.2% (95% CI: 88.8–100%) **LCR (4yr):** 89.8% (95% CI, 75.6–100%) at 4 years	**Acute[32]:** Mucositis: 3/54 (5%) [Grade 1: 2 (3.7)/Grade 2: NR/ Grade 3: 1 (1.9)/Grade 4: 0]; Parotitis: 1 (1.9) **Late[32]:** Grade ≤ 2: 5 (9.3)/ Grade 3: 1 (1.9)/Grade 4: 0 (0)	
Uhl et al. 2014 [42]	Chordoma (n=20) & Chondrosar-coma (n=5)	Prospective; case series; enrolment: 2010-2012; n=25; age: 50 (median, range: 39–76)	14 (median, range: 2–30)	Variable[31] (incl. surgery, other radiation therapies such as photon or proton irradiation)	-	**LPFS (2yr):** 79.3% (95% CI: NR)	**Acute:** Mucosa: 1/25 (NR/1* (4)/0/0); Hypacusis: 3/25 [NR/3 (12)/0 (0)/0 (0)]; Asymptomatic temporal lobe reaction*: 5/25 [5 (20)/0(0)/0 (0)/0 (0)]: Osteoradionecrosis: 1/25 (NR/NR/1 (4)/0(0)] **Late:** NR	

[31] Before, during or after radiation therapy.

[32] Standardised way of reporting not possible due to the lack of clarification in the study (Grade 0 Grade 1).

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Brain (2 studies								
Mizoe et al. 2007 [68]	Anaplastic astrocytoma (AA; n=16), Glioblastoma multiforme (GBM; n=32)	Prospective; case series; enrolment: 1994-2002; n=48; age: 53 (median, range: 18–78)	NR	Surgery + X-RAY radio-therapy + Chemo-therapy	-	**NR**[33]	**Acute:** Skin 36/48 [27 (56)/9 (19)/0 (0)/0 (0)]; White Blood Cells: 37/48 [6 (13)/11 (23)/17 (35)/3 (6)]; Phatelet: 33/48 [7 (15)/17 (35)/6 (13)/3 (6)]; Brain: 6/48 [6 (13)/0 (0)/0 (0)/0 (0)] **Late:** Skin 1/48 [1 (2)/0 (0)/0 (0)/0 (0)]; Brain RTOG/EORTC: 11/48 [7 (15)/4 (8)/0 (0)/0 (0)]; Brain (MR by LENT/SOMA): 14/48 [10 (21)/4 (8)/0 (0)/0 (0)]	At present insufficient scientific evidence indicating superiority/ inferiority of CIRT for brain tumours
Hasegawa et al. 2012 [69]	Diffuse astrocytoma	Prospective; case series/ dose escalation study, enrolment: 1994-2002; n=14; age: 32.5 (median, range: 18-66)	62 (mean, range: 10-152)	Variable[31] (incl. surgery, salvage treatment, i.e., chemo; RT; OP)	-	**OS (5yr):** 43% (95% CI: NR, SEM: 13%) **OS (10yr):** 36% (95% CI: NR, SEM: 13%) **PFS (5yr):** 36% (95% CI: NR; SE: 13%)	**Acute:** Grade ≤1: 12 (86%); Grade 2: 2 (14%); Grade 3: 0; Grade 4: 0 **Late:** skin: 1/12 [1 (8.3)/0 (0)/0 (0)/0 (0)]; brain: 10/12 [8 (66.7)/2 (16.7)/0 (0)/0 (0)]	
ENT-Tumours (5 studies)								
Jensen et al. 2015 [85]	Malignant Salivary Gland Tumours	Prospective; case series/ dose escalation study[34]; enrolment: 2010-2011; n=54; age: 58 (median, range: 25-74)	42.0 (median, range: 11.4-53.1)	Intensity-modulated radiation therapy (IMRT); variable (incl. surgery)	-	**OS (3yr):** 78.4% (95% CI: NR) **PFS (3yr):** 57.9% (95% CI: NR) **LCR (2yr):** 84.3% (95% CI: NR) **LCR (3yr):** 81.9% (95% CI: NR)	**Acute**[35]: Mucosities: Grade 1: 15 (28%); Grade 2: 21 (40%); Grade 3: 14 (26%) Dermatities: Grade 1: 40 (75%); Grade 2: 2 (8%); Grade 3: 3 (6%). Dysphagia: 18 (34%) grade 1, 10 (19%) grade 2; xerostomia: 28 (53%) grade 1, 6 (11%) grade 2 **Late**[35]: e.g.: Dysphagia: 3 (6%) Grade 2; Xerostomia: 26 (49%) Grade 1, 1 (2%) Grade 2; Hemorrhage: 1 (2%) Grade 4; blood brain barrier changes (CNS necrosis): 3 (6%) grade 1	At present insufficient scientific evidence indicating superiority/ inferiority of CIRT for tumours in the ENT region.

[33] However, the median survival time (MST) was measured: **MST (AA):** 35 months; **MST (GBM):** 17 months.
In addition, the median progression-free survival (m-PFS) was measured in months by 1 study [68]: **m-PFS** (AA): 18; **m-PFS** (GBM): 7 months.

[34] Patients received CIRT as a carbon ion boost.

[35] Numerous other toxicities occurred without grades reported: The study [85] did not report on the grades for numerous observed late radiation morbidities.
The reader is referred to the data extraction table to see those further radiation morbidities with unreported respective grades (Table A-4 in the Appendix).

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Jingu et al. 2012 [86]	Unresectable adult bone and soft-tissue sarcoma of the head and neck	Prospective; case series[36]; enrolment: 2001-2008; n=27; age: 46.2 (mean, range: 17–78)	37 (median, range: 4.1 73.0)	NR	-	**OS (3yr):** 74.1% (95% CI: 57.5–90.6%) **OS (5yr):** 57.6% (95% CI: 33.7–81.4%) **LCR (3yr):** 91.8% (95% CI: 81.0–100%) **LCR (5yr):** 80.4% (95% CI: 57.3–100%)	**Acute:** mucosa: 27/27 [8 (29.6)/17 (63)/ 1 (3.7)/0 (0)]; skin: 25/27 [19 (70.4)/6 (22.2)/0 (0)/0 (0)] **Late:** mucosa: 9/26 [9 (34.6%)/0 (0)/ 0 (0)/0 (0)]; skin: 6/26 [6 (23%)/0 (0)/ 0 (0)/0 (0)]; Brain: 5/26 [5 (19.2)/1 (3.8)/ 0 (0)/0 (0)]; Eye: 2/26 [0 (0)/1 (3.8)/0/ 1 (3.8)]; Bone: 6/26 [1 (3.8)/1 (3.8)/ 4 (15.4)/0 (0)]	*continuation:* Indirect comparisons show: No statistical significant difference on the basis of OS, DFS and LRC between CIRT+ Photon when compared to photons alone in locally advanced adenoid cystic carcinoma of the salivary gland [87].
Mizoe et al. 2012 [33]	Various Head and neck carcinoma	Prospective; case series study, enrolment: 1997-2006; n=236; age: 56.5 (median, range: 16–80)	54 (mean, range: 3-162)	Variable[31] (incl. operation; chemo)	-	**OS (5yr)[37]:** 47% (95% CI: NR, SE: 3.2%) (68% **LCR (5yr)[38]:** 68% (95% CI: NR, SE: 3.5%)	**Acute:** mucosa: 196/223 [91 (41)/81 (36)/24 (11)/0 (0)]; skin: 220/236 [115 (49%)/90 (38%)/15 (6%)/0 (0)] **Late:** mucosa: 47/223 [43 (19)/4 (2)/0 (0)/0 (0)]; skin: 108/236 [101 (43%)/7 (3%)/0 (0)/0 (0%)]	
Shirai et al. 2017 [31]	Non-squamous cell carcinoma of the head and neck	Prospective; case series study, enrolment: 2010-2014; n=35; age: 59 (median, range: 31-77)	39 (median, range: 6–70).	none reported[39]	-	**OS (3yr):** 88% (95% CI: 77–99%) (T2: 100%; T3: 88%; T4: 85%) **PFS (3yr):** 71% (95% CI: 56–86%) at 3 years (T2:100%; T3: 63%; T4: 68%) **LCR (3yr):** 93% (95% CI: 84–100%) at 3 years (T2: 100%; T3: 86%; T4: 94%) **Change in HRQoL: MCS**: n. s. short-term and at 3 months; s. s. mid-term and longer term improvements (baseline: MCS: 40.8 ±1.8; 6 m: 45.9±1.7; at 12 m: 47.3±1.4; at 24 months: 48.4 ±1.6): n.s. ; **PCS**: short-term, mid-term and longer term differences n. s.	**Acute:** mucosa: 23/35 [NR/15 (43%)/8 (23%)/0 (0%)]; skin: 11/35 [NR/11 (31%)/0 (0%)/0 (0%)]; Conjunctivitis: 5/35 [NR/5 (14)/0 (0)/0 (0)]; Dysgeusia: 1/35 [NR/1 (3)/0 (0)/0 (0)] **Late:** mucosa: 12/35 [NR/11 (31%)/1 (3%)/0 (0)]; dermatitis: 0/35 [NR/ 0 (0)/0 (0)/0 (0)]; Conjunctivitis: 1/35 [NR/1 (3%)/0 (0%)/0 (0)]; Dysgeusia: 2/35 [NR/2 (6%)/0 (0)/0 (0)]; Brain necrosis: 2/35 [NR/2 (6%)/0 (0)/0 (0)]; Cataract: 2/35 [NR/0 (0)/2 (6)/0 (0)]: Visual imparment: 5/35 [NR/2 (6%)/1 (3%)/2 (6%)]; Trismus: 3/35 [NR/3 (9%)/0 (0%)/0 (0%)]; Otitis media: 5/35 [NR/5 (14)/0 (0)/0 (0)]; Olfactory nerve disorder: 4/35 [NR/4 (11)/0 (0)/0 (0)]	

[36] The study included a statistical analysis using a historical control. However, the purpose may have primarily been to demonstrate which dose is superior/inferior, since the study used as a comparison included patients receiving CIRT as well.

[37] 68% for adenoidcystic carcinoma, 56% for adenocarcinoma and 35% for malignant melanoma).

[38] 75% for the 85 patients with malignant melanoma, 73% for the 69 patients with adenoid cystic carcinoma, 73% for the 27 patients with adenocarcinoma, 61% for the 13 patients with papillary adenocarcinoma, 61% for the 12 patients with squamous cell carcinoma and 24% for the 14 patients with sarcomas.

[39] Reported are only "no other RT in the head and neck region" and no other chemotherapy 1 month before CIRT (history of chemotherapy: NR).

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Schulz-Ertner et al. 2005 [87]	Locally Advanced Adenoid Cystic Carcinoma of Salivary Gland	Case-control study, enrolment: 1995-2003; n=63 (29 photon + CIRT); age: 56 (median, range: 25–76)	16 (median, range: 2–60)	Photons; Variable[31] [incl. Surgery, salvage therapy (reir-radiation)]	34 pts receiving photon RT	**OS (2yr):** CIRT+photon: 86.6% (95% CI: NR); photon alone: 77.9% (95% CI: NR); diff. n. s. **OS (4yr):** CIRT+photon:75.8% (95% CI: NR); photon alone: 77.9% (95% CI: NR); diff. n. s. **DFS (2yr):** CIRT+photon: 71.5% (95% CI: NR); photon alone: 69.2% (95% CI: NR); diff. n. s. **DFS (4yr):** CIRT+photon: 53% (95% CI: NR); photon alone: 23.6% (95% CI: NR); diff. n. s. **LRC (2yr):** CIRT+photon: 77.5% (95% CI: NR); photon alone: 72.2% (95% CI: NR); diff. n. s. **LRC (4yr):** CIRT+photon: 77.5% (95% CI: NR); photon alone: 24.6% (95% CI: NR); diff. n. s.	CIRT+photon[40]: mucosities: Grade 1: NR; Grade 2: NR; Grade 3: 2 (6.5%); local bacterial infection after RT: 2 (6.5%) Photon alone: mucositis: grade 1: NR; grade 2: NR; grade 3: 11 (32.3%)	

[40] The study may have selectively reported on the toxicities, since many grade 1 and grade 2 toxicities were not reported.

Table 6-2: Summary of the included studies for lung and bone & soft tissue cancer

Study	Indication	Method	FU in months (Unit of central tendency, range)	Additional treatment	Control group	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Lung (6 studies)								
Iwata et al. 2010 [100]	NSCLC: stage IA (n=42) + stage IB (n=38)	Case-control study; enrolment: 2003-2007; n=80 (23 CIRT pts); age: 75 y. o. (54-89)	30.5[41] (median, range: 4-66)	None reported	57 pts receiving	**OS (3yr):**[42] CIRT: 86% (95% CI: NR) vs. PRT1: 90% (95% CI: NR) vs. PRT2: 61% (95% CI: NR) **LCR (3yr):** 86% (95% CI: NR) vs. PRT1: 83% (95% CI: NR) vs. PRT2: 81% (95% CI: NR) CSS and DFS only reported for all 80 pts: CSS (3yr): 86% (95% CI, 77%-95%; IA: 84%; IB: 88%) at 3 years DFS (3yr): 54% (95% CI: 43%-68%; IA: 67%; IB: 46%) at 3 years	**Acute**: NR **Late: CIRT (n=23):** lung: 2/23 [NR/2 (8.7)/0 (0.0)/0 (0.0)]; skin: 2/23 (NR/2 (8.7)/0 (0.0)/0 (0.0)); **PRT (n=57):** lung: 8/57 [NR/7 (12.3)/1 (1.8)/0 (0.0)]; skin: 11/57 (NR/8 (14.0)/3 (5.3%)/0 (0)) Footnote: 23% had a grade 2 rib fracture and Gr. 2 soft tissue AE occurred in 6% 138	At present insufficient scientific evidence indicating superiority/ inferiority of CIRT for NSCLC when compared to conventional radiotherapy. Indirect comparisons show: no statistically significant difference on the basis of OS [99, 100], PFS [99] and LCR [99, 100] between CIRT when compared to PRT for stage IB/IIA NSCLC pts.
Iwata et al. 2013 [99]	NSCLC: stage IB (n=47) + stage IIA (n=23)	Case-control study; enrolment: 2003-2009; n=70 (27 CIRT pts); age: 75 y. o. [median, range: 57-92, for all pts (incl. PRT pts)]	44 (median, range: 4–103)	None reported	43 pts receiving PRT	Outcomes only measured for all 70 pts (CRT and PRT pts) **OS (4yr):** 58% (95% CI: 46%–70%; IB: 53%; IIA: 67%) **PFS (4yr):** 46% (95% CI: 33%–59%; IB: 43%; IIA: 52%), 52%) at 4 years **LCR (4yr):** 75% (95% CI: 63%–86%; IB: 70%; IIA: 84%) at 4 years There were no significant differences between PRT and CIRT (rates: NR).	**Acute:** NR **Late:** lung: 12/70 [NR/10 (14.3)/2 (8.7)/0 (0)]; skin: 15/70 [NR/10 (14.3)/4 (5.7)/1 (1.4)]	
Miyamoto et al. 2007a [102]	NSCLC: stage IA (n=42) + stage IB (n=37)	Prospective; case series study; enrolment: 2000-2003; n=79; age: 74.8 y. o. (average, range: 47–88)	38.6 (median, range: 2.5-72.2)	None reported	-	**OS (5yr):** 45% (95% CI: NR; IA: 62%, IB: 25%) **CSS (5yr):** 68% (95% CI: NR; IA: 87%, IB: 42%) **LCR (5yr):** 90% (95% CI: NR; IA 97%, IB 80%)	**Acute:** lung: 1/79 [0 (0)/1 (1.3)/0 (0)/0 (0)]; skin: 80/80 (75 (93.8)/5 (6.3)/0 (0)/0) **Late:** lung: 70/76 [69 (90,8)/1 (1.3)/0 (0)/0 (0)]; skin: 77/77 [76 (98.7)/1 (1.3)/0 (0)/0 (0)]	

[41] FU includes intervention group and control group (if applicable).

[42] CIRT: 52.6 GyE; PRT1: 80 GyE/20 Fr; PRT2: 60 GyE/10 fr.

Study	Indication	Method	FU in months (Unit of central tendency, range)	Additional treatment	Control group	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Miyamoto et al. 2007b [101]	NSCLC: stage IA (n=29) + stage IB (n=21)	Prospective; case series study; enrolment: 1999-2000; n=50; age: 74.1 y. o. (average, range: 61 -84)	59.2 (median, range: 6.0–83.0)	None reported	-	**OS (5yr):** 50.0% (95% CI: NR; IA 55.2, IB: 42.9) **CSS (5yr):** 75.7% (95% CI: NR; IA: 89.4, IB: 55.1) **LCR (5yr):** 94.7% (95% CI: NR; IA: NR, IB: NR)	**Acute:** lung: 2/51 [1 (1.9)/1 (1.9)/0 (0)/0 (0)]; skin: 51/51 [50 (98)/1 (1.9)/0 (0)/0 (0)] **Late:** lung: 50/51 [48 (94.1)/2 (3.9)/0 (0)/0 (0)]; skin: 51/51 [(49 (96)/1 (1.9)/1 (1.9)/0 (0)]	
Takahashi et al. 2015 [98]	Locally Advanced NSCLC (IIA (n=17) + IIB (n=22) + IIIA (n=23)	Prospective; dose escalation study; case series study; enrolment: 2000-2013; n=62; age: 76 y. o. (median, range: 46-88)	25.2 (1.6 - 157.2)	Variable[43] (incl. Neo-adjuvant therapy, salvage chemo)	-	**OS (1yr):** 77.2% (95% CI: 66.7%-87.7%) **OS (2yr):** 51.9% (95% CI: 39.2%-64.5%) **DFS (2yr):** 35.7% (95% CI: NR). **CSS (2yr):** 71.7% (95% CI: NR) **LCR (1yr):** 96.0% (95% CI: 90.5%-100.0) **LCR (2yr):** 93.1% (95% CI: 85.4%-100.0)	**Acute:** lung: 2/62 [NR/1 (1.6)/1 (1.6)/0 (0)]; skin: 5/62 [NR/5 (8)/0 (0)/0 (0)] **Late:** lung: 3/62 [NR/3 (4.8)/0 (0)/0 (0)]; skin: 1/62 [NR/1 (1.6)/0 (0)/0 (0)]; Oesophagus: 1/62 (2) (NR/0/1/0)	
Yamamoto et al. 2017 [97]	NSCLC: stage stage IA (n=123) + stage IB (n=95)	Prospective; dose escalation study; case series study; enrolment: 2003-2012; n=218; age: 75 (median, range: 46-89)	57.8 (median, range: 1.6-160.7)	None reported	-	**OS (3yr):** 68.3% (95% CI: NR) **OS (5yr):** 49.4% (95% CI: NR) **LCR (3yr):** 77.9% (95% CI: NR) **LCR (5yr):** 72.7% (95% CI: NR)	**Acute:** 215/218 [212 (97.2)/3 (1.3)/0 (0.0)/(0.0)] **Late:** 208/212 [207 (97.6%)/1 (0.4)/0 (0.0)/0 (0.0)]	
Bone & Soft tissue (1 study)								
Sugahara et al. 2012 [126]	Localised primary sarcoma of the extremities (medically inoperable or declined surgery)	Prospective; case series; dose escalation study; enrolment: 2000 -2010; n=17; age: 53 (median; range: 14–87 years)	37 (median; range: 11–97 months)	Variable[43] (incl. surgery, chemo)	-	**OS (3yr)**: 68% (95% CI: 42–86%) **OS (5yr):** 56% (95% CI: 29–80%) **LCR (3yr):** 76% (95% CI: 51–93%) **LCR (5yr):** 76% (95% CI: 51–93%)	**Acute:** Skin: 16/17 [16 (94)/0 (0)/0 (0)/0 (0)] **Late:** 1 pt with grade 2 skin toxicities (5.9%); 4 pts had grade 2 neurological toxicity (23.5%); 3 pts had lower limb tumours; 1 pt had an upper limb tumour; 1 pt with a grade 3 femoral fracture (5,9%)	At present insufficient scientific evidence indicating superiority/ inferiority of CIRT

[43] Before, during or after radiation therapy.

Table 6-3: Summary of the included studies for prostate and gastrointestinal cancer

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Prostate (8 studies)								
Habl et al. 2016 [132]	Localised prostate cancer (Prostatic Neoplasms)	randomised, controlled, parallely assigned, open-label, toxicity study; enrolment: 2012-2013; n=92[44] (45 CIRT pts); age: 68 y. o. (median, range: 50-80)	22.3 (median time, range: NR)	Variable[45] (incl. ADT)	46 pts receiving PRT	Change in HRQoL: **QLQ-C30 & PR25 scores: Comparable between treatment arms: only some subscales were s s. different** (urinary **symptom and bowel symptom score**[46]): **Pre-interventional**: urinary: CIRT: 20 (±14) vs PRT: 19 (±14); bowel: CIRT: 5 (±9) vs PRT: 2 (±4) **Post-interventional**: urinary: 47 (±23) vs. 37 (±17); bowel: 14 (±19) vs. 6 (±10) **Mid-term (at 6 weeks)**: urinary: 34 (±26) vs. 25 (±13); bowel: 11 (±15) vs. 3 (±6); **at 6 months**: urinary: 28 (±24) vs. 20 (±16); bowel: 8 (±15) vs. 4 (±8)	**Acute:** **Proctitis:** CIRT: 6/45 [5 (11.1)/1 (2.2)/0 (0)/0 (0)) vs. PRT: 12/46 [6 (13.0)/4 (8.7)/2 (4.3)/0 (0)]; **Diarrhoea:** CIRT: 25/45 [25 (55.6)/0 (0)/0 (0)/0 (0)] vs. PRT: 32/46 [28 (60.9)/4 (8.7)/0 (0)]; **Cystitis:** CIRT: 19/45 [13 (28.9)/6 (13.3)/0 (0)/0 (0)] vs. PRT: 28/46 [18 (39.1)/10 (21.7)/0 (0)/0 (0)] Toxicity profiles between arms: n. s. **Late: NR**	At present insufficient scientific evidence indicating superiority/ inferiority of CIRT for prostate cancer Direct comparisons show n. s. difference in acute radiation morbidity profiles between CIRT and PRT patients Comparable HRQoL when comparing CIRT to PRT (only some subscales were s. s. different in 1 study: lower urinary and bowel symptoms).
Ishikawa et al. 2015 [133]	Prostate: T1-T3b	Prospective; before-after study; feasibility study; enrolment: 2010-2011; n=76; age: 66 (median, range: 53-88)	51 (median time, range: 8-58)	Variable[45] (incl. Adjuvant/ neoadjuvant ADT)	-	**OS (4yr)**: 97.4% (95% CI: 93.8-100.0%) **BRFS (4yr)**: 94.6% (95% CI: 89.4-99.8%) **Change in HRQoL (SF-8):** slight **s. s. long-term (>6m) of PCS score:** baseline: PCS: 51.14 (1.85); short-term (at 1 m): 51.14 (1.85); mid-term (at 3 m): 50.76 (1.87) (diff. to baseline n. s.); long-term (at 12m): PCS: 47.71 (1.84)* diff. to baseline s. s.; **n. s. diff in MCS**: pre-interventional: MCS: 49.18 (1.96); short-term (at 1m): 48.45 (1.96); mid-term (at 3 m): MCS: 51.63 (1.98); long-term (at 12 m): MCS: 49.75 (1.95).	**Acute:** GU: 50/76 [43 (57)/7 (9)/0 (0)/0 (0)] GI: 1/76 [1 (1)/(0)/0 (0)/0 (0)] **Late:** GU: 40/76 [35 (46)/5 (7)/0 (0)/0 (0)] GI: 7/76 [6 (8)/1 (1)/0 (0)/0 (0)]	
Ishikawa et al. 2006 [139]	Prostate: T1-T3	Prospective; case series, feasibility study; enrolment: 2000-2003; n=175; age: 70 y. o. (median, range: 53–83)	46 (median time, range: NR)	Variable[45] (incl. Neo-adjuvant/ adjuvant hormonal therapy; surgical castration)	-	**OS (4yr):** 91% (95% CI: 87–96%) **CSS (4yr):** 97% (95% CI: 95–100%) at 4 years **bNED (4yr)**: 88% (95% CI: 83–93%) **FACT-G (**1yr): d=1.8 (± 1.1), n. s. (p=0.1) **FACT-P (1yr):** d: 2.6 (±1.4), n. s. (p=0.07)	**Acute:** GU: 57/175 [57 (33)/0 (0)/0 (0)/0 (0)]; GI: 2/175 [2 (1)/0 (0)/0 (0)/0 (0)] **Late:** GU: 117/175 [108 (62)/9 (5)/0 (0)/0 (0)]; GI: 27/175 [23 (13)/4 (2)/0 (0)/0 (0)]	

[44] 92 patients were enrolled in the clinical study; 1 pt dropped out and it was not clear whether this patient received CIRT or PRT (total sample size = 92).

[45] Before, during or after radiation therapy.

[46] Further changes over time for all enrolled pts can be found in the data extraction table. No other QLQ-C30 & PR25 scores subscales between treatment arms were statistically significantly different. The results must be interpreted with caution since the study failed to mention at which time point or time period those differences were statistically different.

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Niko-ghosyan et al. 2011 [136]	inter-mediate risk prostate cancer pts	Prospective; case series study; enrolment 1997-2007; n=14; age: 68 (median, range 55 – 75)	28 (median, range: 12-36)	Variable[45] (incl. Adjuvant hormonal therapy)	-	**OS (actuarial, 3yr)**: 100% (95% CI: NR) **BRFS (3yr):** 86% (95% CI: NR) **Distant metastastes free survival (1yr):** 100%	**Acute:** GU: 12/14 [7 (50)/5 (35,7)/ 0 (0)/(0/0)]; GI: 5/14 [5 (35)/0 (0)/0(0)/0(0)] **Late:** NR	
Maruyama et al. 2017 [134]	inter-mediate and high risk prostate cancer pts	Before-after study; enrolment: 2000-2007; n=417; age: 69 y. o. (median, range: 47–92)	60 (NR, range: NR)	Variable[45] (incl. Adjuvant/ neoadjuvant ADT)	-	**HRQoL: preinterventional**: FACT-G: 84.2 (12.6), FACT-P (baseline): 119.5 (16.9), TOI (baseline): 81.8 (12.0); **Post-interventional:** NR; **short-term:** FACT-G (1 m): 83.7 (12.9), n. s.; FACT-P (1m): 116.2* (17.1), s. s.TOI (1m): 77.8* (12.1), s. s.; **mid-term:** NR; **longer-term**: FACT-G (12 m): 82.6 (13.7), s. s. ; at 36m: 82.4* (14.3), s. s., at 60 m: 82.7*(15.0), s. s.; FACT-P: 12 m: 116.9* (18.4) s. s., 36 months: 117.5 (19.3) s. s., 60 months: 117.6* (20.2) s. s.; TOI: 12 m: 80.3 (13.0) n. s., 36 m: 81.6 (13.7) n. s., 60 m: 81.4 (14.6) n. s.	**Acute: NR** **Late:** **GU**: 58/416 at 12 months [56 (13.5)/2 (0.5)/0 (0.0)/0 (0.0)]; 114/402 at 36 months[108 (26.9)/ 6 (1.5)/0 (0.0)/0 (0.0)]; 77/394 at 60 months [66 (16.8)/10 (2.5)/ 1 (0.3)/0 (0.0)] **GI:** 4/417 at 12 months [4 (1.0)/ 0 (0.0)/0 (0.0)/0 (0.0)]; 32/402 at 36 months [29 (7.2)/3 (0.7)/ 0 (0)/0 (0)]; 18/394 at 60 months [16 (4.1)/2 (0.5)/0 (0.0)/0 (0)]	
Nomiya et al. 2016 [138]	Prostate: T1-T3b	Prospective; multi-institutional observational case series study; enrolment: 2003-2014; n=2,157; age: 67 y. o. (mean, range: 45–92)	29 (NR, range: NR)	Variable[45] (incl. Adjuvant hormonal therapy)	-	**OS (5yr): low risk:** 100% (95% CI: NR); Intermediate risk group: 99% (95% CI: NR) at 5 years; High-risk group: 96% (95% CI: NR) **OS (10yr)**: low risk: 96% (95% CI: NR); intermediate risk group: 78% (95% CI: NR) at 10years; high-risk group: 88% (95% CI: NR) at 10years **CSS (5yr):** low-risk: 100% (95% CI: NR); Intermediate risk: 100% (95% CI: NR); High-risk group: 99% (95% CI: NR) **CSS (10yr)**: low-risk: 100% (95% CI: NR); intermediate risk: 88% (95% CI: NR); high-risk: 98% (95% CI: NR). **BRFS (5yr):** Low-risk group: 92% (95% CI: NR); Intermediate risk: 89% (95% CI: NR); high-risk: 92% (95% CI: NR). **BRFS (10yr):** low risk: 77% (95% CI: NR); intermediate risk: 70% (95% CI: NR); high-risk: 79% (95% CI: NR). **LCR (5yr):** Low-risk: 98% (95% CI: NR); Intermediate risk: 96% (95% CI: NR); High-risk: 99% (95% CI: NR).	**Acute**[47]**:** GU: Grade 0–1: 2037 (94.4%); Grade 2: 119 (5.5%); Grade 3: 1 (0.0%); Grade 4: 0 (0%) GI: Grade 0-1: 2157 (100%); Grade 2: 0 (0%); Grade 3: 0 (0%); Grade 4: 0 (0%) **Late:** GU: Grade 0-1: 1840 (95.4%); Grade 2: 88 (4.6%); Grade 3: 1 (0.0%); Grade 4: 0 (0%) GI: Grade 0-1: 1921 (99.6%); Grade 2: 8 (0.4%); Grade 3: 0 (0%); Grade 4: 0 (0%)	

[47] Standardised way of reporting not possible due to the lack of clarification in the study (grade 0; grade 1).

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Nomiya et al. 2016 *(continuation)*						**LCR (10yr):** Low-risk: 98% (95% CI: NR); intermediate-risk: 95% (95% CI: NR); high-risk: 98% (95% CI: NR)		
Tsuji et al. 2005 [137]	T1 prostate cancer pts	Prospective; dose-escalation, prospective case series study using 3 study protocols; enrolment: 1995-2004; n=201; age: NR	NR	Variable[45] (incl. Neo-adjuvant/ adjuvant hormonal therapy; surgery;)	-	**OS (5yr):** 89.2% (95% CI: NR) **DSS (5yr):** 92.2% (95% CI: NR) **bNED (5yr):** 83.2% (95% CI: NR) **LCR (10yr):** 100% (95% CI: NR) at 5 years	**Acute:** NR **Late:** Bladder/urethra: 95/201 [83 (41.3)/12 (6.0)/0 (0.0)/0 (0.0)]; Rectum: 9/201 [7 (3.5)/2 (1.0)/0 (0.0)/0 (0.0)]	
Wakatsuki et al. 2008 [135]	T1-T3 prostate cancer pts	Prospective; before-after-study focusing on HRQoL; enrolment: 2000-2004; n=194; age: 69 (median, range: 53–83)	NR	Variable[45] (incl. Neo-adjuvant/ adjuvant hormonal therapy; surgery;)	-	HRQoL[48]: patients receiving **CIRT alone (n=25): no significant differences in FACT-G and FACT-P** results when comparing baseline scores to the postinterventional and at 12 months after CIRT: **baseline:** FACT-G: 88.4 (13.2), FACT-P 122.6 (19.8); **postinterventional:** FACT-G: 89.2 (11.3), n. s., FACT-P: 122.4 (16.6) n. s.; **short-term**: NR; **mid-term:** NR; **longer-term (at 12m**): FACT-G: 89.1 (13.6), n.s., FACT-P: 123.8 (20.3). pts receiving **CIRT+ADT (n=125): s. s. lower FACT-G and FACT-P** scores at 12 months when compared to baseline: baseline: FACT-G: 86.1 (19.4), FACT-P: 120.0 (26.1); postinterventional: FACT-G: 85.5 (21.2), FACT-P: 118.0 (28.4); short-term: NR; mid-term: NR; longer-term (12m): FACT-G: 83.9 (21.7),s. s., FACT-P: 116.7 (29.1) s. s.	NR	
Gastrointestinal (2 studies)								
Akutsu et al. 2012 [106]	T1-T3 thoracic esophageal squamous cell carcinoma	Prospective; dose-escalation, case series study; enrolment: 2004-2008; n=31; age: 65.4 y. o. (mean; range: NR, SD: 7.1)	NR	Variable[45] (incl. Surgery)	-	**OS (1yr):** Stage 1: 91%(95% CI: NR); Stage 2: 100% (95% CI: NR); Stage 3: 71% (95% CI: NR) **OS (3yr):** stage 1: 81% (95% CI: NR); stage 2: 85% (95% CI: NR); stage 3: 43%(95% CI: NR)	**Acute:** Oesophagus: 31/31 [19 (61.3)/12 (38.7)/0 (0)/0 (0)]; Skin 27/31 [27 (87.1)/0 (0)/0 (0)/0 (0)]; respiratory: 1/31 [0 (0)/0 (0)/1 (3.2)/0 (0)]; blood: 6/31 [4 (12.9)/2 (6.4)/0 (0)/0 (0)]	

[48] **UCLA-PCI** scores were measured for a fragment of patients: no significant difference between baseline, postinterventional and at 12 months scores. Also, the study reported on the specific FACT-G and FACT-P subscales, but those subscores were not extracted due to the scope of this report.

Study	Indication	Method	FU in months (unit of central tendency, range)	Additional treatment	Control	Efficacy: reported crucial and relevant outcomes	Safety: Radiation morbidities: Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Conclusion
Akutsu et al. 2012 [106] *(continuation)*	(ESCC): T1 (n=12) + T2 (n=8) + T3 (n=11)					**OS (5yr):** stage 1: 61%(95% CI: NR); stage 2: 77%(95% CI: NR) at 5 years; stage 3: 29%(95% CI: NR) **CSS (1yr):** 97% (95% CI: NR); stage 1: 100% (95% CI: NR); stage 2: 100% (95% CI: NR); stage 3: 83% (95% CI: NR) **CSS (3yr):** 79% (95% CI: NR); stage 1: 90% (95% CI: NR); stage 2: 85% (95% CI: NR); stage 3: 50% (95% CI: NR) **CSS (5yr):** 71% (95% CI: NR); stage 1: 90% (95% CI: NR); stage 2: 77% (95% CI: NR); stage 3: 33% (95% CI: NR) **RFS (1yr):** 87% (95% CI: NR); stage 1: 100% (95% CI: NR); stage 2: 92% (95% CI: NR); stage 3: 51% (95% CI: NR) **RFS (3yr):** 62% (95% CI: NR); stage 1: 80%(95% CI: NR) ; stage 2: 69% (95% CI: NR); stage 3: 17% (95% CI: NR) **RFS (5yr):** 62% (95% CI: NR); stage 1: 80% (95% CI: NR); stage 2: 69% (95% CI: NR); stage 3: 17% (95% CI: NR)	**Late:** "No Toxicities including operative complications were observed after the 91st day from the first treatment" (data not shown in the study).	At present insufficient scientific evidence indicating superiority/ inferiority of CIRT for gastro-intestinal tumours
Yamada et al. 2016 [107]	Rectal cancer without distant metastasis	Prospective, dose escalation, case series study; enrolment: 2001-2012; n=184; age: 61.3 y. o. (median, range: 37-79)	42 (median; range: 7-131)	Variable[45] (incl. Primary tumour operation)	-	**OS (3yr)**: 72% (95% CI: 66%-79) **OS (5yr):** 53% (95% CI: 45%-62%) **LCR (5-yr):** 35% (95% CI: 2%-76%)-88% (95% CI: 80%-93%) (dose dependent)	**Acute:** **dose-escalation (n=37):** Skin: 22/37 [20 (54)/2 (5.4)/0 (0)/0 (0)]; GI tract: 1/37 [0 (0)/1 (2.7)/0 (0)/0 (0)] ;Urinary: 1/37 [0 (0)/1 (2.7)/0 (0)/0 (0)] **Phase 2 (n=143):** skin: 117/143 [112 (78.3)/5 (3.5)/0 (0)/0 (0)]; GI: 3/143 [0 (0)/3 (2.1)/0 (0)/0 (0)]; Urinary: 0/143 [0 (0)/0 (0)/0 (0)/0 (0)] **Late:** **dose-escalation (n=37):** Skin: 15/37 [14 (37.8)/1 (2.7)/0 (0)/0 (0)]; GI tract: 1/37 [0 (0)/1 (2.7)/0 (0)/0 (0)]; Urinary: 0/37 [0 (0)/0 (0)/0 (0)/0 (0)] **Phase 2 (n=143): s**kin: 66/143 [64 (44.8)/0 (0)/2 (1.4)/0 (0)]; GI tract: 3/143 [1 (0.6)/1 (0.6)/1 (0.6)/0(0)]; urinary: 2/143 [1 (0.6)/1 (0.6)/0 (0)/0 (0)]	

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Appendix

Data extraction tables of individual studies included for clinical effectiveness and safety

Table A-1: Carbon ion radiotherapy (CIRT): Results from randomised controlled trials

First Author		**Habl [132]**		
Year		2016		
Country		Germany		
Cancer Therapy Centre (s)		Heidelberg Ion Beam Therapy Centre (HIT)		
Sponsor		Heidelberg University		
Sample Size		92[49]		
CIRT Sample		45		
Time Frame of Patient Enrolment		May 2012 and December 2013		
Study Type		Interventional		
Study Design		Randomised, parallel assigned, open-label, pilot study		
The Phase of Clinical Trial		Phase 2		
Intervention		**Hypofractionated irradiation in a raster scan technique with protons and C-ions.** **PRT (n=46):** 20 x 3.3 GyE C-ions (arm A) **CIRT (n=45)**: 20 x 3.3 GyE protons (arm B) **Co-intervention:** Androgen deprivation therapy (ADT): 21 patients received neoadjuvant/adjuvant ADT.		
Control (C)		Historical control , PRT		
Age in years (Unit of Central Tendency, Range)		68 (median, range: 50-80)		
Sex, Female (%) vs. Male (%)		0 (0) vs. 92 (100)		
Population	Indication	**Localised prostate cancer (Prostatic Neoplasms)**		
			Protons (arm A)	C-ions (arm B)
	Initial PSA (ng/mL)	<10 10-20 >20	32 12 2	33 13 0

[49] 1 patient dropped out due to a small intestine loop directly next to the prostate.

First Author		Habl [132]		
	Gleason Score	5 6 7 (3 + 4) 7 (4 + 3) 8 9	0 17 15 11 3 0	2 16 13 11 3 1
	Tumour Stage/TNM Classification	T1a T1b T1c T2a T2b T2c T3a T3b	0 0 37 6 0 3 0 0	1 1 31 8 1 1 2 1
Follow-Up in Months (Unit of Central Tendency; Range)		22.3 (median time, range: NR)		
The Loss to Follow-Up n (%)		NR		
Methods and Statistical Analysis		"The study was designed to answer 2 questions: (1) is the toxicity of carbon ion irradiation (arm B) noninferior compared to that of standard radiation? and (2) is the toxicity of the proton irradiation (arm A) noninferior compared to that of standard radiation? Therefore, the null hypothesis H0: SFR<87.5% versus H1: SFR≥97.5% was tested for each arm with a type I error of aZ10% and a power of at least 90%,calculated using PASS software (Number Cruncher Statistical Systems, Kaysville, UT) and the procedure of Blackwelder for noninferiority trials; the study needed to recruit n=41 patients per arm. To account for dropout, a total of n=92 patients (n=46 per arm) were enrolled". **Statistical Analysis:** 1-sample binomial testing (for SFR hypothesis testing)[50] Descriptive, "exploratory" data analysis (for the analysis of HRQoL) with a statistical significance at p<0.05		

[50] The pilot study [132] tested whether CIRT (and PRT) was non-inferior when compared to standard irradiation (using a threshold created from data of historical controls). Therefore, the secure feasibility rate (SFR) was calculated (no grade ≥3 AE, or minor AE leading to the drop-out of CIRT, within 6 weeks after CIRT) and compared to a threshold of 97.5% using a 1-sample binomial test (H0: SFR<87.5% versus H1: SFR ≥97.5%). However, the test was limited to the secure feasibility and was, therefore, not extracted and described in the qualitative synthesis. It was tested whether the SFR for both arms was higher than or equal to 97.5%. The authors found out that – within the CIRT sample – 0 out of 45 patients (95% CI: 0.0%-7.87%) had any ≥grade 3 toxicity or terminated prematurely. The authors concluded that the therapy is feasible.

First Author		Habl [132]		
Outcomes				
Efficacy				
Overall Survival (OS) in % (95% CI)		-		
Cause-Specific Survival (CSS) in % (95% CI)		-		
Disease-Free Survival (DFS) in % (95% CI)		-		
Recurrence-Free survival(RFS) in %(95% CI)		-		
Progression-Free Survival (PFS)in % (95% CI)		-		
Local Control Rate (LCR) in % (95% CI)		-		
Health-Related Quality of Life (HRQOL)	Results	"Reduced QoL was evident mainly in fatigue, pain, and urinary symptoms during therapy and 6 weeks thereafter. All European Organization for Research and Treatment of Cancer QLQC30 and -PR25 scores improved during follow-up." Comparable HRQoL. Statistically significant differences were only found in urinary and bowel symptoms between **PRT vs. CIRT**. Higher urinary and bowel symptoms scores within the PRT group when compared to the score of the CIRT group at different time points were observed[51]. No other subscores were statistically significantly different between treatment arms. Before (t0) Urinary symptom score (PR25): 20 (±14) vs 19 (±14) Bowel symptom score (PR25): 5 (±9) vs 2 (±4) At the end of CRT/PRT (t1) Urinary symptom score (PR25): 47 (±23) vs 37 (±17) Bowel symptom score (PR25): 14 (±19) vs 6 (±10) At 6 weeks after therapy (t2) Urinary symptom score (PR25): 34 (±26) vs 25 (±13) Bowel symptom score (PR25): 11 (±15) vs 3 (±6) At 6 months after therapy (t3) Urinary symptom score (PR25): 28 (±24) vs 20 (±16) Bowel symptom score (PR25): 8 (±15) vs 4 (±8)		
		Change in HRQOL (s. s. with p<0.05)		
		Dt1-to*	Dt2-to*	Dt3-to*

[51] The authors stated that the differences between treatment groups were statistically significant for urinary symptoms (p=0.026) and bowel symptoms (p=0.046). However, it was not stated in the study on which time point or time period this difference between treatment arms was statistically significant. No other subscales of the QLQC30 and -PR25. The authors wrote that they found "(…) significant differences between proton and carbon ion therapy in urinary and bowel symptoms (urinary P=.026; bowel P=.046). Bowel symptom increases were statistically significant at the end of therapy (t1) compared to initial values but were improved in the sixth week follow-up (t2) (P=.046), indicating a slightly better tolerance for carbon ions" [132]. It remains unclear to the authors, whether this difference is the difference between the scores at different time points (depicted above), or differences of treatment arms of the changes over time (depicted in Change in HRQoL).

First Author		Habl [132]		
		to: Before t1: At the end of PRT/CIRT t2: At 6 weeks after therapy t3: At 6 months after therapy		
	QLQ-C30 tool			
	Global health status	-8 (p<.001)	1 (p=.6)	2 (p=.3)
	Functional scales			
	Physical functioning	-3 (p=.008)	-2 (p=.030)	-2 (p=.2)
	Role functioning	-12 (p=.095)	-9 (p <.001)	-6 (p=.010)
	Emotional functioning	-1 (p=.4)	4 (p=.027)	4 (p=.013)
	Cognitive functioning	-1 (p=.4)	-2 (p=.2)	-2 (p=.034)
	Social functioning	-8 (p<.001)	-3 (p=.3)	-2 (p=.3)
	Symptom scales			
	Fatigue	15 (p<.001)	7 (p<.001)	6 (p<.001)
	Nausea and vomiting	1 (p=.08)	0 (p=1)	1 (p=.1)
	Pain	13 (p<.001)	5 (p=.023)	5 (p=.061)
	Dyspnea	-1 (p=.7)	3 (p=.058)	2 (p=.1)
	Insomnia	3 (p=.5)	2 (p=1)	3 (p=.7)
	Appetite loss	7 (p<.001)	2 (p=.047)	2 (p=.025)
	Constipation	6 (p=.023)	2 (p=.3)	-1 (p=.6)
	Diarrhoea	11 (p<.001)	3 (p=.094)	3 (p=.2)
	Financial difficulties	3 (p=.3)	1 (p=.6)	-2 (p=.3)
	PR25 tool			
	Symptom scales			
	Urinary	23 (p<.001)	10 (p<.001)	5 (p=.071)
	Bowel	6 (p<.001)	3 (p=.007)	2 (p=.045)
	Treatment-related	2 (p=.027)	3 (p=.005)	4 (p=.001)
	Functional scales			
	Sexual activity	-11 (p<.001)	-1 (p=.6)	-1 (p=.7)
	Sexual functioning	-6 (p=.067)	-4 (p=.060)	-3 (p=.3)

First Author		Habl [132]		
Safety				
Toxicity		No statistically significant differences in toxicity profiles between arms were found.		
The incidence of acute adverse events (≤6 months)		CTCAE Version 4.02	Protons (n=46)	C-ions (n=45)
	Proctitis	Grade 1 Grade 2 Grade 3 Grade 4	6 (13.0%) 4 (8.7%) 2 (4.3%)[52] 0 (0%)	5 (11.1%) 1 (2.2%) 0 (0%) 0 (0%)
	Diarrhoea	Grade 1 Grade 2 Grade 3 Grade 4	28 (60.9%) 4 (8.7%) 0 (0%) 0 (0%)	25 (55.6%) 0 (0%) 0 (0%) 0 (0%)
	Cystitis	Grade 1 Grade 2 Grade 3 Grade 4	18 (39.1%) 10 (21.7%) 0 (0%) 0 (0%)	13 (28.9%) 6 (13.3%) 0 (0%) 0 (0%)
	Others		No other toxicities occurred/were reported	No other toxicities occurred/were reported
Late radiation morbidity		NR		

Abbreviations: ADT – Androgen Deprivation Therapy; CIRT – carbon ion radiotherapy; HRQoL – Health-Related Quality of Life; PRT – proton radiotherapy; SFR – Secure Feasibility Rate

[52] The grade 3 toxicities were rectum fistula.

Table A-2: Carbon ion radiotherapy (CIRT) for cancers in the bone and soft tissue region: Results from observational studies

First Author		Sugahara [126]
Year		2012
Country		Japan
Cancer Therapy Center		Heavy Ion Medical Accelerator in Chiba (HIMAC)
Sponsor		Research Project with Heavy Ions at National Institute of Radiological Sciences (NIRS) – Heavy Ion Medical Accelerator in Chiba (HIMAC)
Sample Size		17
CIRT Sample		17
Time Frame of Patient Enrolment		April 2000 – May 2010
Study Type		Observational
Study Design		Prospective case series, dose escalation study
The Phase of Clinical Trial		Phase 1/2
Intervention		**CIRT:** 16 fixed fractions over 4 weeks at a mean dose of 67.9GyE: 52.8 GyE (3.3 GyE/fr.) in 1 pt 64.0 GyE (4.0 GyE/fr.) in 3 pts 70.4 GyE (4.4 GyE/fr.) in 13 pts **Previous treatment:** Patients with recurrent resection (n=8): surgical resection alone in three patients and surgical resection followed by chemotherapy in five pts. Chemotherapy for 10 pts with grade ≥2 tumours more than 4 weeks prior to radiation therapy.
Control		-
Age in Years (Unit of Central Tendency, Range)		53 (median; range: 14–87 years)
Sex, Female (%) vs. Male (%)		5 (29) vs. 12 (71)
Patient Population	Indication	Localised primary sarcoma of the extremities (medically inoperable or declined surgery)
	Histology	**Bone tumour (n = 4)** Osteosarcoma: 3 pts Chondrosarcoma: 1 pt **Soft tissue tumour (n = 13)** Synovial sarcoma: 2 pts Rhabdomyosarcoma: 2 pts Liposarcoma: 2 pts Pleomorphic sarcoma: 2 pts Myxofibrosarcoma: 1 pt Fibrosarcoma: 1 pt Spindle cell sarcoma: 1 pt Leiomyosarcoma: 1 pt ASPS: 1 pt
	Tumour Site	Upper limbs: 4 pts Lower limbs: 13 pts
	Tumour Stage/TNM Classification	**Histological grade:** Bone tumours (n=4): Grade 1: 2 pts Grade 2: 0 pt Grade 3: 2 pts Soft tissue tumour (n = 13) Grade 1: 0 pt Grade 2: 5 pts Grade 3: 8 pts
	Tumour Status	Primary tumours: 9 pts Recurrent tumours: 8 pts
Follow-Up in Months (Unit of Central Tendency; Range)		37 (median; range: 11–97 months)

First Author		Sugahara [126]
The Loss to Follow Up		NR
Methods & Statistical Analysis		"Survival time and local control time were defined as the interval between the initiation of CIRT and the date of death or the date of diagnosis of local failure, respectively. The cut-off date for the analysis was April 30, 2011. The survival and local control curves were generated by the **Kaplan–Meier method** using SPSS software (SPSS Inc., Chicago, IL, USA)".
Outcomes		
Efficacy		
Overall Survival (OS) in % (95% CI)		68% (95% CI: 42–86%) at 3 years 56% (95% CI: 29–80%) at 5 years
Cause-Specific Survival (CSS) in % (95% CI)		-
Disease-Free Survival (DFS) in % (95% CI)		-
Recurrence-Free Survival (RFS) in % (95% CI)		-
Progression-Free Survival (PFS) in % (95% CI)		-
Local Control Rate (LCR) in % (95% CI)		76% (95% CI: 51–93%) at 3 years 76% (95% CI:51–93%) at 5 years
Health-Related Quality of Life (HRQOL)		-
Safety		
Acute Radiation Morbidity	Criteria Classification	CTCAE v3.0 Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))
		Skin: 16/17 [16 (94)/0 (0)/0 (0)/0 (0)] The authors stated that there were no other acute reactions
	Criteria Classification	CTCAE v3.0
Late Radiation Morbidity	Criteria	CTCAE v3.0
		1 pt with Skin toxicities (Grade 2) 4 pts had neurological toxicity (Grade 2) 3 pts had lower limb tumours 1 pt had an upper limb tumour 1 pt with a femoral fracture (Grade 3) The authors stated that there were no other observed severe reactions (grade ≥3).

Abbreviations: CIRT – carbon ion radiotherapy; CTCAE – Common Terminology Criteria for Adverse Events; fr. – fraction; Gr. – Grade; GyE – Gray Equivalent; pt – patient; pts – patients.

Table A-3: Carbon ion radiotherapy (CIRT) for cancers in the brain region: Results from observational studies

First Author	Mizoe [68]	Hasegawa [69]
Year	2007	2012
Country	Japan	Japan
Cancer Therapy Centre	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)
Sponsor	National Institute of Radiologic Sciences-Heavy Ion Medical Accelerator in Chiba (NIRS-HIMAC).	NR
Sample Size	48	14
CIRT Sample	48	14
Time Frame of Patient Enrolment	Between October 1994 and February 2002	Between October 1994 and February 2002
Study Type	Observational	Observational
Study Design	Prospective case series[53]	Dose-escalation, prospective [53]case series study
The Phase of Clinical Trial	Phase 1/2	Phase 1/2
Intervention	X-RAY radiotherapy + Chemotherapy + **CIRT:** X-Ray: 50 GyE/25 fractions/5 weeks CIRT: 16.8-24.8GyE/8 fractions/2 weeks Chemotherapy: ACNU **Co-interventions:** All patients underwent surgical intervention prior to treatment[54]	CIRT: total dose ranging from 46.2-55.2 GyE (24 fractions over 6 weeks) low-dose group (n=9):46.2 GyE for 2 pts and 50.4 GyE for 7 pts high-dose group (n=5): 55.2 GyE **Surgical intervention prior to CIRT:** gross total resection for 1 pt; partial resection for 6 pts biopsy for 5 pts Salvage treatment: Chemotherapy in 2 pts; operation in 6 pts; RT in 1 pt.
Control	-	-
Age in Years (Unit of Central Tendency, Range)	53 (median, range: 18–78)	32.5 (median, range: 18-66)
Sex, Female (%) vs. Male (%)	19 (40) vs. 29 (60)	5 (36) vs. 9 (64)

[53] Enrolment was judged to be prospective.

[54] Extent of surgical resection: Gross total in 8 patients (17%), subtotal in 8 patients (17%), partial in 27 patients (56%), and biopsy in 5 patients (10%).

First Author		Mizoe [68]	Hasegawa [69]
Population	Indication	Anaplastic astrocytoma, Glioblastoma multiforme	Diffuse astrocytoma
	Histology	Anaplastic astrocytoma (AA): 16 (33%) Glioblastoma multiforme (GBM): 32 (67%)	Diffuse astrocytoma
	Tumour site	**Tumour location** Frontal: 22 pts (46%) Temporal: 10 pts (21%) Parietal: 5 pts (10%) Occipital: 6 pts (13%) Others: 5 pts (10%)[55]	**Tumour location:** Frontal: 4 pts Frontal/temporal: 3 pts Temporal: 1 pt Occipital/parietal: 2 pts Others: 4 pts
	Tumour stage (WHO classification)	WHO grade III (anaplastic astrocytoma) + WHO grade IV tumours (glioblastoma multiforme)	Grade II (WHO)
Follow-Up in Months (Unit of Central Tendency; Range)		NR	62 (mean, range: 10-152)
Loss to Follow-Up n (%)		NR	NR
Methods & Statistical Analysis		The **Kaplan-Meier Method** was used for survival rates and local control.[56]	The **Kaplan-Meier Method** was used for survival rates and local control.[56]
Outcomes			
Efficacy			
Overall Survival (OS) in % (95% CI)		NR[57]	43% (95% CI: NR, SEM: 13%) at 5 years 36% (95% CI: NR, SEM: 13%) at 10 years
Cause-Specific Survival (CSS) in % (95% CI)		-	-
Disease-Free Survival in % (95% CI)		-	-
Recurrence-free Survival(RFS) in %(95% CI)		-	-
Progression-Free Survival (PFS)in % (95% CI)		NR[58]	36% (95% CI: NR; SE: 13%) at 5 years low dose: 11% (95% CI: NR; SEM: 11%) high dose: 80% (95% CI: NR; SEM: 18%) at 5 years
Local Control Rate (LCR)in % (95% CI)		-	-
Health-Related Quality of Life (HRQOL)		-	-

[55] Others = thalamus (2 patients), putamen (1 patient), corpus callosum (1 patient), and cerebellum (1 patient).

[56] Further analysis was undertaken in both studies including univariate and multivariate analysis [68]. Predictor variables were, inter alia, age and sex in both studies. However, no comparison to conventional radiotherapy was undertaken. A log-rank test was used to elaborate the differences between survival probabilities [68]/prognostic factors [69].

[57] However, the median survival time (MST) was measured: **MST (AA):** 35 months; **MST (GBM):** 17 months.

[58] The progression free survival (PFS) in % was not reported in this study, but the median progression free survival time was measured: AA: 18 months; GBM: 7 months.

First Author		Mizoe [68]	Hasegawa [69]
Safety			
Acute Radiation Morbidity	Criteria	RTOG	RTOG
		Cases/n [(Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	[59]
	Region Unspecified	-	Grade ≤1: 12 (86%) Grade 2: 2 (14%) Grade 3: 0 Grade 4: 0
	Skin	36/48 [27 (56)/9 (19)/0 (0)/0 (0)]	-
	White Blood Cells	37/48 [6 (13)/11 (23)/17 (35)/3 (6)]	-
	Phatelet	33/48 [7 (15)/17 (35)/6 (13)/3 (6)]	-
	Brain	6/48 [6 (13)/0 (0)/0 (0)/0 (0)]	-
	Others	No other toxicities occurred/were reported.	No other toxicities occurred/were reported.
Late Radiation Morbidity	Criteria	RTOG/EORTC (+LEnT-SOMA)	RTOG/EORTC
		Cases/n [(Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/n [(Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]
	Skin	1/48 [1 (2)/0 (0)/0 (0)/0 (0)]	1/12 [1 (7)/0 (0)/0 (0)/0 (0)]
	Brain	RTOG/EORTC 11/48 [7 (15)/4 (8)/0 (0)/0 (0)] Brain (MR by LENT/SOMA) 14/48 [10 (21)/4 (8)/0 (0)/0 (0)]	10/12[60] [8 (66.7)/2 (16.7)/0 (0)/0 (0)]
	Others	No other toxicities occurred/were reported.	No other toxicities occurred/were reported.

Abbreviations: AA – anaplastic astrocytoma; CIRT – carbon ion radiotherapy; EORTC – European Organisation for Research and Treatment of Cancer; fr. – fraction; GBM – glioblastoma multiforme; Gr. – Grade; GyE – Gray Equivalent; LENT-SOMA – Late Effects Normal Tissue Task Force Subjective, Management Analytic, Objective; pt – patient; pts – patients; RTOG – Radiation Therapy Oncology Group; WHO – World Health Organisation

[59] The format of reporting on acute radiation morbidities Cases/n [(Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)] was not used for this study since the study did not separate grade 0 and grade 1 acute radiation morbidities.

[60] 2 patients dropped out because of local recurrence within 3 months after carbon ion radiotherapy.

Table A-4: Carbon ion radiotherapy (CIRT) for cancers in the Ear-Nose-Throat (ENT) region: Results from observational studies

First Author	Jensen [85]	Jingu [86]	Mizoe [33]	Shirai [31]	Schulz-Ertner [87]
Year	2015	2012	2012	2017	2005
Country	Germany	Japan	Japan	Japan	Germany
Cancer Therapy Centre (s)	Heidelberg Ion Beam Therapy Centre (HIT)	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Gunma University Heavy Ion Medical Center (GHMC)	Heidelberg Ion Beam Therapy Centre
Sponsor	NR	NR	NR	NR	Tumor Center Heidelberg/ Mannheim
Sample Size	54[61]	27	236	35	63
CIRT Sample	54	27	236	35	29
Time Frame of Patient Enrolment	Between July 2010 and August 2011	Between April 2001 and February 2008	Between April 1997 and February 2006	Between June 2010 and November 2014	Between June 1995 and December 2003
Study Type	Observational	Observational	Observational	Observational	Observational
Study Design	Dose-escalation study, prospective case series study	Prospective case series (including a comparative historical control[62])	Prospective Case series	Prospective Case series	Case-control study
The Phase of Clinical Trial	Phase 2	NR	Phase 2	NR	NR
Intervention (I)	Raster Scanned carbon ion boost **(CIB)** immediately followed by Intensity-modulated Radiation Therapy (IMRT) over 7 weeks: CIB (5-6 fractions/week): 24 Gy(RBE) in 3 Gy (RBE) per fraction IMRT(5 fractions/week): 50Gy IMRT in 2 GyE per fraction **Co-intervention:** Prior Surgery in 37 pts	**CIRT** at a total dose of 70.4 GyE/16 fractions (fr) in 4.4 GyE per fraction. **Co-interventions:** NR	**CIRT**: 64.0 GyE/16 fractions/ 4 weeks (57.6 GyE/16 fractions/ 4 weeks in case a wide range of skin was included in the target volume) **Co-intervention:** Post operation (PO) in 52 pts Post chemotherapy (PC) in 27 pts PC+PO in 8 pts	**CIRT:** 64.0 Gy (RBE)/16 fractions for 32 pts (91%) and 57.6 Gy (RBE)/16 fractions for 3 pts (9%) **Co-interventions:** no other RT of head and neck; no chemotherapy at least 1 month before CIRT (history of chemotherapy: NR)	**Photons + CIRT**: A median tumour dose of 72 GyE (54 Gy with photons and 18 GyE with C-ions) for 29 patients. **Co-intervention:** surgery prior to CIRT[63]; salvage therapy in 2 pts (re-irradiation)

[61] 1 person was, but not considered to be, lost to follow-up.

[62] The study included a statistical analysis using a historical control. However, the purpose may have primarily been to demonstrate which dose is superior/inferior, since the study used as a comparison included patients receiving CIRT as well.

[63] Partial resection in 20 patients; biopsy in 7 patients; recurrence in 2 patients: perineural tumour spread in 8 patients.

First Author		Jensen [85]	Jingu [86]	Mizoe [33]	Shirai [31]	Schulz-Ertner [87]
Control (C)		-	-	-	-	Photon RT: FSRT (n=13) or IMRT (n=21) with a median tumour dose of 66 Gy (range: 54.0 –70.4 Gy) for 34 patients **Co-intervention:** surgery[64]
Age in Years (Unit of Central Tendency, Range)		58 (median, range: 25-74)	46.2 (mean, range: 17–78)	56.5 (median, range: 16–80)	59 (median, range: 31-77)	I: 56 (median, range: 25–76); C: 56 (median, range: 22–78)
Sex, Female (%) vs. Male (%)		NR	14 (52) vs. 13(48)	111 (47) vs. 125 (53)	20 (57) vs. 15 (43)	33 (52) vs. 30 (48);
Patient Population	Indication	Malignant Salivary Gland Tumours Resectiom status: **R1**: microscopically in-complete resections (n=20) **R2:** gross residual disease (n=17) inoperable disease (n=16)	Unresectable adult bone and soft-tissue sarcoma of the head and neck	Head and neck carcinoma	Non-squamous cell carcinoma of the head and neck	Locally Advanced Adenoid Cystic Carcinoma of Salivary Gland[65]
	Histology	Adenoid cystic carcinoma: 47 pts (89%) Mucoepidermoid: 3 pts (6%) Adeno: 1 pt (2%) Squamous cell carcinoma: 1 pt (2%) Not otherwise specified: 1 pt (2%)	Osteosarcoma: 9 pts Malignant Fibrous Histiocytoma: 5 pts Hemangioperisarcoma:3 pts Myxoid fibrous sarcoma: 2 pts Leiomyosarcoma: 2 pts Chondrosarcoma: 2 pts PNET: 1 pt Fibrosarcoma: 1 pt Small round cell sarcoma: 1 pt Spindle cell sarcoma: 1 pt	Mucosal malignant melanoma: 85 pts Adenoid cystic carcinoma: 69 pts Adenocarcinoma:27 pts Sarcomas: 14 pts Papillary adenocarcinoma: 13 pts Squamous cell carcinoma: 12 pts Mucoepidermoid carcinoma: 7 pts Myoepithelial carcinoma 3 pts Odontogenic clear cell carcinoma: 1 pt Malignant pleomorphic adenoma: 1 pt Cylindrocelluar carcinoma:1 pt Undifferentiated carcinoma: 1 pt Sebaceous carcinoma: 1 pt Acinic cell carcinoma: 1 pt	Adenoid cystic carcinoma: 21 pts (60%) Olfactory neuroblastoma: 5 pts (14%) Mucoepidermoid carcinoma: 4 pts (11%) Adenocarcinoma: 2 pts (6%) Others: 3 pts (9%)	12 pts diagnosed with the cribriform subtype, 1 pt was diagnosed with a tubular tumour, 7 pts had solid tumours, 12 pts presented with tumours of mixed histology, and 31 pts with no histologic subclassification performed

[64] **Resection status:** Partial resection in 17 patients; biopsy in 16 patients; recurrence in 1 patient; perineural tumour spread in 6 patients.

[65] Only patients were considered with "macroscopic tumour residual after resection, inoperable tumors, or recurrent tumors" [87].

First Author		Jensen [85]	Jingu [86]	Mizoe [33]	Shirai [31]	Schulz-Ertner [87]
	Tumour Site	The base of skull 2 pts (4%) External auditory canal 1 pt (2%) Lacrimal gland/lacrimal duct 3 pts (6%) Maxilla 1 pt (2%) Nasopharynx 5 pts (9%) Palate 7 pts (13%) Paranasal sinus 18 pts (34%) Parotid 7 pts (13%) Petrous bone 1 pt (2%) Submandibular gland 8 pts (15%)	Nasal and paranasal: 11 pts Maxillary bone: 8 pts Mandibular bone: 2 pts Skull base: 2 pts Parapharyngeal space: 1 pt Temporal: 1 pt Frontal bone: 1 pt Parotid gland: 1 pt	Paranasal sinus: 60 pts Nasal cavity: 56 pts Salivary gland: 30 pts Oral cavity: 26 pts Pharynx: 23 pts Orbita: 20 pts Thyroid: 11 pts Ears: 5 pts Temporal bone: 2 pts Maxillar bone: 2 pts Mandibular bone: 1 pt	Maxillary sinus: 9 pts (26%) Nasal cavity: 9 pts (26%) Parotid gland: 6 pts (17%) Oral cavity: 5 pts (14%) Pharynx: 4 pts (11%) External auditory canal: 2 pts (6%)	-
	Tumour Stage	Tumour stage T1: 1 pt (2%) T2: 7 pts (13%) T3: 12 pts (23%) T4a: 12 pts (23%) T4b: 17 pts (32%) T4c: 1 pt (2%) T4 unspecified: 1 pt (2%) Unknown: 1 pt (2%) No TNM: 1 pt (2%) N+: 6 pts (11%) M1: 7 pts (13%)	Histopathological grade (UICC-2002) Grade 1–2 (low): 16 pts Grade 3–4 (high): 10 pts Unknown: 1 pt	Tumour stage for 149 (63%)* T1/N0: 3 pts T2/N0: 22 pts T3/N0: 25 pts; T3/N1: 2 pts; T3/N2: 2 pts; T4/N0: 79 pts; T4/N1: 12 pts; T4/N2: 4 pts	Tumour stage T2/N0: 5 pts (14%) T3/N0: 8 pts (23%) T4/N0: 22 pts (63%)	**T** (tumour) All but 3 patients had tumours infiltrating the skull base (T4), and the remaining 3 patients had **T**3 tumours infiltrating the orbits. **N** (node status): Positive lymph **n**ode status: I: 2/29 C: 5/34 **M**1: I: 2/29 C: 3/34
Follow-Up in Months (Unit of Central Tendency; Range)		42.0 (median, range: 11.4-53.1)	37.0 (median, range: 4.1-73.0)	54 (mean, range: 3-162)	39 (median, range: 6–70).	I: 16 (median, range: 2–60), C: 24 (median, range: 2–92)
The Loss to Follow-Up n (%)		NR	NR	NR	NR	NR
Methods		The **Kaplan-Meier Method** was used for survival rates and local control. "Log-rank test; Chi-square and Kruskal-Wallis tests were used to compare groups for nominal and ordinal variables. All tests were 2-tailed (level of significance: <0.05)"	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05) HRQoL: SF-8	The **Kaplan-Meier product-limit Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)

First Author	Jensen [85]	Jingu [86]	Mizoe [33]	Shirai [31]	Schulz-Ertner [87]
Outcomes					
Efficacy					
Overall Survival (OS) in % (95% CI)	78.4% (95% CI: NR) at 3 years R1: 79.2% (95% CI: NR) at 3 years R2: 87.5% (95% CI: NR) at 3 years inoperable: 74.5% (95% CI: NR) at 3 years Difference: n. s.	74.1% (95% CI: 57.5–90.6%) at 3 years 57.6% (95% CI: 33.7–81.4%) at 5 years	47% (95% CI: NR, SE: 3.2%) at 5 years (68% for adenoid cystic carcinoma, 56% for adenocarcinoma and 35% for malignant melanoma)	88% (95% CI: 77–99%) at 3 years (T2: 100%; T3: 88%; T4: 85%) Maxillary sinus/nasal cavity (n=18): 88% Oral cavity/pharynx (n=9): 100% Parotid gland (n=6): 100% External auditory canal (n=2): 0%	I: 86.6% at 2 years and 75.8% at 4 years C: 77.9% at 2 years and 77.9% at 4 years Diff.: n. s. (p=0.64; log-rank test)
Cause-Specific Survival (CSS)	-	-	-	-	-
Disease-Free Survival in % (95% CI)	-	-	-	-	I: 71.5% at 2 years and 53% at 4 years C: 69.2% at 2 years and 23.6% at 4 years Diff.: n. s. (p= 0.19; log-rank test)
Recurrence-Free Survival(RFS) in %(95% CI)	-	-	-	-	-
Progression-Free Survival (PFS)	57.9% (95% CI: NR) at 3 years (median time: 42.3 months) R1: 64.6% (95% CI: NR) at 3 years R2: 58.8% (95% CI: NR) at 3 years inoperable: 49.2% (95% CI: NR) at 3 years Difference: n. s.	-	-	71% (95% CI: 56–86%) at 3 years (T2:100%; T3: 63%; T4: 68%)	-
Local Control Rate (LCR)	84.3% (95% CI: NR) at 2 years 81.9% (95% CI: NR) at 3 years R1:89.7% (95% CI: NR) at 3 years R2: 86.9% (95% CI: NR) at 3 years inoperable: 75.0% (95% CI: NR) at 3 years Difference: n. s.	91.8% (95% CI: 81.0–100%) at 3 years 80.4% (95% CI: 57.3–100%) at 5 years	68% (95% CI: NR, SE: 3.5%) at 5 years 75% for the 85 pts with malignant melanoma, 73% for the 69 pts with adenoid cystic carcinoma, 73% for the 27 pts with adenocarcinoma, 61% for the 13 pts with papillary adenocarcinoma,61% for the 12 pts with squamous cell carcinoma and 24% for the 14 pts with sarcomas.	93% (95% CI: 84–100%) at 3 years (T2: 100%; T3: 86%; T4: 94%) Maxillary sinus/nasal cavity (n=18): 93% Oral cavity/pharynx (n=9): 100% Parotid gland (n=6): 83% External auditory canal (n=2): –	Locoregional control (LRC): I: 77.5% at 2 years and 77.5% at 4 years C: 72.2% at 2 years and 24.6% at 4 years Diff.: n. s. (p=0.08; log-rank test)

First Author		Jensen [85]	Jingu [86]	Mizoe [33]	Shirai [31]	Schulz-Ertner [87]
Health-Related Quality of Life (HRQOL)	Pre-Interventional	-	-	-	SF-8 Before CIRT: PCS: 46.9 (1.7) MCS: 40.8 (1.8)	-
	Postinterventional	-	-	-	NR	-
	Short-Term(<6 weeks)	-	-	-	1 month: PCS: 42.3 (1.6) (n. s.) MCS: 41.1 (1.6) (n. s.)	-
	Mid-Term (>6weeks- ≤ 6 months)	-	-	-	3 months: PCS: 46.1 (1.3) (n. s.) MCS: 45.0 (1.6) (n. s.) 6 months: PCS: 46.0 (1.2) (n. s.) MCS: 45.9 (1.7) (s. s.)[66]	
	Longer Term (>6 months): Mean Score (Standard Deviation)				12 months: PCS: 46.9 (1.3) MCS: 47.3 (1.4) (s. s.). 24 months: PCS: 48.4 (1.2) MCS: 48.4 (1.6) (s. s.)	-
Safety						
Acute Radiation Morbidity	Criteria	CTCAE version 3	National Cancer Institute-Common Toxicity Criteria, version 2.0	RTOG	CTCAE version 4.0	CTCAE version 3
			Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Cases/n [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	Cases/n [(Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	
	Mucosa	At completion: Mucosities[67]: Grade 1: 15 (28%) Grade 2: 21 (40%) Grade 3: 14 (26%)	Mucous membrane: 27/27 [8 (29.6)/17 (63)/1 (3.7)/ 0 (0)]	196/223 [91 (41)/81 (36)/24 (11)/ 0 (0)]	Mucositis: 23/35 [NR/15 (43%)/8 (23%)/ 0 (0%)]	I: Mucosities Grade 1: NR Grade 2: NR Grade 3: 2 (6.5%) local bacterial infection after RT: 2 (6.5%)

[66] Score is statistically significantly different to baseline score, with $p<0.05$. The author's interpretation of this difference was by stating that the patients possibly had fear and anxiety due to the treatment before the therapy being improved after the therapy. No analysis including fear or anxiety as variables in their analysis was undertaken [31].

[67] The study [85] also measured on acute radiation morbidities **after 6-8 weeks** with selectively reporting on the grade of the morbidities: Mucositis (grade 1):4 (8%); hyperpigmentation (grade 1): 9 (17%); dysphagia (grade 1): 6 (11%) weight loss: 8 (15%); xerostomia (grade 1): 37 (70%); xerostomia (grade 2): 6 (11%); Impairment of taste 47 (89%); middle ear effusion: 12 (23%); otitis: 2 (4%);hearing impairment: 3 (6%); trismus: 9 (17%); facial nerve paralysis: 1 (2%); xerophthalmia: 5 (9%); epiphora: 3 (6%); keratitis: 1 (2%); conjunctivitis: 2 (4%); lymphedema: 10 (19%); tissue defect (Tx response): 1 (2%).

First Author		Jensen [85]	Jingu [86]	Mizoe [33]	Shirai [31]	Schulz-Ertner [87]
	Mucosa *(continuation)*					C: Mucosities Grade 0: NR Grade 1: NR Grade 2: NR Grade 3: 11 (32.3%)
	Skin	Dermatities Grade 1: 40 (75%) Grade 2: 8(15%) Grade 3: 3 (6%)	25/27 [19 (70.4)/6 (22.2)/0 (0)/ 0 (0)]	220/236 [115 (49%)/90 (38%)/ 15 (6%)/0 (0)]	11/35 [NR/11 (31%)/0 (0%)/ 0 (0%)]	NR
	Others	At the completion of CIRT[67]: Epitheliolysis: 11 (21%); **Dysphagia: 18 (34%)** **Grade 1, 10 (19%) Grade 2;** Dysphagia preexistent/ postoperatively: 4 (8%); Weight loss: 41 (77%); feeding tube (PEG): 4 (8%); **Xerostomia: 28 (53%)** **Grade 1 and 6 (11%) Grade 2;** Loss of taste: 47 (89%); Middle ear effusion: 16 (30%); Otitis: 1 (2%); Hearing impairment: 3 (6%); Trismus: 13 (25%); Trismus postoperatively/ due to tumour: 10 (19%); Facial nerve paralysis: 1 (2%); Facial nerve paralysis postoperatively: 1 (2%); Xerophthalmia: 5 (9%); Conjunctivitis 2: (4%); Paresthesia: 3 (6%); Paresthesia postoperatively: 1 (2%) Lymphedema: 2 (4%) Rhinitis: 1 (2%)	-	-	Conjunctivitis 5/35 [NR/5 (14)/0 (0)/0 (0)] Dysgeusia 1/35 [NR/1 (3)/0 (0)/0 (0)]	NR

First Author		Jensen [85]	Jingu [86]	Mizoe [33]	Shirai [31]	Schulz-Ertner [87]
Late Radiation Morbidity	Criteria	CTCAE version 3[68]	RTOG/EORTC or LENT-SOMA	RTOG/EORTC	CTCAE version 4.0	CTCAE version 3
			Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%))
	Mucosa	-	**Mucous membrane** 9/26 [9 (34.6%)/0 (0)/ 0 (0)/0 (0)]	47/223 [43 (19)/4 (2)/0 (0)/ 0 (0)]	**Mucositis** 12/35 [NR/11 (31%)/1 (3%)/ 0 (0)]	NR
	Skin	-	6/26 [6 (23%)/0 (0)/0 (0)/ 0 (0)]	108/236 [101 (43%)/7 (3%)/ 0 (0)/0 (0%)]	**Dermatitis** 0/35 [NR/0 (0)/0 (0)/0 (0)]	NR
	Others	**Dysphagia: 3 (6%) Grade 2;** Odynophagia: 3 (6%); **Xerostomia: 26 (49%) Grade 1, 1 (2%) Grade 2;** Impairment of taste: 5 (9%); Middle ear effusion: 6 (11%); Hearing impairment: 13 (25%); Hearing loss: 1 (2%); Vestibular problems: 2 (4%); Trismus: 8 (15%); Facial nerve paralysis: 1 (2%); Anosmia: 1 (2%); Xerophthalmia: 2 (4%); Epiphora: 4 (8%); Lacrimal duct stenosis: 3 (6%); Enophthalmos: 1 (2%); Paresthesia: 1 (2%); Fatigue: 2 (4%); **Blood brain barrier changes (CNS necrosis) 3 (6%) Grade 1;** Meningitis: 1 (2%); Loss of teeth: 1 (2%); Osteoradionecrosis: 2 (4%); Lymphedema: 5 (9%); Tissue defect: 2 (4); Tissue necrosis: 1 (2%) ; Impaired healing: 2 (4%); **Hemorrhage: 1 (2%) Grade 4;** Rhinitis sicca: 2 (4%); Pain: 3 (6%)	Brain 5/26 [5 (19.2)/1 (3.8)/0 (0)/ 0 (0)] Eye 2/26 [0 (0)/1 (3.8)/0/1 (3.8)] Bone 6/26 [1 (3.8)/1 (3.8)/ 4 (15.4)/0 (0)] No other toxicities occurred/were reported	No other toxicities occurred/were reported	Conjunctivitis 1/35 [NR/1 (3%)/0 (0%)/0 (0)] Dysgeusia 2/35 [NR/2 (6%)/0 (0)/0 (0)] Brain necrosis 2/35 [NR/2 (6%)/0 (0)/0 (0)] Cataract 2/35 [NR/0 (0)/2 (6)/0 (0)] Visual impairment 5/35 [NR/2 (6%)/1 (3%)/2 (6%)] Trismus 3/35 [NR/3 (9%)/0 (0%)/ 0 (0%)] Otitis media 5/35 [NR/5 (14)/0 (0)/0 (0)] Olfactory nerve disorder 4/35 [NR/4 (11)/0 (0)/0 (0)] No other toxicities occurred/were reported	I: 1/NR (NR/NR/NR/1/NR) No other toxicities were reported

Abbreviations: CIB – Carbon Ion Boost; CIRT – Carbon Ion Radiotherapy; CTCAE – Common Terminology Criteria for Adverse Events; EORTC – European Organisation for Research and Treatment of Cancer; fr. – fraction; Gr. – Grade; GyE – Gray Equivalent; LENT-SOMA – Late Effects Normal Tissue Task Force Subjective, Objective, Management Analytic; n.s. – not statistically significant; pt – patient; pts – patients; RTOG – Radiation Therapy Oncology Group; s. s. – statistically significant; v. – version.

[68] The authors did not stringently report on the grade of the morbidities. The reader is referred to the "others" section of this table below.

Table A-5: Carbon ion radiotherapy (CIRT) for cancers in the gastrointestinal (GI) region: Results from observational studies

First Author		Akutsu [106]	Yamada [107]
Year		2012	2016
Country		Japan	Japan
Cancer Therapy Centre		Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)
Sponsor		Research Project with Heavy Ions at NIRS-HIMAC and 21st Century COE Project of Japanese Ministry of Education, Culture Sports, Science and Technology for Chiba University	Research Project with Heavy Ions of the National Institute of Radiological Sciences in Japan.
Sample Size		31	184[69]
CIRT Sample		31	184
Time Frame of Patient Enrolment		Between July 2004 and June 2008	From April 2001 to August 2012
Study Type		Observational	Observational
Study Design		Prospective, dose escalation, case series study	Prospective, dose escalation, case series & nonrandomised, open-label, single-centre, case series study
The Phase of Clinical Trial		Phase 1/2	Phase 1 & Phase 2
Intervention		**Neoadjuvant CIRT**: 8 fractions over 2 weeks Dose escalation: from 28.8 GyE in 5% increments up to 36.8 GyE when no severe adverse events (CTCAE grade3 and more) were observed. **Co-intervention**: surgery	**CIRT**: 16 fractions in 4 weeks Dose escalation (n=37): 67.2 to 73.6 Gy (RBE); RBE-weighted absorbed dose: 4.2 to 4.6 Gy (RBE)/fraction Phase 2 (n=143) trial: 70.4 GyE and 73.6 GyE for 4 and 139 patients respectively **Co-intervention:** primary tumour operation before CIRT[70]
Control (C)		-	-
Age in Years (Unit of Central Tendency, Range)		65.4 (mean; range: NR, SD: 7.1)	61.3 (median, range: 37-79)
Sex, Female (%) vs. Male (%)		6 (19) vs. 25 (81)	127 (71) vs. 53 (29)
Population	Indication	Thoracic esophageal squamous cell carcinoma (ESCC)	Locally recurrent rectal cancer
	Histology	Well-differentiated SCC: 3 Moderately differentiated SCC: 22 Poorly differentiated SCC: 4 Unclear: 2	Well-differentiated adenocarcinoma: 58 (32%) Moderate: 111 (62%) Poor: 4 (2%); Mucinous: 6 (3%) Adenosquamous: 1 (1%)
	Tumour Site	Upper thoracic: 3 Middle thoracic: 18 Lower thoracic: 10	Presacral: 70 (39%) Sidewall: 77 (43%) Perineal: 28 (16%) Perianastomosis: 5 (3%)

[69] 184 pts with 190 lesions and the study excluded 4 patients due to pretreatmeant subarachnoid or distant metastasis..

[70] According to the patient characteristics table provided, some information on previous treatments could have been retrieved: abdominoperineal excision in 92 pts (51%) pts; low anterior resection in 83 pts (46%); Hartmann's resection in 3 pts (2%); "other" in 3 pts (2%).

First Author		Akutsu [106]	Yamada [107]
	Tumour Stage/TNM Classification	**T category** T1: 12 T2: 8 T3: 11 **N category** No: 22 N1: 8 N2: 1 N3: 0 **Stage grouping** Stage I: 10 Stage II: 14 Stage III: 7	**Tumour stage/TNM classification**: NR **Tumour size (in cm)**: Range: 1.0-14.0 Average: 3.4 (SD: 1.4)
Follow-Up in Months (Unit of Central Tendency; Range)		NR	42 (median; range: 7-131)
The Loss to Follow-Up n (%)		NR	NR
Outcomes			
Efficacy			
Overall Survival (OS) in % (95% CI)		**All patients: NR** **Stage 1 cases:** 91%(95% CI: NR) at 1 year 81% (95% CI: NR) at 3 years 61%(95% CI: NR) at 5 years **Stage 2 cases:** 100%(95% CI: NR)at 1 year 85% (95% CI: NR) at 3 years 77%(95% CI: NR) at 5 years **Stage 3 cases:** 71% (95% CI: NR)at 1 year 43%(95% CI: NR) at 3 years 29%(95% CI: NR) at 5 years	All patients: 72% (95% CI: 66%-79%) at 3 years 53% (95% CI: 45%-62%) at 5 years Within the phase 2 study at 73.6 GyE (n=139): 91% (95% CI: NR) at 2 years 59% (95% CI: 50%-68%) at 5 years Within the dose-escalation part of the study (n=37): 20%-78% (depending on the dose of CIRT)
Cause-Specific Survival (CSS) in % (95% CI)		**All patients:** 97% (95% CI: NR) at 1 year 79% (95% CI: NR) at 3 years 71% (95% CI: NR) at 5 years **Stage 1 cases:** 100% (95% CI: NR) at 1 year 90% (95% CI: NR) at 3 years 90% (95% CI: NR) at 5 years **Stage 2 cases:** 100% (95% CI: NR) at 1 year 85% (95% CI: NR) at 3 years 77% (95% CI: NR) at 5 years	-

First Author	Akutsu [106]	Yamada [107]
Cause-Specific Survival (CSS) in % (95% CI) *(continuation)*	**Stage 3 cases:** 83% (95% CI: NR) at 1 year 50% (95% CI: NR) at 3 years 33% (95% CI: NR) at 5 years	
Disease-Free Survival (DFS) in % (95% CI)	-	-
Recurrence-Free Survival (RFS)/ Recurrence-Free Survival (RFS) in % (95% CI)	**All patients:** 87% (95% CI: NR) at 1 year 62% (95% CI: NR) at 3 years 62% (95% CI: NR) at 5 years **Stage 1 cases:** 100% (95% CI: NR) at 1 year 80%(95% CI: NR) at 3 years 80% (95% CI: NR) at 5 years **Stage 2 cases:** 92% (95% CI: NR) at 1 year 69% (95% CI: NR) at 3 years 69% (95% CI: NR) at 5 years **Stage 3 cases:** 51% (95% CI: NR) at 1 year 17% (95% CI: NR) at 3 years 17% (95% CI: NR) at 5 years	-
Progression-Free Survival (PFS)in % (95% CI)	-	-
Local Control Rate (LCR)in % (95% CI)	-	Overall 5-year LCR: 35% for 10 pts at 67.2 Gy (RBE) (95% CI: 2%-76%), 77% for 19 pts at 70.4 Gy (RBE) (95% CI: 49%-91%) 88% for 151 pts at 73.6 Gy (RBE) (95% CI: 80%-93%)
Health-Related Quality of Life (HRQOL)	-	-

First Author		Akutsu [106]	Yamada [107]
Safety			
Acute Radiation Morbidity	Criteria	CTCAE v. 3.0	CTCAE v. 3.0
		Cases/n [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/n [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]
		Toxicities[71] including operative complications were observed within 90 days after the onset of the first treatment **Oesophagus 31/31** [19 (61.3)/12 (38.7)/0 (0)/0 (0)] **Skin 27/31** [27 (87.1)/0 (0)/0 (0)/0 (0)] **Respiratory 1/31** [0 (0)/0 (0)/1 (3.2)/0 (0)] **Blood 6/31** [4 (12.9)/2 (6.4)/0 (0)/0 (0)]	Within the **Phase 2 Study (n=143)** using the NCI-CTC ≤ 3 months **Skin:** 117/143 [112 (78.3)/5 (3.5)/0 (0)/0 (0)] **GI:** 3/143 [0 (0)/3 (2.1)/0 (0)/0 (0)] **Urinary:** 0/143 [0 (0)/0 (0)/0 (0)/0 (0)] **Within the Phase 1/2 (n=37) part of the study** **Skin:** 22/37 [20 (54)/2 (5.4)/0 (0)/0 (0)] **GI tract:** 1/37 [0 (0)/1 (2.7)/0 (0)/0 (0)] **Urinary:** 0/37 [0 (0)/0 (0)/0 (0)/0 (0)]
Late Radiation Morbidity	Criteria	CTCAE v. 3.0	RTOG/EORTC
		Cases/n [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/n [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]
		No Toxicities including operative complications were observed after the 91st day from the first treatment (data not shown in the study).	Within the **Phase 2 Study (n=143)** **Skin:** 66/143 [64 (44.8)/0 (0)/2 (1.4)/0 (0)] **GI tract:** 3/143 [1 (0.6)/1 (0.6)/1 (0.6)/0(0)] **Urinary:** 2/143 [1 (0.6)/1 (0.6)/0 (0)/0 (0)] **Phase 1/2 (n=37)** Skin: 15/37 [14 (37.8)/1 (2.7)/0 (0)/0 (0)] GI tract: 1/37 [0 (0)/1 (2.7)/0 (0)/0 (0)] Urinary: 0/37 [0 (0)/0 (0)/0 (0)/0 (0)]

Abbreviations: CIRT – Carbon Ion Radiotherapy; CTCAE – Common Terminology Criteria for Adverse Events; fr. – fraction; GI – gastrointestinal; Gr. – Grade; GyE – Gray Equivalent; LCR – Local Control Rate; n.s. – not statistically significant; pt – patient pts – patients; RBE – relative biological effectiveness; RTOG – Radiation Therapy Oncology Group; s. s. – statistically significant; TNM – Tumour Node Metastases; v. – version.

[71] The authors did not explicitly report on grade 4 radiation morbidities. It was assumed that no grade 4 radiation morbidities occurred since the authors wrote that only 1 radiation morbidity "exceeded" grade 3. It was assumed that the respiratory grade 3 radiation morbiditiy was hereby meant by the authors.

Table A-6: Carbon ion radiotherapy (CIRT) for cancers in the lung region: Results from observational studies

First Author	Iwata[100]	Iwata[99]	Miyamoto[102]	Miyamoto[101]	Takahashi [98]	Yamamoto[97]
Year	2010	2013	2007a	2007b	2015	2017
Country	Japan	Japan	Japan	Japan	Japan	Japan
Cancer Therapy Center	Hyogo Ion Beam Medical Center (HIBMC)	Hyogo Ion Beam Medical Center (HIBMC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)
Sponsor	Japanese Ministry of Education, Culture, Sports, Science, and Technology	NR	National Institute of Radiological Sciences (NIRS) under its research project on heavy ions at NIRS-HIMAC	National Institute of Radiological Sciences (NIRS) under its research project on heavy ions at NIRS-HIMAC	NR	NIRS
Sample Size	80	70	79[72]	50[73]	62	218
CIRT Sample	23	27	79	50	62	218
Time Frame of Patient Enrolment	April 2003 to April 2007	April 2003 to December 2009	From December 2000 to November 2003	April 1999 and December 2000	May 2000 to February 2013	Between April 2003 and February 2012
Study Type	Observational	Observational	Observational	Observational	Observational	Observational
Study Design	Case-control study	Case-control study	Prospective case series[74]	Prospective Case series[74]	Dose-escalation and prospective case series study	Dose-escalation prospective case series study
Phase of Clinical Trial	NR	NR	Phase 2	Phase 1/2	Phase 1/2	Phase 1/2
Intervention (I)	**CIRT:** 52.8 GyE/4 Fr. for 23 pts **Co-intervention:** none reported	**CIRT:** 52.8 GyE/4 fr. for 16 pts; 66 GyE/10 fr. for 8 pts; 68.4 GyE/9 fr. for 3 pts **Co-intervention:** none reported	**CIRT** in four fractions during 1 week: 52.8 GyE/4fr for stage IA NSCLC 60.0 GyE/4fr for stage IB NSCLC **Co-intervention:** none reported	**CIRT**: A fixed total dose of 72 GyE/9fr at a fraction dose of 8GyE over 3 weeks **Co-intervention:** none reported	**CIRT:** Phase 1 (dose escalation, n=36): 68 to 72 GyE and then to 76 GyE, using 16 fractions over 4 weeks Phase 2 (n=26): 72 GyE using 16 fractions over 4 weeks **Co-intervention:** Neoadjuvant therapy (not within 1 month of CIRT) and salvage chemotherapy after recurrence/ metastases, with 5 and 3 patients undergoing those therapies respectively.	**CIRT** (single-fraction): 28-50GyE **Co-intervention:** none reported

[72] 79 patients with 80 primary lesions.

[73] 1 patient died before the start of CIRT. 50 patients with 51 lesions.

[74] Enrolment judged to be prospective.

First Author		Iwata[100]	Iwata[99]	Miyamoto[102]	Miyamoto[101]	Takahashi [98]	Yamamoto[97]
Control (C)		**PRT:** 80 GyE/20 Fr. for 20 pts and 60 GyE/10 Fr. for 37 pts **Co-intervention:** none reported	**PRT:** 70.2GyE/26 fr. for 1 pts; 66 GyE/10 fr. for 8 pts; 60 GyE/10 fr. for 20 pts; 80 GyE/20 fr. for 14 pts **Co-intervention:** none reported	-	-	-	-
Age in Years (Unit of Central Tendency, Range)		All: 76 (median, range: 48-89)[75] CIRT-sample: 75 (54-89)	75 (median, range: 57-92)[76]	74.8 (average, range: 47–88)	74.1 (average, range: 61 -84)	76 (median, range: 46-88)	75 (median, range: 46-89)
Sex, Female (%) vs. Male (%)		23 (28.8) vs. 57 (71.2)	19 (27.1) vs. 51 (72.9)	25 (31.6) vs. 54 (68.4)	12 (24) vs. 38 (76)	14 (23) vs. 48 (77)	61 (28) vs. 157 (72)
Patient Population	Indication	Non-Small-Cell Lung Cancer (NSCLC)	Non-Small-Cell Lung Cancer (NSCLC)	Non-Small-Cell Lung Cancer (NSCLC)	Non-Small-Cell Lung Cancer (NSCLC)	Locally Advanced Non-Small Cell Lung Cancer (NSCLC)	Non-Small-Cell Lung Cancer (NSCLC)
	Histology	Squamous cell carcinoma: 27 pts Adenocarinoma: 47 pts Others: 6 pts	Squamous cell carcinoma: 21 pts Adenocarinoma: 39 pts Others: 10 pts	Adenocarinoma: 53 pts Squamous cell carcinoma: 24pts Large-cell carcinoma: 2pt adenosquamous carcinoma: 1pt	Adenocarinoma: 32 pts Squamous cell carcinoma: 19 pts	Squamous cell carcinoma 33 (53%) Adenocarinoma 25 (40%) Large-cell carcinoma 3 (5%) Non–small cell lung cancer, not otherwise specified 1 (2%)	Squamous cell carcinoma: 68 pts Adenocarinoma: 146 pts Large-cell carcinoma: 3 pts Mucoepidermoid carcinoma: 1 pt
	Tumour Site	-	-	-	-	-	-
	Tumour Stage/TNM Classification	UICC 6th Edition (2002)[77]	UICC 7th Edition[77]	UICC (Edition: NR)[77]	UICC (Edition: NR)[77]	UICC 7th edition[77]	UICC 6th edition[77]
		42 (52.5%) stage IA pts (T1N0M0) 38 (47.5%) stage IB pts (T2N0M0) **CIRT (52.8 GyE/4 fr.):** 15 stage IA pts (T1N0M0) 8 stage IB pts (T2N0M0) **PRT (80 GyE/20 fr.):** 6 stage IA pts 14 stage IB (T2N0M0) **PRT (60 GyE/10 fr.):** 21 stage IA pts (T1N0M0) 16 stage IB (T2N0M0)	47 (67%) stage IB pts (T2aN0M0) pts 23 (33%) stage IIA (T2bN0M0) pts	42 (53%) stage IA pts 37 (47%) stage IB pts	29 (58%) stage IA pts (with 30 lesions) 21 (42%) stage IB pts	17 (27%) stage IIA pts 22 (35%) stage IIB pts 23 (37%) stage IIIA pts	Tumour stage: 123 (56%) stage IA pts (45 T1a , 78 T1b) 95 (44%) stage IB pts (87 T2a, 8 T2b)

[75] 23 CIRT pts (52.8 GyE): 75 (54-89); 20 PRT pts (receiving 80 GyE): 75 (48-87); 37 PRT pts (receiving 60 GyE): 78 (57-87).

[76] 47 T2aN0M0 pts: 75 (57–87); 23 T2bN0M0 pts: 76 (60–92).

[77] For more information on the UICC criteria, see https://www.uicc.org/resources/tnm (download on 10.12.2017).

First Author	Iwata[100]	Iwata[99]	Miyamoto[102]	Miyamoto[101]	Takahashi [98]	Yamamoto[97]
Follow-Up in Months (Unit of Central Tendency; Range)	30.5 (median, range: 4-66)	44 (median, range: 4–103)	38.6 (median, range: 2.5-72.2)	59.2 (median, range: 6.0–83.0)	25.2 (1.6 - 157.2)	57.8 (median, range: 1.6-160.7)
Loss to Follow-Up n (%)	NR	NR	NR	NR	NR	NR
Methods	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)[78]	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)[78]	The **Kaplan-Meier Method** was used for survival rates and local control. Wilcoxon test for differences between survival rates of different tumour stage (N-stage) groups[78] (level of significance: <0.05)	The **Kaplan-Meier Method** was used for survival rates and local control. Log-rank test for differences between survival rates (level of significance: <0.05)[78].
Outcomes						
Efficacy						
Overall Survival (OS) in % (95% CI)	75% (95% CI: 64%-86%; stage IA: 74%; IB: 76%) at 3 years There were no significant differences in the treatment results among the 3 protocols CIRT (52.8 GyE/4 Fr): 86% (95% CI: NR) at 3 years PRT (80 GyE/20 Fr): 90% (95% CI: NR) at 3 years PRT (60 GyE/10): 61% (95% CI: NR) at 3 years	58% (95% CI: 46%-70%; IB: 53%; IIA: 67%) at 4 years There were no significant differences in OS between PRT and CIRT patients[79]	45% (95% CI: NR) at 5 years IA: 62% (95% CI: NR) at 5 years IB: 25% (95% CI: NR) at 5 years	50.0% (95% CI: NR) at 5 years IA 55.2 (95% CI: NR) at 5 years IB: 42.9 (95% CI: NR) at 5 years	77.2% (95% CI: 66.7%-87.7%) at 1 year 51.9% (95% CI: 39.2%-64.5%) at 2 years	68.3% (95% CI: NR) at 3 years 49.4% (95% CI: NR) at 5 years
Cause-Specific Survival (CSS) in % (95% CI)	86% (95% CI, 77%-95%; IA: 84%; IB: 88%) at 3 years[80]	-	68% (95% CI: NR) at 5 years IA: 87% (95% CI: NR) at 5 years IB: 42% (95% CI: NR) at 5 years	75.7% (95% CI: NR) at 5 years IA: 89.4 (95% CI: NR) at 5 years IB: 55.1 (95% CI: NR) at 5 years	71.7% (95% CI: NR) at 2 years	-

[78] The results regarding statistical significance of those potential differences was not extracted since it was only tested whether patients with different characteristics or tumour stage had statistically significant differences in survival, i.e. overall survival (OS), or local tumour control (LCR) and no comparison between OS or LCR of CIRT patients and OS or LCR of patients undergoing another therapy was compared statistically.

[79] Survival and local control rates of the patients undergoing CIRT or PRT were not reported.

[80] Results/differences between different therapy groups were not reported.

First Author	Iwata[100]	Iwata[99]	Miyamoto[102]	Miyamoto[101]	Takahashi [98]	Yamamoto[97]
Clinical Recurrence-Free Survival (CRFS) in % (95% CI) Biochemical Recurrence-Free Survival (BRFS)in % (95% CI)	-	-	-	-	-	-
Disease-Free Survival (DFS) in % (95% CI)	54% (95% CI: 43%-68%; IA: 67%; IB: 46%) at 3 years	-	-	-	35.7% (95% CI: NR) at 2 years	
Recurrence-Free Survival (RFS) in % (95% CI)						
Progression-Free Survival (PFS)in % (95% CI)	-	46% (95% CI: 33%-59%; IB: 43%; IIA: 52%), 52%) at 4 years There were no significant differences in PFS between PRT and CIRT pts[79]	-	-	-	NR[81]
Local Control Rate (LCR) in % (95% CI)	82% (95% CI,72%-92%: IA: 87%; IB: 77%) at 3 years Differences between treatment results among the 3 protocols n. s.: CIRT (52.8 GyE/4 Fr): 86% (95% CI: NR) at 3 years PRT (80 GyE/20 Fr): 83% (95% CI: NR) at 3 years PRT (60 GyE/10): 81% (95% CI: NR) at 3 years	75% (95% CI: 63%-86%; IB: 70%; IIA: 84%) at 4 years There were no significant differences between PRT and CIRT[79]	90% (95% CI: NR) at 5 years IA 97% (95% CI: NR) at 5 years IB 80% (95% CI: NR) at 5 years	94.7% (95% CI: NR) at 5 years IA: NR IB: NR	96.0% (95% CI: 90.5%-100.0) at 1 year 93.1% (95% CI: 85.4%-100.0) at 2 years	77.9% (95% CI: NR) at 3 years 72.7% (95% CI: NR) at 5 years
Health-Related Quality of Life (HRQOL)	-	-	-	-	-	-

[81] Data on the progression free survival (PFS) in % was not found in the included study. However, the authors stated that PFS was measured in the study [97].

First Author		Iwata[100]	Iwata[99]	Miyamoto[102]	Miyamoto[101]	Takahashi [98]	Yamamoto[97]
Safety							
Acute Radiation Morbidity	**Criteria**	**CTCAE v.4.0**	**CTCAE v.4.1**	**RTOG**	**RTOG**	**CTCAE v.3.0**	**NCI-CTC**
		Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (Gr.1/Gr.2/Gr.3/Gr.4)	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))
	Lung	NR[83]	NR[83]	Overall[82]: 1/79 [0 (0)/1 (1.3)/ 0 (0)/0 (0)] T1 IA: 0/41 (0 (0)/0 (0)/ 0 (0)/0) T2 IB: 1/38 [0 (0)/1 (2.6)/ 0 (0)/0 (0)]	2/51 [1 (1.9)/1 (1.9)/0 (0)/0 (0)][82] T1 IA: NR T2 IB: NR	**Radiation pneumonitis: 2/62** [NR/1 (1.6)/1 (1.6)/0]	See below
	Skin	NR[83]	NR[83]	Overall[82]: 80/80 (75 (93.8)/ 5 (6.3)/0 (0)/0) T1 IA: 42/42 [40 (95.2)/ 2 (4.8)/0 (0)/0 (0)] T2 IB: 38/38 [35 (92.1)/ 3 (7.9)/0 (0)/0 (0)]	51/51 [50 (98)/1 (1.9)/ 0 (0)/0 (0)][82] T1 IA: NR T2 IB: NR	Radiation dermatitis: 5/62 [NR/5 (8)/0 (0)/ 0 (0)]	See below
	Others	NR[83]	NR[83]	No other toxicities occurred/were reported	No other toxicities occurred/were reported	No other toxicities occurred/were reported	Not specified: 215/218 [212 (97.2)/3 (1.3)/0 (0.0)/(0.0)]
Late Radiation Morbidity	Criteria	CTCAE v.4.0	CTCAE v.4.1	RTOG/EORTC	RTOG/EORTC	RTOG/EORTC	RTOG/EORTC
		Cases/N [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/N [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/N [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/N [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/N [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	Cases/N [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]
	Lung	**Radiation pneumonitis**[83] **CIRT (n=23)** **2/23** [NR/2 (8.7)/ 0 (0.0)/0 (0.0)] **PRT (n=57)** **8/57** [NR/7 (12.3)/ 1 (1.8)/0 (0.0)]	**Radiation pneumonitis**[83] **12/70 [NR/10 (14.3)/ 2 (2.9)/0 (0)]**[84] **IB NSCLC pts (n=47)** **7/47** [NR/7 (14.9%)/ 0 (0.0%)/0 (0.0%)] [84] **IIA NSCLC pts (n=23)** **5/23** [NR/3 (13%)/ 2 (8.7%)/0 (0.0%))	**Overall**[82][85] **70/76 [69 (90,8)/1 (1.3)/0 (0)/0 (0)]** IA: 36/40 [35 (90)/ 1 (2.5)/0 (0)/0 (0)] IB: 34/36 [34 (94.4)/ 0 (0)/0 (0)/0 (0)]	50/51 [48 (94.1)/2 (3.9)/0 (0)/0 (0)][82] IA: NR IB: NR	3/62 [NR/3 (4.8)/0 (0)/0 (0)]	See below

[82] The denominator refers to the number of lesions of the included patients.

[83] The authors stated that most of the toxicities occurred in the late phase. However, the time frame was unclear and it remained unclear whether those radiation morbidities occurred in the acute or late phase.

[84] Toxicities of the patients undergoing CIRT or PRT were not reported.

[85] A clinical assessment of lung and skin reaction was conducted in 76 and 77 patients respectively. 3 patients were lost to observation.

First Author		Iwata[100]	Iwata[99]	Miyamoto[102]	Miyamoto[101]	Takahashi [98]	Yamamoto[97]
	Skin	[83] CIRT pts (n=23) 2/23 (NR/2 (8.7)/0 (0.0)/0 (0.0)) PRT pts (n=57) 11/57 (NR/8 (14.0)/3 (5.3%)/0 (0))	15/70 [NR/10 (14.3)/ 4 (5.7)/1 (1.4)] [84] IB NSCLC (n=47) 10/47 [NR/7 (14.9%)/ 3 (6.4%)/0 (0)] IIA NSCLC pts (n=23) 5/23 [NR/3 (13%)/ 1 (4.4%)/1 (4.4%)]	Overall [82 85] 77/77 [76 (98.7)/1 (1.3)/ 0 (0)/0 (0)] IA: 40 [40 (100)/0 (0)/ 0 (0)/0 (0)] IB: 37 [36 (97.3)/ 1 (2.7)/0 (0)/0 (0)]	51/51 [(49 (96)/1 (1.9)/1 (1.9)/0 (0)][82] IA: NR IB: NR	1/62 [NR/1 (1.6)/0 (0)/0 (0)]	See below
	Others	23% had a grade 2 rib fracture and Gr. 2 soft tissue AE occurred in 6%[83] No other toxicities occurred/were reported	No other toxicities occurred/were reported	No other toxicities occurred/were reported	No other toxicities occurred/were reported	Oesophagus: 1/62 (2) (NR/0/1/0) No other toxicities occurred/were reported	208/212[207 (97.6%)/ 1 (0.4)/0 (0.0)/0 (0.0)] No other toxicities occurred/were reported

Abbreviations: CIRT – Carbon Ion Radiotherapy; CTCAE – Common Terminology Criteria for Adverse Events; EORTC – European Organisation for Research and Treatment of Cancer; fr. – fraction; Gr. – Grade; GyE – Gray Equivalent; n.s. – not statistically significant; NCI-CTC – National Cancer Institute-Common Toxicity Criteria; NR – not reported; OS – overall survival; PFS – Progression-Free Survival; pt – patient; pts – patients; RTOG – Radiation Therapy Oncology Group; s. s. – statistically significant; TNM – Tumour Node Metastases; UICC – Union Internationale Contre le Cancer; v. – version

Table A-7: Carbon ion radiotherapy (CIRT) for cancers in the prostate region: Results from observational studies (part 1)

First Author	Ishikawa [133]	Ishikawa [139]	Nikoghosyan [136]	Maruyama [134]
Year	2015	2006	2011	2017
Country	Japan	Japan	Germany	Japan
Cancer Therapy Centre (s)	Gunma University Heavy Ion Medical Center (GHMC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Gesellschaft für Schwerionenforschung (GSI) in Darmstadt	Heavy Ion Medical Accelerator in Chiba (HIMAC)
Sponsor	Ministry of Education, Culture, Sports, Science, and Technology of Japan.	Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan	European Network for light ion hadrontherapy (ENLIGHT) with EU support	Japan Society for the Promotion of Science (JSPS)
Sample Size	76	175	14	417
Time Frame of Patient Enrolment	Between March 2010 and February 2011	Between April 2000 and November 2003,	Between 1997 and 2007	Between April 2000 and January 2007
Study Design	Before-after study; feasibility study	Case series, feasibility study	Prospective case series: Interim report of acute side effects of intermediate-risk PC	Before-after study
The Phase of Clinical Trial	Phase 2	Phase 2	Phase 1/2	N.A.

First Author		Ishikawa [133]	Ishikawa [139]	Nikoghosyan [136]	Maruyama [134]
Intervention		**CIRT**: 57.6 GyE/16 fractions over 4 weeks (with a fractional dose of 3.6 GyE for 4 fractions per week) **Co-Intervention**: Androgen deprivation therapy (ADT) Intermediate- and high-risk groups received neoadjuvant ADT for 6 months before the start of C-ion RT. Adjuvant ADT without antiandrogens was continued only for high-risk patients, in whom ADT was administered for 24 months. If patients with T1c-T2b disease had a GS of 7 (3+4) and iPSA value <10 ng/mL, they were considered to have intermediate-risk cancer but received C-ion RT without ADT.	**CIRT**: 66.0 GyE/20 fractions over 5 weeks (fraction dose: 3.3 GyE) **Co-intervention**: androgen deprivation therapy (ADT) for high-risk patients (n=142), consisting of medical or surgical castration with or without anti-androgen. Length of neo-adjuvant ADT: 2-6 months before CIRT; length of adjuvant ADT: ≥12months (median time: 22months [range: 1-57 months].	IMRT+CIRT: photon IMRT with a total target dose of 60 Gy prescribed to the median dose of the planning target volume (PTV, weekly fractionation 5 x 2.0 Gy) and a carbon ion boost with a total boost dose of 18 GyE (weekly fractionation 6 x 3 GyE) to the prostate (gross target volume = GTV). **Co-intervention:** Adjuvant hormonal therapy (6-42 months)	**CIRT**: Total dose of 63–66 Gray-equivalents (GyE) in 20 fractions over 5 weeks **Co-intervention:** Androgen deprivation therapy (ADT) Intermediate-risk group: 6 months of ADT + 2-6 months of neoadjuvant therapy. High-risk group: 24 months of ADT + 2-6 months of neoadjuvant therapy.
Control (C)		-	-	-	-
Age in Years (Unit of Central Tendency, Range)		66 (median, range: 53-88)	70 (median, range: 53–83)	68 (median, range 55 – 75)	69 years (median, range: 47–92)
Sex, Female (%) vs. Male (%)		Male	Male	Male	Male
Patient Population	Indication/Risk Group	**Patients were stratified into three (3) risk groups:** low-risk: T1–T2a, initial prostate-specific antigen (iPSA) < 10 ng/mL, and Gleason sum (GS) ≤6 (n=3 [4%]) intermediate-risk: not low-risk and not highrisk (n=29 [38%]) high-risk: T2c–T3b or iPSA ≥20 ng/mL or GS≥8 (n=40 [53%]) Castration resistant (n=4)	**Patients were stratified into two (2) groups:** low risk: T1/T2aNoMo with an iPSA < 20 ng/mL and a GS <7 (n=33) high risk: T2b/T3 or iPSAP ≥20 ng/mL or GS ≥7 (n=142)	Intermediate-risk prostate cancer: (PSA between 10.1 ng/mL and 20 ng/mL or at least T2b tumour or a Gleason Score of at least 7), no distant metastases	intermediate and high-risk prostate cancer
	Initial PSA (ng/mL)	<10.00: 41 (54%) 10.00-19.99: 16 (21%) ≥20.00: 19 (25%)	-19.9: 100 (57%) 20.0–49.9: 46 (26%) 50.0+: 29 (21%) 29 (17%)	<10.00: 0 (0%) 10.00-19.99: 14 (100%) ≥20.00: 0 (0%)	Median PSA: 14.0 ng/mL (range: 2.1–260)
	Gleason Score	<6: 4 (5%) 7 (3+4): 23 (30%) 7 (4+3): 19 (25%) ≥8: 30 (40%)	Gleason sum: 4–5: 19 (11%) 6: 35 (20%) 7: 80 (46%) 8–9: 41 (23%)	<6: 0 (0%) 7: 9 (64%) 8: 4 (29%) 9: 1 (7%)	≤6: 119 (28.5) 7: 183 (43.9) ≥8: 115 (27.6)

First Author		Ishikawa [133]	Ishikawa [139]	Nikoghosyan [136]	Maruyama [134]
	Tumour Stage/TNM Classification	23 (30%)T1c pts 16 (21%)T2a-b pts 10 (13%)T2c pts 24 (32%)T3a pts 2 (3%)T3b pts 1 (1%)T4 pts	56 (32%) T1 pts with 22 (67%) and 34 (24%) in the low and high risk group respectively. 24 (14%) T2a pts with 11 (33%) and 13 (9%) in the low and high risk group respectively 29 (16%) T2b pts with 0 (0%) and 29 (20%) in the low and high risk group respectively 66 (38%) T3 with 0 (0%) and 66 (47%) in the low and high risk group respectively	4 T1c pts 4 T2a pts 3 T2b pts 2 T2c pts 1 T3 pt	109 (26.1%) ≤T1c pts 87 (20.9%) T2a pts 81 (19.4%) T2b pts 140 (33.6%) T3a–b pts
Follow-Up in Months (Unit of Central Tendency; Range)		51 (median time, range: 8-58)	46 (median time, range: NR)	28 (median, range: 12 – 36)	60 (NR, range: NR)
The Loss to Follow-Up n (%)		NR	NR	NR	NR
Methods		Survival rates: NR **Change in QoL:** Physical Component Summary (PCS) and Mental Component Summary (MCS) using the Japanese version of SF-8 questionnaire before, immediately after completion, at 3 and 12 months after CIRT **Statistical analysis**: Linear mixed models for comparison of the scores at different time points (not further specified)	**Survival rates:** Kaplan–Meier method (comparison: log-rank tes; s. s. with p<0.05) **QoL**: FACT-G and FACT-P before, immediately after and 1 year after CIRT (further statistical analysis: NR)		**HRQOL:** Japanese Version of the Functional Assessment of Cancer Therapy-General (FACT-G) and for prostate Cancer Patients (FACT-P) questionnaire (measured immediately before (t1), after (t2) and after 12 (t3), 36 (t4) and 60 (t5) months after CIRT. **Statistical analysis**: Paired t-test. Statistical significance was set at p < 0.05
Outcomes					
Efficacy					
Overall Survival (OS) in % (95% CI)		97.4% (95% CI: 93.8-100.0%) at 4 years	91% (95% CI: 87-96%) at 4 years low-risk group: 94% (95% CI: 90–98%) high-risk group: 91% (95% CI: 85–96%)	Actuarial: 100%(95% CI: NR) at 3 years	-
Cause-Specific Survival (CSS) in % (95% CI)		NR	97% (95% CI: 95–100%) at 4 years low-risk group: 100% (95% CI: NR) High-risk group: 97% (95% CI: 95–98%)	-	-
Disease-Free Survival in % (95% CI)		-	-	-	-
Recurrence-Free survival (RFS) in % (95% CI)		NR	-	-	-

First Author		Ishikawa [133]	Ishikawa [139]	Nikoghosyan [136]	Maruyama [134]
Biochemical Recurrence-Free Survival (BRFS) in % (95% CI)		4-year BRF rate: 94.6% (95% CI: 89.4-99.8%)	4-year rate bNED: 88% (95% CI: 83-93%) low-risk group: 87% (95% CI: 77-98%) high-risk group: 88% (95% CI: 82-94%)	Actuarial three year biochemical relapse-free survival: 86%	-
Progression-Free Survival (PFS) in % (95% CI)		-	-	-	-
Local Control Rate (LCR) in % (95% CI)		NR	-	-	-
Health-Related Quality of Life (HRQOL)	Instruments Results	Japanese Version of the SF-8 **slight and statistically significant (p<0.05) decrease of PCS score**	**FACT-G & FACT-P** **No statistically significant changes in FACT-G or FACT-P scores.**	-	FACT-G, FACT-P & TOI **Short-term**: s. s. reduction in FACT-P and TOI; no statistical difference in FACT-G score **Long-term:** s. s. reduced FACT-P & Fact-G score, no statistical difference in TOI score s. s.= diff to baseline, with p<0.05
	Pre-Interventional: Mean (Standard Deviation)	**SF-8** Before CIRT: PCS: 51.14 (1.85) MCS:49.18 (1.96)	**FACT-G:** Before CIRT: 89.1 (13.3) **FACT-P:** Before CIRT: 123.1 ± 18.5	-	**FACT-G:** Before: 84.2 (12.6) **FACT-P:** Before: 119.5 (16.9) **TOI:** Before: 81.8 (12.0)
	Post-Interventional: Mean Score (Standard Deviation)	NR	NR	-	NR
	Short-Term (<6 weeks) Mean Score (Standard Deviation)	**SF-8** After 1 month: PCS: 51.14 (1.85) MCS: 48.45 (1.96)	NR	-	**FACT-G:** At 1 month: 83.7 (12.9), n. s. **FACT-P:** 1 month: 116.2* (17.1), s. s. **TOI:** 1 month: 77.8* (12.1), s. s.
	Mid-Term (>6 weeks – ≤6 months) Mean Score (Standard Deviation)	**SF-8** After 3 months: PCS: 50.76 (1.87) MCS: 51.63 (1.98)	NR	-	

First Author		Ishikawa [133]	Ishikawa [139]	Nikoghosyan [136]	Maruyama [134]
	Longer Term (>6 months): Mean Score (Standard Deviation)	**SF-8** After 12 months: PCS: 47.71 (1.84)* diff: s. s. MCS: 49.75 (1.95)	**FACT-G** At 1 year after CIRT: 87.3 (15.5) Difference to baseline d: 1.8 (1.1), p=0.1 (n. s.) **FACT-P** At 1 year after CIRT: 120.4 ± 21.1 Difference d: 2.6 ± 1.4, p = 0.07 (n. s.)		**FACT-G** At 12 months: 82.6*[86] (13.7), s. s. At 36 months: 82.4 (14.3), s. s. At 60 months: 82.7* (15.0), s. s. **FACT-P** 12 months: 116.9* (18.4) s. s. 36 months: 117.5* (19.3) s. s. 60 months: 117.6* (20.2) s. s. **TOI:** 12 months: 80.3 (13.0), n. s. 36 months: 81.6 (13.7), n. s. 60 months: 81.4 (14.6), n. s.
Safety					
Acute Radiation Morbidity	Criteria	CTCAE Version 4.03 Cases/Total [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	RTOG Cases/Total [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	CTCAE Version 3.0 Cases/Total [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	-
	Genitourinary (GU)	50/76 [43 (57)/7 (9)/0 (0)/0 (0)]	Bladder/urethra: 57/175 [57 (33)/0 (0)/0 (0)/0 (0)]	12/14 [7 (50)/5 (35.7)/0 (0)/ (0/0)]	NR
	Gastrointestinal (GI)	1/76 [1 (1)/(0)/0 (0)/0 (0)]	Rectum: 2/175 [2 (1)/0 (0)/0 (0)/0 (0)]	5/14 [5 (35)/0 (0)/0(0)/0(0)]	NR
Late Radiation Morbidity	Criteria	CTCAE Version v. 4.03 Cases/Total [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	RTOG/EORTC Cases/Total [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]	-	RTOG/EORTC Cases/Total [Gr.1 (%)/Gr.2 (%)/ Gr.3 (%)/Gr.4 (%)]
	Genitourinary (GU)	40/76 [35 (46)/5 (7)/0 (0)/0 (0)]	Bladder/urethra: 117/175 [108 (62)/9 (5)/ 0 (0)/0 (0)]	-	**Bladder/Urethra** At 12 months: 58/416 [56 (13.5)/2 (0.5)/0 (0.0)/ 0 (0.0)] At 36 months: 114/402[108 (26.9)/6 (1.5)/0 (0.0)/0 (0.0)] At 60 months: 77/394[66 (16.8)/10 (2.5)/1 (0.3)/0 (0.0)]
	Gastrointestinal (GI)	7/76 [6 (8)/1 (1)/0 (0)/0 (0)]	Rectum: 27/175 [23 (13)/4 (2)/0 (0)/0 (0)]	-	**Rectum** At 12 months: 4/417 [4 (1.0)/0 (0.0)/0 (0.0)/ 0 (0.0)] At 36 months: 32/402 [29 (7.2)/ 3 (0.7)/0 (0)/0 (0)] At 60 months: 18/394 [16 (4.1)/ 2 (0.5)/0 (0.0)/0 (0)]

[86] * Statistically significantly different to the baseline score, with $p<0.05$.

Table A-7: Carbon ion radiotherapy (CIRT) for cancers in the prostate region: Results from observational studies (part 2)

First Author	Nomiya [138]	Tsuji 2005 [137]	Wakatsuki [135]
Year	2016	2005	2008
Country	Japan	Japan	Japan
Cancer Therapy Centre (s)	Heavy Ion Medical Accelerator in Chiba (HIMAC) Gunma University Heavy Ion Medical Center (GHMC) Heavy Ion Medical Accelerator in Tosu (HIMAT) in Saga	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heavy Ion Medical Accelerator in Chiba (HIMAC)
Sponsor	Japan Society for the Promotion of Science (JSPS)	NR	NR
Sample Size	2157[87]	201[88]	194
Time Frame of Patient Enrolment	Between December 2003 and December 2014	between June 1995 and February 2004	between April 2000 and February 2004
Study Design	Multi-institutional analysis of prospective case series studies	Dose-escalation, prospective case series study using 3 protocols	Before-after study
The Phase of Clinical Trial	Phase 1 & 2	Phase 1 & 2	N.A.
Intervention	**CIRT:** once daily/6-8 times per two weeks **Dosage/fractions:** **People treated (%)** 66 Gy(RBE)/20 fr.: 78 (3.6%) 63 Gy(RBE)/20 fr.: 213 (9.9%) 57.6 Gy(RBE)/16 fr.: 1296 (60.1%) 51.6 Gy(RBE)/12 fr.: 570 (26.4%) **Co-intervention**: androgen deprivation therapy (ADT) HIMAC: low risk: none intermediate: NAADT 4–6 months high: NAADT + adjv. ADT totalP 24 months GHMC: low risk: none	Hypofractionated **CIRT** (20 fractions): **Dose-escalation**: 54.0–72.0 GyE for stage B2–C patients in the time period of 06/95–12/97 (+hormone therapy) Protocol 9402 (n=35) 60.0–66.0 GyE for stage A2–B1 patients in the time period of 01/98–02/00 (no hormone therapy). Protocol 9703 (n=20) **Fixed-dose:** 66.0 GyE for patients with cancer in the B2–C tumour stage in the time period of 01/98–02/00 (+hormone therapy). Protocol 9703 (n=42).	**CIRT**: once daily, four days/week at 66.0 Gy equivalents (GyE)/20 fractions (with a fraction dose of 3.3 GyE). **Co-intervention**: Hormonal treatment for patients in the high-risk group (n=125), i.e., neoadjuvant therapy, such as medical or surgical castration with or without an antiandrogen, for 2-6 months before CIRT with continued adjuvant therapy for at least 1 year after CIRT.

[87] It is assumed that the sample of Maruyama et al. 2017 [134] is also included in Nomiya et al. 2016 [138].
However, none of the studies was excluded due to overlapping sample since both studies included different crucial endpoints in their analysis.

[88] It is assumed that the sample of Wakatsuki et al. 2008 is also included in Tsuji et al. 2005.
However [135] was not excluded due to overlapping sample due to the fact that the crucial endpoint was reported in this study, while not being reported in [137].

First Author		Nomiya [138]	Tsuji 2005 [137]	Wakatsuki [135]
Intervention *(continuation)*		intermediate: NAADT 6-8 months high:NAADT + adjv. ADT total 24 months HIMAT: low risk: none intermediate: NAADT 4-8 months high: NAADT + adjv. ADT total 24-36 months	66.0 GyE for patients with prostate cancer in the A2–C tumour stage in the time period of 04/00–02/04 (hormone therapy stratified by risk factors). Protocol 9904 (n=176) **Co-intervention:** neoadjuvant hormonal therapy (i.e., medical/surgical castration with or without antiandrogen) before CIRT for the high-risk group (time period: 2-6 months). Continuation of adjuvant hormonal therapy for at least 1 year.	
Control (C)		-	-	-
Age in Years (Unit of Central Tendency, Range)		67 (mean, range: 45–92)	NR	69 (median, range: 53–83)
Sex, Female (%) vs. Male (%)		Male	Male	Male
Patient Population	Indication/Risk Group	**Patients were stratified into three (3) risk groups:** low-risk: T1–T2a, initial prostate-specific antigen (iPSA) < 10 ng/mL, and Gleason sum (GS) ≤6 (n=263 [12%]) intermediate-risk: not low-risk and not high risk (n=679 [31%]) high-risk: T2c–T3b or iPSA >20 ng/mL or GS≥7 (n=1215 [56%])	Prostate cancer	**Patients were stratified into two groups:** low risk: Patients with T1/T2aN0M0 with an iPSA level <20 ng/mL, and a Gleason score (GS) <7 high risk: T2b/T3 or iPSA level ≥20 ng/mL or GS ≥7
	Initial PSA (ng/mL)	≤10: 1268 (58.8%) 10 < and ≤20: 523 (24.2%) >20: 366: (17.0%)	<20: 107 (53%) ≥20: 94 (47%)	16.6 ng/mL (median, range: 3.4–260.0 ng/mL).
	Gleason Score	5: 7 pts (0.3%) 6: 407 pts (18.9%) 7: 1074 pts (49.8%) 8: 279 pts (12.9%) 9: 381 pts (17.7%) 10: 9 pts (0.4%)	≤ 6: 63 (31%) 7: 79 (39%) ≥ 8: 52 (26%) Not evaluated (N.E.): 7 (4%)	NR
	Tumour Stage/TNM Classification	1 (0.0%)T1b pt 682 (31.6%) 1c pts 527 (24.4%) 2a pts 73 (3.4%) 2b pts 388 (18.0%) 2c pts 397 (18.4%) 3a pts 89 (4.1%) 3b pts	T1–T2a: 81 (PSA score: 63pts <20, 18pts ≥20) T2b: 39(PSA score: 19pts <20, 20pts ≥20) T3: 81≥(PSA score: 25pts <20, 56pts ≥20)	46 T1c pts 25 T2a pts 20 T2b pts 59 T3 pts

First Author	Nomiya [138]	Tsuji 2005 [137]	Wakatsuki [135]
Follow-Up in Months (Unit of Central Tendency; Range)	29 (NR, range: NR)[89]	NR	NR
The Loss to Follow-Up n (%)	NR	NR	NR
Methods	Survival rates: Kaplan-Meier Method(comparison: log-rank test; significance level: NR)	**Survival rates:** Kaplan–Meier method (comparison: log-rank test; s. s. with p<0.05)	HRQOL: self-administered questionnaires before, just after, at 12 months after CIRT using the following questionnaires: FACT-P; FACT-G and UCLA-PCI questionnaires Statistical analysis: Paired t-test. Statistical significance was set at p < 0.05
Outcomes			
Efficacy			
Overall Survival (OS) in % (95% CI)	**Low-risk group**: 100% (95% CI: NR) at 5 years; 96% (95% CI: NR) at 10 years **Intermediate risk group**: 99% (95% CI: NR) at 5 years; 78% (95% CI: NR) at 10years **High-risk group:**96% (95% CI: NR) at 5 years; 88% (95% CI: NR) at 10years	89.2% (95% CI: NR) at 5 years	-
Cause-Specific Survival (CSS) in % (95% CI)	**Low-risk group:** 100% (95% CI: NR) at 5 years; 100% (95% CI: NR) at 10 years **Intermediate risk group**: 100% (95% CI: NR) at 5 years; 88% (95% CI: NR) at 10years **High-risk group: 99%** (95% CI: NR) at 5 years; 98% (95% CI: NR) at 10years	Disease-specific survival: 92.2% (95% CI: NR) at 5 years	-
Disease-Free Survival in % (95% CI)	-	-	-
Recurrence-Free survival (RFS) in % (95% CI)	-	-	-
Biochemical Recurrence-Free Survival (BRFS) in % (95% CI)	**Low-risk group**: 92% (95% CI: NR) at 5 years; 77% (95% CI: NR) at 10 years **Intermediate risk group**: 89% (95% CI: NR) at 5 years; 70% (95% CI: NR) at 10years **High-risk group**: 92% (95% CI: NR) at 5 years; 79% (95% CI: NR) at 10 years	5-year bNED: 83.2% (95% CI: NR) low-risk group: 100% (95% CI: NR) high-risk group: 80.5% (95% CI: NR)	-
Progression-Free Survival (PFS) in % (95% CI)	-	-	-

[89] The median follow-up periods of surviving patients in NIRS, GHMC, and HIMAT were 43, 23, and 7 months, respectively [138].

First Author		Nomiya [138]	Tsuji 2005 [137]	Wakatsuki [135]	
Local Control Rate (LCR) in % (95% CI)		**Low-risk group**: 98% (95% CI: NR) at 5 years; 98% (95% CI: NR) at 10 years **Intermediate risk group**: 96% (95% CI: NR) at 5 years; 95% (95% CI: NR) at 10years **High-risk group:** 99% (95% CI: NR) at 5 years; 98% (95% CI: NR) at 10years	100% (95% CI: NR) at 5 years	-	
Health-Related Quality of Life (HRQOL)	Instruments Results	-	-	CIRT alone (n=25)[90] Patients showed no significant change compared to those before C-ion RT when using results from the FACT-G or FACT-P questionnaire No significant change in the average of the UCLA-PCI scores[91] in the low-risk patients was seen at 12 months.	CIRT+ADT (n=125)[90] FACT-G (100): Score at 12 months stat. significantly lower than at baseline with p<0.01 FACT-P (148): Score at 12 months stat. significantly lower than at baseline with p<0.05 No significant change in the average of the UCLA-PCI scores[91] in the low-risk patients was seen at 12 months.
	Pre-Interventional: Mean (Standard Deviation)	-	-	**FACT-G:** 88.4 (13.2 **FACT-P** 122.6 (19.8)	**FACT-G:** Before CIRT: 86.1 (19.4) **FACT-P:** Before CIRT: 120.0 (26.1)
	Post-Interventional: Mean Score (Standard Deviation)	-	-	**FACT-G:** 89.2 (11.3), n. s., **FACT-P:** 122.4 (16.6) n. s.	**FACT-G:** Just after: 85.5 (21.2) **FACT-P:** Just after: 118.0 (28.4)
	Short-Term (<6 weeks) Mean Score (Standard Deviation)	-	-	NR	NR
	Mid-Term (>6 weeks – ≤6 months) Mean Score (Standard Deviation)	-	-	NR	NR
	Longer Term (>6 months): Mean Score (Standard Deviation)	-	-	**FACT-G:** 89.1 (13.6), n.s., **FACT-P:** 123.8 (20.3), n.s..	**FACT-G** At 12 months: 83.9 (21.7) (s. s. with p<0.01) **FACT-P** At 12 months: 116.7 (29.1)* (s. s. with p<0.05)

[90] Response rate: 77.3% (FACT-P) and 78.1% (UCLA-PCI).

[91] The UCLA-PCI questionnaire was only used for the low-risk group and not extracted.

First Author		Nomiya [138]	Tsuji 2005 [137]	Wakatsuki [135]
Safety				
Acute Radiation Morbidity	Criteria	CTCAE Version 4		-
	Genitourinary (GU)	Grade 0–1: 2037 (94.4%) Grade 2: 119 (5.5%) Grade 3: 1 (0.0%) Grade 4: 0 (0%)	NR	-
	Gastrointestinal (GI)	Grade 0-1: 2157 (100%) Grade 2: 0 (0%) Grade 3: 0 (0%) Grade 4: 0 (0%)	NR	-
Late Radiation Morbidity	Criteria	CTCAE v. 4	RTOG/EORTC + LENT SOMA Cases/Total [Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%)]	
	Genitourinary (GU)	n= 1929 (excluded patients with a follow-up <6months from the analysis of late morbidities) **Genitourinary (GU)** Grade 0-1: 1840 (95.4%) Grade 2: 88 (4.6%) Grade 3: 1 (0.0%) Grade 4: 0 (0%)	**Bladder/urethra:** 95/201 [83 (41.3)/12 (6.0)/0 (0.0)/0 (0.0)]	-
	Gastrointestinal (GI)	Grade 0-1: 1921 (99.6%) Grade 2: 8 (0.4%) Grade 3: 0 (0%) Grade 4: 0 (0%)	Rectum: 9/201 [7 (3.5)/2 (1.0)/ 0 (0.0)/0 (0.0)]	-

Abbreviations: ADT – Androgen Deprivation Therapy; bNED or BRF – biochemical relapse-free rate; CIRT – Carbon Ion Radiotherapy; CTCAE – Common Terminology Criteria for Adverse Events; EORTC – European Organisation for Research and Treatment of Cancer; FACT-G – Functional Assessment of Cancer Therapy-General; FACT-P – Functional Assessment of Cancer Therapy-Prostate; fr. – fraction; GHMC – Gunma University Heavy Ion Medical Center; Gr. – Grade; GS – Gleason Score; GyE – Gray Equivalent; HIMAC – Heavy Ion Medical Accelerator in Chiba; HIMAT – Heavy Ion Medical Accelerator in Tosu; iPSA – initial prostate-specific antigen; LENT-SOMA – Late Effects Normal Tissue Task Force Subjective, Objective, Management, Analytic ml. – millilitre; N.A. – not applicable; n.s. – not statistically significant; NAADT – Neoadjuvant ADT; ng. – nanogram; pt – patient; pts – patients; RTOG – Radiation Therapy Oncology Group; TNM – Tumour Node Metastases; TOI – Trial Outcome Index; v. – version

Table A-8: Carbon ion radiotherapy (CIRT) for cancers in the skull base region: Results from observational studies

First Author	Mizoe [44]	Schulz-Ertner [43]	Uhl [42]
Year	2009	2007	2014
Country	Japan	Germany	Germany
Cancer Therapy Centre	Heavy Ion Medical Accelerator in Chiba (HIMAC)	Heidelberg Ion Beam Therapy Centre (HIT)	Heidelberg Ion Beam Therapy Centre (HIT)
Sponsor	NR	NR	NR
Sample Size	33[92]	54	25
CIRT Sample	33	54	25
Time Frame of Patient Enrolment	Between June 1995 and June 2007	Between November 1998 and September 2005	Between January 2010 and October 2012
Study Type	Observational	Observational	Observational
Study Design	Prospective; Pilot study; dose-escalation study [93]	Prospective case series [93]	Prospective case series [93]
The Phase of Clinical Trial	Phase 1/2 & Phase 2	Phase 1/2	NR
Intervention	**CIRT** (16 fr./4 weeks) : Pilot study: total dose of 48.0 GyE/16 fr. (4 cases) Dose-escalation: 48.0, 52.8, 57.6, and 60.8 GyE/16 fr. (16 cases) Phase 2 study: 60.8 GyE/16 fr. (14 cases) Previous treatment: Surgery?[94]	**CIRT (raster scan technique)**: a median total dose of 60 CGE (weekly fractionation 7 x 3.0 CGE) **Previous treatment:** At least 1 surgery in all patients	**CIRT Reirradiation (active raster scanning technique)** using a median total dose of 51 GyE (range: 45–60 GyE) in five to six fractions of 3 GyE per week[95] **Previous treatment:** **Photon** (n=2;hypofractionated) 3 × 7 Gy (80% isodose) 5 × 5 Gy (80% isodose) **Photon** (n=9; normofractionated) 66 Gy (38-72.5 Gy) **Proton** (n=2; normofractionated): 68.4 GyE; 72 GyE **Carbon ion** (n=12; hypofractionated): 60 GyE (42-60 GyE) Surgery for 24 pts
Control	-	-	-

[92] 34 cases in 33 patients.

[93] Enrolment judged to be prospective.

[94] In the study, it was stated that "(…) each patient had recovered from the effects of surgery before entry into the study" (see [44]).

[95] 23 pts were previously treated with irradiation (once), and 2 pts twice. Of all 25 pts, 14 were previously treated with particle therapy.

First Author		Mizoe [44]	Schulz-Ertner [43]	Uhl [42]
Age in Years (Unit of Central Tendency, Range)		47 (median, range: 16-76)	46 (median, range: 6-74)	50 (median, range: 39-76)
Sex, Female (%) vs. Male (%)		19 (58) vs. 14 (42)	27 (50) vs. 27 (50)	8 (32) vs. 17 (68)
Patient Population	Indication	Chordoma of the skull base and the paracervical spine	Low-grade and intermediate-grade chondrosarcomas of the skull base	Recurrence of skull base chondrosarcoma (n=5) or skull base chordoma (n=20)
	Histology	Not further specified	Not further specified	Chordoma: 20 Chondrosarcoma: 5
	Tumour Site	Of 34 cases, 7 (21%) involved the paracervical spine.	Ethmoidal/paranasal sinus 8 (14.8%) Parasellar 18 (33.3%) Sphenopetrosal 20 (37.0%) Temporooccipital 5 (9.3%) Clivus 3 (5.6%)	Skull base: Not further specified
	Tumour Stage	-	Grade 1: 37 (68.5%) Grade 2: 12 (22.2%) Grade 1 with focal Grade 2 areas: 5 (9.3%)	-
Follow-Up in Months (Unit of Central Tendency; Range)		53 (median, range: 8-29)	33 (median, range: 3-84)	14 (median, range: 2-30)
The Loss to Follow-Up n (%)		NR	NR	NR
Outcomes				
Efficacy				
Overall Survival (OS) in % (95% CI)		87.7% (95% CI: NR, SE: 7%) at 5 years 67% (95% CI: NR, SE: 14%) at 10 years	98.2% (95% CI: 94.6-100%) at 3 and 4 years[96]	NR
Cause-Specific Survival (CSS) in (95% CI)		NR	NR	NR
Disease-Free Survival (DFS) in % (95% CI)		NR	NR	NR
Recurrence-Free Survival (RFS) in % (95% CI)		NR	NR	NR
Progression-Free survival (PFS) in % (95% CI)		NR	NR	2-year-local progression-free survival (LPFS): 79.3% (95% CI: NR)
Local Control Rate (LCR)in % (95% CI)		85.1% (95% CI: NR, SE: 8%) at 5 years 63.8% (95% CI: NR, SE: 19%) at 10 years	Cumulative local control rates: 96.2% (95% CI: 88.8–100%) at 3 years 89.8% (95% CI, 75.6–100%) at 4 years	NR
Health-Related Quality of Life (HRQOL)		-	-	-

[96] The included study stated in the abstract that the 5-year OS for 54 patients with chondrosarcomas was 98.2%. In the results section, this rate is referred to be for 3 and 4 years respectively. Moreover, it is stated that only 9 patients survived 5 years possibly without having calculated the respective 5-year OS.

First Author		Mizoe [44]	Schulz-Ertner [43]	Uhl [42]
Safety				
Acute Radiation Morbidity	Criteria	RTOG	CTCAE v.3.0	CTCAE v.4.03
		Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (%)	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))
	Mucosa	12/34 [6 (17.6)/6 (17.6)/0(0)/0(0)]	Mucositis: 3/54 (5)* Grade 1: 2 (3.7) Grade 2: NR Grade 3: 1 (1.9) Grade 4: 0 (0)	1/25 (NR/1* (4)/0/0)
	Skin	13/34 [12 (35.3)/1 (2.9)/0 (0)/0 (0)]	-	-
	Others	-	Parotitis: 1 (1.9) [97]	Hypacusis: 3/25 [NR/3 (12)/0 (0)/0 (0)] Asymptomatic temporal lobe reaction*: 5/25 [5 (20)/0(0)/0 (0)/0 (0)] Osteoradionecrosis: 1/25 (NR/NR/1 (4)/0(0)]
Late Radiation Morbidity	Criteria	RTOG/EORTC	RTOG/EORTC	NR
		Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))	Cases/n (%)	Cases/n (Gr.1 (%)/Gr.2 (%)/Gr.3 (%)/Gr.4 (%))
	Mucosa	2/34 [2 (5.9)/0 (0)/0 (0)/0 (0)]	see below	NR
	Skin	2/34 [2 (5.9)/0 (0)/0 (0)/0 (0)]	see below	NR
	Others	Brain: 6/34 [5 (14.7)/1 (2.9)/0 (0)/0 (0)]	Grade ≤ 2: 5 (9.3)[98] Grade 3: 1 (1.9) Grade 4: 0 (0)	NR

Abbreviations: CGE – Cobalt Gray Equivalent; CIB – carbon ion boost; CIRT – carbon ion radiotherapy; CTC – Common Toxicity Criteria; CTCAE – Common Terminology Criteria for Adverse Events; fr. – fraction; FSRT – fractionated stereotactic radiation therapy; Gy – gray; GyE – gray equivalent; IMRT – intensity-modulated radiation therapy; NR – not reported; PFS – progression-free survival; RT – radiation therapy; RTOG – Radiation Therapy Oncology Group; v. – version; WHO – World Health Organisation.

[97] Other toxicities were also reported without a nuanced description of the frequency and severity using a standardised tool: "Minor acute toxicity included focal hair loss in 6 patients with superficial tumor location. Temporary middle ear effusion, sinusitis, and mastoiditis were frequent findings in patients at risk for this toxicity because of their tumor location".

[98] Not further specified.

IHE checklist used for the risk of bias assessment

Table A-9: IHE-18 Quality appraisal checklist for case series and instructions for use (adapted to the assessment) [156]

Study objective	
1.	Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section? **Yes**: The hypothesis/aim/objective of the study was clearly reported (includes patients, intervention and outcome). **Partial**: Only one or two components (patients, intervention, or outcome) were included. **No**: The hypothesis/aim/objective was not reported.
Study design	
2.	Are the characteristics of the participants included in the study described? **Yes**: All of the most relevant characteristics of the patients were reported: • Number, • Age, • Gender, • Severity of disease/condition, • Comorbidity, or • Etiology **Partial**: Some (at least 2) of the most relevant characteristics were reported. **No**: Less than 2 of the described characteristics of patients were reported.
3.	**Were the cases collected in more than one centre?** **Yes**: Cases were collected in more than one centre (multicentre study). **Unclear**: It was unclear whether patients from one or more cancer-therapy centre were included in the study. **No**: Cases were collected from one centre.
4.	**4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?** **Yes**: Both inclusion and exclusion criteria were reported. **Partial**: Either the inclusion or exclusion criteria were reported. **No**: Neither inclusion nor exclusion criteria was reported.
Study population	
5.	**Were participants recruited consecutively?** **Yes**: All of the most relevant characteristics of the patients were reported (for example, number, age, gender, ethnicity, the severity of disease/condition, comorbidity, or etiology). **Partial**: Some, but not all, of the most relevant characteristics, were reported. **No**: Only the number of patients was reported.
6.	**Did participants enter the study at a similar point in the disease?** **Yes**: The baseline data presented in the study (tables of patients' characterises) suggests that the majority (**at least 80%**) of patients entered the study at similar point of disease (i.e., regarding severity of the disease and the presence of complications: **histological TU type, clinical stage** based on **TNM/WHO** classification were used to make a judgement regarding similarity of the patient's diseases). **Unclear**: There was no/not enough baseline information on **clinical and histological** stage/type to make a judgment (e.g., only data on tumour dimensions, histological type or information on primary tumour for metastases and locally advanced TU) **No**: The baseline data presented in the study (tables of patients' characterises) suggests that the majority (**at least 80%**) of patients did not enter the study at similar point of disease (i.e., regarding severity of the disease and the presence of complications: **histological TU type, clinical stage** based on **TNM/WHO** classification were used to make a judgement regarding similarity of the patient's diseases).
7.	**Was the intervention of interest clearly described?** **Yes**: All of the most relevant characteristics of the intervention were reported: **Dosage** **Frequency or duration** of intervention, **Administration methods** **Characteristics of CIRT** **Partial**: Some (>1), but not all, of the most relevant characteristics were reported. **No**: Only the name (or ≤1 of the characteristics described above) of the intervention was reported.

Intervention and co-intervention	
8.	**Were additional interventions (co-interventions) clearly described?** **Yes**: All of the most relevant characteristics of the co-intervention(s) were reported (for example, **different type, dosage, the frequency of administration**, or **duration**); or the study clearly stated that a co-intervention was not administered for clinical reasons. **Partial**: Some, but not all, of the most relevant characteristics of the co-intervention, were reported. Authors report on other prior or concurrent interventions, i.e. photon therapy, but other possible co-interventions were not mentioned. **No**: No information regarding co-intervention(s) was provided; or only the name(s) of the co-intervention(s) were mentioned.
9.	**Were relevant outcome measures clearly stated and defined in introduction or methods section?** **Yes**: All relevant outcome measures were stated and defined in the introduction or methods section. **Partial**: Some, but not all, of the relevant outcome measures, were stated and defined in the introduction or method section, or all outcomes were stated but not defined. **No**: None of the relevant outcome measures was stated in the introduction or method section.
Outcome measures	
10.	**Were the relevant outcomes measured using appropriate objective/subjective methods?** **Yes**: All relevant outcomes were measured with appropriate methods. These measures can be objective (for example, gold standard tests or standardised clinical tests), subjective (for example, self-administered questionnaires, standardised forms, or patient symptoms interview forms), or both. **Partial**: Some, but not all, relevant outcomes were measured with appropriate methods. **No**: The methods used to measure the relevant outcomes were inappropriate.
11.	**Were the relevant outcome measures made before and after the intervention?** **Yes**: The relevant outcome measures were made pre- and post-intervention; or baseline measurements were not possible (for example, death). **Unclear**: The study did not report when the outcome measures were made. **No**: The outcome(s) were only measured post-interventional.
12.	**Were the statistical tests used to assess the relevant outcomes appropriate?** **Yes**: The statistical tests were used appropriately (for example, parametric test for normally distributed population vs nonparametric test for non-Gaussian population). Answer yes if no statistical analysis was performed and reasons for this were stated. **Unclear**: The statistical tests were not (rigorously) described in the methods section of the study, or it was not clearly stated for which purpose a certain test was used. **No**: The statistical tests used were inappropriate.
13.	**Was follow-up long enough for important events and outcomes to occur?** **Yes**: It was clear from the information provided that the follow-up period was long enough for the majority (at least 80%) of patients, to allow for important events and outcomes (for example, changes in clinical status, adverse events) to occur. Partial: Some indicators for the length of follow up are reported, but not all (i.e., median follow-up time but no range) **Unclear**: The length of follow-up was not clearly reported **No**: It is clear from the information provided that the follow-up period was not long enough to allow for important events and outcomes to occur. *Note: Assessor(s) should define the appropriate duration of follow-up for each outcome of interest (for example, short-term and long-term adverse events*
Statistical analysis	
14.	**Were losses to follow-up reported?** **Yes**: The number or proportion of patients lost to follow-up was clearly reported; the authors reported outcome results on all patients initially included, or the number lost to follow-up can be clearly subtracted from the number of patients enrolled, and the number of patients included in the final analysis. **Partial:** If Author did not clearly report on loss to follow-up (i.e., the reader may be able to draw conclusions on the loss to follow up without eradicating uncertainties regarding the true number or proportion having been lost to follow-up). **Unclear**: There was a discrepancy between the number or proportion of patients reported in tables, figures, and text. **No**: The number or proportion of patients lost to follow-up was not reported.

Results and conclusions	
15.	**Did the study provide estimates of random variability in the data analysis of relevant outcomes?** **Yes**: The estimates of the random variability (for example, standard error, standard deviation, the confidence interval for normally distributed data or range and interquartile range for non-normally distributed data) were reported for all of the relevant outcomes or could be calculated from the raw data presented in the study. **Partial**: The estimates of the random variability were reported for some, but not all of the relevant outcomes. **No**: The estimates of the random variability were not reported for any of the relevant outcomes.
16.	**Were the adverse events reported?** **Yes**: The undesirable or unwanted events during the study period or within a pre-specified time period were reported, or the absence of adverse event(s) was mentioned in the study. **Partial**: Some, but not all, important adverse events were reported. **No**: There was no statement about the presence or absence of adverse events.
17.	**Were the conclusions of the study supported by the results?** **Yes**: The conclusions of the study were supported by the evidence presented in the results and discussion sections. **Unclear**: Unclear conclusion statement that makes it difficult to link the presented evidence to conclusions. **Partial:** Some, but not all, conclusions are supported by the evidence presented in the results and discussion sections. **No**: The conclusions were not supported by the evidence presented in the results and discussion sections.
18.	**Were both competing interests and sources of support for the study reported?** **Yes**: Both competing interests and sources of support (financial or other) received for the study were reported, or the absence of any competing interest and source of support was acknowledged. **Partial**: Either the competing interest or source of support was reported. **No**: Neither competing interests nor sources of support were reported.

Risk of bias tables

Internal validity of the included studies was judged by 2 independent researchers (GG, MM). In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [2] and in the Guidelines of EUnetHTA [16, 17].

Table A-10: Risk of bias – study level (randomised studies), Cochrane Risk of Bias Tool see [16]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Habl, 2016 [132]	Yes[99]	Unclear[100]	No	No	Yes	No[101]	high

[99] Block randomization was used in the study: "randomization is performed in blocks of lenths [sic!] 4 stratified by one dichotomized factor (presence/absence of anti-hormonal therapy during radiation). GS and PSA values will be used for defining post-randomization strata" [157].

[100] The authors do not provide a clear description of how/if the allocation was concealed. That is to say; the researchers involved in randomly assigning the patients may have had foreknowledge regarding forthcoming allocations.

[101] Block randomization in combination with a lack of blinding increases the probability of compromising, and thus leading to a threat to, the random assignment process (see for a description of critical combinations between certain elements of selected allocation and blinding strategies [158]).

Table A-11: Risk of bias for prostate cancer studies – study level (case series) see [156]

Study reference/ID	Akakura, 2004 [159]	Ishikawa, 2015 [133]	Ishikawa, 2006 [139]	Maruyama, 2017 [134]	Nikoghosyan, 2011 [136]	Nomiya, 2016 [138]	Shimazaki, 2010 [160]	Shimazaki, 2006 [161]	Tsuji, 2005 [137]	Wakatsuki, 2008 [135]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial[102]	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial
3. Were the cases collected in more than one centre?	No	No	No	No	No	Yes	No	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Yes	Yes	Partial	Yes	No	No	Yes	Yes
5. Were participants recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
6. Did participants enter the study at a similar point in the disease?	No	No	No	No	Yes	No	No	No	No	No
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Partial	Partial	Partial	Partial	Yes	Partial	Partial	Yes	Partial	Partial
9. Are the outcome measures clearly defined in the introduction or methods section?	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
14. Was the loss to follow-up reported?	No	No	No	No	No	No	No	No	No	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
17. Are the conclusions of the study supported by results?	Yes	Yes	No	Yes	Yes	No	No	Partial	Yes	Yes
18. Are both competing interest and source of support for the study reported?	No	Yes	Partial	Yes	Yes	Partial	Partial	Partial	No	Partial
Total points	10,5	13,5	12	13,5	13,5	12	10	9,5	12,5	12
Risk of Bias	High	moderate	moderate	moderate	moderate	moderate	High	High	moderate	moderate

[102] Outcome measures were not reported in the introduction or methods section.

Table A-12: Risk of bias for brain, ENT, eye, and skull base tumour studies – study level (case series) see [156] (part 1)

Study reference/ID	Combs, 2009 [162]	Combs, 2013a [163]	Combs, 2013c [164]	Debus, 2000 [165]	Hasegawa, 2012 [69]	Jensen 2015 [85]	Jingu 2012 [86]	Mizoe 2004 [32]	Mizoe 2012 [33]	Mizoe, 2007 [68]	Mizoe, 2009 [44]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Partial	No	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial
3. Were the cases collected in more than one centre?	No	No	No	No	No	No	No	No	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	No	No	No	No	Partial	Partial	Partial	Partial	Partial	Partial	Partial
5. Were participants recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
6. Did participants enter the study at a similar point in the disease?	No	No	No	No	Unclear	No	Unclear	No	No	No	Unclear
7. Was the intervention clearly described in the study?	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	No	No	Partial	Yes	Partial	Partial	No	No	Yes	Yes	No
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Partial	No	Yes	Yes	Yes	Yes	Yes	Yes	No
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Was the length of follow-up reported?	Yes	Yes	Yes	Partial	Yes	Partial	Yes	Yes	Yes	No	Yes
14. Was the loss to follow-up reported?	No	No	No	No	No	No	No	No	No[103]	No[103]	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	No	No	No	Yes	No	Yes	No	Partial	Yes	Yes
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Yes	Yes	Unclear	No	Yes	Yes	Yes	No	No	Yes	Yes
18. Are both competing interest and source of support for the study reported?	Unclear[104]	Yes	Partial	Partial	No	Partial	Partial	Partial	Partial	Yes	No
Total points	10	9,5	9,5	8,5	12,5	11	12,5	10	11,5	12,5	11
Risk of Bias	High	High	High	High	moderate	moderate	moderate	High	moderate	moderate	moderate

[103] The authors reported that no patient was "lost to follow up". However and critically speaking, people who died were not considered as "loss to follow up".

[104] The authors wrote that they "made no disclosure" regarding the conflict of interest [162].

Table A-12: Risk of bias for brain, ENT, eye, and skull base tumour studies – study level (case series) see [156] (part 2)

Study reference/ID	Mizoguchi 2015 [166]	Rieken, 2012 [167]	Schulz-Ertner, 2002 [168]	Schulz-Ertner, 2003 [169]	Schulz-Ertner, 2005 [87]	Schulz-Ertner, 2007 [43]	Shirai 2017 [31]	Takahashi, 2009 [170]	Tsuji 2007 [171]	Uhl, 2014 [42]	Yanagi 2009 [172]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	No	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial	Partial
3. Were the cases collected in more than one centre?	No	No	No	No	No	No	No	No	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Partial	No	No	No	No	No	Yes	No	Partial	No	No
5. Were participants recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
6. Did participants enter the study at a similar point in the disease?	Unclear	No	No	No	Yes	No	No	Unclear	No	Unclear	Unclear
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	No	Yes	No	No	No	Yes	No	Yes	No	Yes	No
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
13. Was the length of follow-up reported?	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	No	No	No	No	No	No	No	Partial	No	No	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	No	No	No	No	Yes	Yes	Yes	No	No	No
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	Yes	Unclear	No	No	Yes	No	Yes	No[105]	No	No	No
18. Are both competing interest and source of support for the study reported?	No[106]	Partial	No	Partial	Partial	Partial	Partial	No	No	Partial	Partial
Total points	10,5	9,5	9	9,5	11,5	11,5	12	10,5	8,5	11	10
Risk of Bias	High	High	High	High	moderate	moderate	moderate	High	High	moderate	High

[105] The study concluded, inter alia, that the Quality of Life (QoL) for patients with skull base chordomas will be improved by a combination of surgical removal and CIRT without having measured quality of life within the study.

[106] The authors report on both competing interest and source of support. However, source of support is vaguely formulated: "(…) there has been no significant financial support for this work that could have influenced its outcome" [166].

Table A-13: Risk of bias for GI tumour studies – study level (case series) see [156]

Study reference/ID	Akutsu, 2012 [106]	Kasuya, 2017 [173]	Kato, 2004 [174]	Yamada, 2016 [107]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Partial	Partial	Partial	Partial
3. Were the cases collected in more than one centre?	Yes	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Yes	Partial	Yes
5. Were participants recruited consecutively?	Unclear	Unclear	Unclear	Unclear
6. Did participants enter the study at a similar point in the disease?	No	No	No	No
7. Was the intervention clearly described in the study?	Yes	Partial	Yes	No
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	No	Yes	No
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Yes	Yes	Unclear
13. Was the length of follow-up reported?	Partial	Yes	Yes	Yes
14. Was the loss to follow-up reported?	No	No	No	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	No	Yes	Yes	Yes
16. Are adverse events reported?	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	No	No[107]	No	Yes
18. Are both competing interest and source of support for the study reported?	Partial	No	Partial	Yes
Total Points	11,5	10,5	12	11,5
Risk of Bias (RoB)	moderate	High	moderate	moderate

[107] The study [173] draws conclusions on the effectiveness of CIRT in the selected patient group on the basis of the underlying results. However, the study was neither a randomised controlled study nor a controlled study. In addition, no indirect comparison of the observed survival rates with the survival of conventional therapies (or other types of radiotherapy) was conducted leading to an inability to draw such conclusions – even more so when considering that they stated that the intervention was effective while having found no favourable results when using patient relevant outcomes (i.e., survival rates).

Table A-14: Risk of bias for NSCLC studies – study level (case series) see [156]

Study reference/ID	Iwata, 2010 [100]	Iwata, 2013 [99]	Koto, 2004[108] [30]	Miyamoto, 2003 [29]	Miyamoto[108], 2007a [102]	Miyamoto, 2007b [101]	Takahashi, 2015 [98]	Yamamoto, 2013 [175]	Yamamoto, 2017 [97]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Partial	Partial	No	Partial	Partial	Partial	Partial	No	Partial
3. Were the cases collected in more than one centre?	No	No	No	No	No	No	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Partial	Partial	No	No	Partial	Partial	Yes	Partial	Yes
5. Were participants recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
6. Did participants enter the study at a similar point in the disease?	Yes	Yes	Yes	No	Yes	No	No	No	Yes
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Partial	Yes	No	No	No	No	No	No	No
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes	Unclear[109]	Yes	Yes	Partial	Yes	Unclear[110]	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Unclear[109]	Yes	Yes	Yes	Yes	Unclear[110]	Yes
13. Was the length of follow-up reported?	Yes	Yes	Yes	Partial[111]	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	No	No	No	No	Partial[112]	Partial[112]	No	No	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes
16. Are adverse events reported?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
17. Are the conclusions of the study supported by results?	No	No	Yes	Yes	No	No[113]	Yes	No	Yes
18. Are both competing interest and source of support for the study reported?	Partial	Partial	No	Partial	Yes	Yes	Yes	No	Yes
Total points	12.5	13	8	10	13	11.5	13	8	14
Risk of Bias (RoB)	Moderate	Moderate	High	High	Moderate	Moderate	Moderate	High	Moderate

[108] 2 Studies [29, 30] used the same sample in their analysis. None of the studies were excluded prior to the risk of bias assessment since the studies reported on different endpoints.

[109] The authors did not sufficiently report on the methods and statistical analysis used in the study.

[110] A clear description of the subjective/objective methods as well as the statistical analysis used in this study was absent.

[111] The median follow-up time was reported without including the range.

[112] The authors stated that no patients were lost to follow-up. However, people dying were not considered as a loss to follow up.

[113] The study draws conclusions on improved quality of life (QoL) for patients, without having measured QoL.

Table A-15: Risk of bias for bone and soft tissue tumour studies – study level (case series) see [156]

Study reference/ID	Kamada, 2002 [176]	Sugahara, 2012[126]
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	Yes
2. Are the characteristics of the participants included in the study described?	Partial	Partial
3. Were the cases collected in more than one centre?	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	Partial
5. Were participants recruited consecutively?	Unclear	Unclear
6. Did participants enter the study at a similar point in the disease?	No	No
7. Was the intervention clearly described in the study?	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	No	No
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes
12. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
13. Was the length of follow-up reported?	Yes	Yes
14. Was the loss to follow-up reported?	No	No
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes	Yes
16. Are adverse events reported?	Yes	Yes
17. Are the conclusions of the study supported by results?	No	Partial
18. Are both competing interest and source of support for the study reported?	Partial	Yes
Total Points	11.5	12
Risk of Bias (RoB)	Moderate	Moderate

Applicability table

Table A-16: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	In total, the sum of all of all samples of the included studies lead to approximately 4,095 patients enrolled patients[114] in 27 included clinical studies and 3,914 received carbon ion radiotherapy (CIRT). Most patients suffered from prostate, lung or ENT tumours, with 2,715[115], 559 and 415 enrolled patients with cancer in those areas respectively. In addition, 215 and 112 patients suffered from different gastrointestinal tumours and skull base tumours respectively. Brain and bone & soft tissue sarcomas were less frequently prevalent in the patient population of the included studies, with 62 and 17 enrolled patients respectively. The majority of the patients were adults, with a median age of all included patients above 18 years and the gender was predominantly male due to the large proportion of prostate cancer patients enrolled in the included studies. Within all enrolled patients,the stage and histology of the tumours were heterogenous of the included studies due to the scope of this assessment.
Intervention	Carbon ion radiotherapy was used as the intervention in all of the included studies at different dosages. However, varieties of co-interventions (e.g., prior chemotherapy, surgery, photon RT, androgen deprivation therapy, etc.) were indicated for the enrolled patients, depending on the histology and grade of a tumour.In addition, 1 study described the use of raster scanned carbon ion as a boost (CIB) in combination with other forms of RT (e.g., intensity-modulated RT).
Comparators	Only 1 of the included studies, focusing on the safety of CIRT solely, included a comparison group. Indirect comparisons were undertaken by some of the included studies. Thus, efficacy and safety could insufficiently be assessed due to the lack of controlled studies.
Outcomes	Most of the included studies reported on mortality related endpoints that is; overall survival (OS) was most frequently reported but also other survival related crucial endpoints were reported by some of the included studies, such as progression-free survival (PFS) or disease-free survival (DFS). Most of the statistical tests for those outcomes were not performed to compare those outcomes with patients undergoing other types of radiotherapy. As such, only 5 studies (1 case series and 1 case-control study in the ENT area and 2 case-control studies in the lung area) statistically compared the efficacy and/or safety related outcomes with patients undergoing other forms of radiotherapy. Some studies used a historical control group, and others used a case-control study design. As such, most of the studies used statistical tests to either elaborate predictor variables for certain outcomes, and/or to elaborate the ideal dose for CIRT (i.e., the studies with a dose-escalation study design). Other crucial patient-reported outcomes (PRO) such as Health-related Quality of Life were only reported in some of the included studies. For safety parameters, a variety of different acute and late radiation morbidities were observed, and only 1 study compared those with a historical control of conventional radiotherapy.
Setting	One of the included studies was a multi-centre study. The rest of the studies were single centre studies. All of the included studies were based in Japan or Germany, with 21 and 6 included studies from those countries respectively. Many ongoing studies are currently undertaken in the same geographical regions, but ongoing controlled studies were also found in countries such as Italy, France and China. All included studies were published between 2005 and 2017. Applicability issues regarding the different geographical settings are not expected.

[114] Patients may have enrolled in multiple studies. In case it was clearly stated or obvious (i.e., quality of life assessments of patients being enrolled in other included studies), patients were only calculated once for the applicability table.

[115] 2 included studies [134, 135], assessed the quality of life for 611 patients being already included in other included studies. The reader is referred to the data extraction table (Table A-7) for more information.

List of ongoing randomised and non-randomised clinical trials

Table A-17: Ongoing controlled studies elaborating on the efficacy and/or safety of carbon ion radiotherapy (CIRT)

Source & Identifier/ Trial Name	Conditions	Phase	Target Group	Study Types	Study Designs	Intervention	Comparison	Enrolled Patients	Primary Outcome	Primary Completion Date	Sponsor
Bone and Soft Tissue Sarcoma											
ClinicalTrials.gov NCT01811394	Sacral Chordoma	Ph. 2	Adults	Interventional	Allocation: Randomised/Intervention Model: Parallel Assignment/Masking: None (Open-Label)/ Primary Purpose: Treatment	PRT: Treatment is performed using 16 x 4 GyE protons	CIRT: Treatment is performed using 16 x 4 GyE C-ions	100	Safety and feasibility (incidence of Grade 3-5 toxicity)	June 2020	Heidelberg University
ClinicalTrials.gov NCT02986516	Sacral Chordoma	NR	Adults	Interventional	Allocation: Randomised/Intervention Model: Parallel Assignment/Masking: None (Open-Label)/ Primary Purpose: Treatment	Randomised Cohort: Surgical treatment with a different approach, based on the characteristics of the tumour or definitive high dose radiotherapy (carbon ion radiotherapy, proton-therapy, mixed photons-proton therapy) will be assigned by randomization	Prospective cohort: Surgical treatment or definitive high dose radiotherapy will be selected by the patients and will be prospectively evaluated	100	Relapse-Free Survival (RFS)	September 2021	Italian Sarcoma Group
Brain & skull base Cancer											
ClinicalTrials.gov NCT01182779	Chordoma	Ph. 3	Adults	Interventional	Allocation: Randomised Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	CIRT: Total dose to the PTV2 - 45 Gy E in 3 Gy E/d, 4-6 days a week, 15 fractions Total dose to the PTV1 - 63 Gy E ± 5%, further 5-7 fractions a 3 Gy E	PRT: Total dose to the PTV2 - 50 to 56 Gy E in 2 Gy E/d, 4-6 days a week, 28 fractions Total dose to the PTV1 - 72 Gy E ± 5%, further 6-9 fractions a 2 Gy E	319	Local-progression-free survival (LPFS)	August 2015[116]	Heidelberg University

[116] The completion date is unknown: no study publishing results of this study was identified through the systematic search. The last update of the study in clinicaltrials.gov was in August 2010 (see https://clinicaltrials.gov/ct2/show/NCT01182779, download on 10/10/2018).

Source & Identifier/ Trial Name	Conditions	Phase	Target Group	Study Types	Study Designs	Intervention	Comparison	Enrolled Patients	Primary Outcome	Primary Completion Date	Sponsor
ClinicalTrials.gov NCT01795300	Meningioma	Ph. 1/ Ph. 2	Adults	Interventional	Allocation: Randomised Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	CIRT: Total Dose 45 Gy E, 15 fractions, 3 Gy E single dose; PRT: 45 Gy E, 15 fractions, 3 Gy E single dose; Hypofractionated Photon Therapy: 3 Gy E Total Dose 45 Gy E, 15 fractions, 3 Gy E single dose;	Conventional Photon Radiotherapy: 1.8 Gy E Total Dose 57.6 Gy E, 32 fractions, 1.8 Gy E single dose	80	Toxicity graded according to CTCAE Version 4.1 after 1 year	February 2015[117]	University Hospital Heidelberg
ClinicalTrials.gov NCT01182753	Chondro-sarcoma	Ph. 3	Adults	Interventional	Allocation: Randomised Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	CIRT: Total dose to the PTV2 - 45 Gy E in 3 Gy E/d, 4 - 6 days a week, 15 fractions Total dose to the PTV1 - 60 Gy E ± 5%, further 4 - 6 fractions a 3 Gy E	PRT: Total dose to the PTV2 - 50 to 56 Gy E in 2 Gy E/d, 4 - 6 days a week, 25 - 28 fractions Total dose to the PTV1 - 70 Gy E ± 5%, further 6 - 10 fractions a 2 Gy E	154	Local-Progression Free Survival (LPFS) [Time Frame: 5 years]	August 2022	Heidelberg University
ClinicalTrials.gov NCT01165671	Primary Glioblastoma	Ph. 2	Adults	Interventional	Allocation: Randomised/Intervention Model: Parallel Assignment/Masking: None (Open-Label)/ Primary Purpose: Treatment	CIRT: up to 18 Gy E in 3 Gy E fractions to the macroscopic tumour	Proton Radiotherapy: up to 10 Gy E in 2 Gy E fractions to the macroscopic tumour	150	Overall Survival/ Progression-free Survival/ Toxicity	June 2014[118]	University Hospital of Heidelberg (Germany)
ClinicalTrials.gov NCT01166308	Recurrent Gliomas	Ph. 1/ Ph. 2	Adults	Interventional	Allocation: Randomised/Intervention Model: Parallel Assignment/Masking: None (Open-Label)/ Primary Purpose: Treatment	CIRT: 10 x 3Gy E to 16 x 3 Gy E	Fractionated Stereotactic Radiotherapy (FSRT): Standard Treatment as Re-Irradiation performed as Fractionated Stereotactic Radiotherapy (FSRT)up to 36 Gy in single doses of 2 Gy	436	Overall Survival/ Progression-free Survival	July 2014[119]	University Hospital of Heidelberg (Germany)

[117] The completion date is unknown: No study publishing results of this study was identified through the systematic search. The last update of the study in clinicaltrials.gov was in February 2013 (see https://clinicaltrials.gov/ct2/show/NCT01795300, download on 10/10/2018).

[118] 1 publication [177] was identified within the systematic literature review: no results were included in this publication. Information regarding this study on the website on clinicaltrials.gov was last updated on 20/02/2013 (see https://clinicaltrials.gov/ct2/show/NCT01165671, download on 01/02/2018).

[119] 1 publication [178] (study protocol) was identified within the systematic literature review: no results were included in this publication. Information regarding this study on the website on clinicaltrials.gov was last updated on 20/02/2013 (see https://clinicaltrials.gov/ct2/show/NCT01166308, download on 02/02/2018).

Source & Identifier/ Trial Name	Conditions	Phase	Target Group	Study Types	Study Designs	Intervention	Comparison	Enrolled Patients	Primary Outcome	Primary Completion Date	Sponsor
Cancer in the Ear-Nose-Throat Region											
ClinicalTrials.gov NCT02838602	Adenoid Cystic Carcinoma and Sarcoma	NR	Adults	Interventional	Randomised, parallelly assigned, open-label, controlled study	Radiation: C-ions therapy	Radiation: Advanced external radiotherapy by X-rays or protons	250	Progression-free survival (PFS)	May 2024	Hospices Civils de Lyon
Gastrointestinal (GI) Carcinoma											
ClinicalTrials.gov NCT02802124	Hepato-cellular Carcinoma	Ph. 1	Adults	Interventional	Allocation: Non-Randomised/Intervention Model: Parallel Assignment/Masking: None (Open Label)/Primary Purpose: Treatment	CIRT: Four dose levels [55 Gray equivalent (GyE)/10 fractions (Fx), 60GyE/10Fx, 65GyE/10Fx, 70GyE/10Fx]	PRT + CIRT: Four dose levels (proton 50GyE/ 25Fx+ carbon 15GyE/ 5Fx, proton 34GyE/ 17Fx+ carbon 30GyE/ 10Fx, proton 18GyE/ 9Fx+ carbon 45GyE/ 15Fx, carbon 60GyE/ 20Fx)	48	Number of participants with treatment-related adverse events as assessed by CTCAE v4.0	June 2019	Shanghai Proton and Heavy Ion Center
Lung Cancer											
Particle Therapy Co-Operative Group UMIN000023183	Small-sized peripheral non-small cell lung cancer with clinical stage IA	Ph. 2	Adults	Interventional	Parallel, non-randomised, open-label, controlled study	CIRT: not specified	Surgical removal	525	Five-year overall survival (OS)	NR[120]	Kanagawa Cancer Center, Kanagawa Prefectural Hospital Organization

Abbreviations: CIRT – carbon ion radiotherapy; CTCAE – Common Terminology Criteria for Adverse Events; Fx. – fraction; Gy – gray; GyE – gray equivalent; Ph. – Phase.

[120] The anticipated start of the trial was in August 2016. No information regarding the estimated completion date is provided (see https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000026513, download on 10.10.2017).

Potential indications for the use of carbon ion radiotherapy (CIRT) according to clinical studies

Table A-18: Potential indications for CIRT according to the MedAustron list (frequencies of identified clinical studies with patients with specific indications)

	Indication	The frequency of clinical studies including pts with indication
Skull Base Tumours	Skull base tumours	
	Chordoma	**6**
	Chondrosarcoma	**6**
	Meningioma grade II/grade III	**4**
	Meningioma grade I (complex)	**2**
	Craniopharyngioma	**1**
	Pituitary adenoma (not suitable for stereotaxy)	**1**
	Acoustic neuroma	0
	Other neurinomas	0
	Glomus tumour	0
	Retinoblastoma	0
	Lacrimal gland tumours	**1**
	Sarcomas incl. Ewing's sarcoma	0
	Rhabdomyosarcomas of the skull base and orbit	0
Eye	**Choroid Melanoma**	**1**
Brain	**Brain**	
	Glioma grade II	**3**
	Glioma grade III	**3**
	Glioblastoma	**3**
	Ependymoma	0
	Medulloblastoma	0
	Other childhood brain tumours	0
	Orbital tumours[121]	**1**
ENT-Tumours	**ENT-Tumours**	
	Tumour of the nasal cavity and paranasal sinus	**5**
	Maxillary sinus carcinoma	**3**
	Nasopharyngeal carcinoma[122]	**3**
	Oropharyngeal carcinoma[122]	3
	Tonsil carcinoma	0
	Tongue base carcinoma	0
	Salivary gland carcinoma (pleomorphic)	0
	Salivary gland carcinoma (adenoid cystic)	**5**
	Sarcoma in the ENT area including Ewing's sarcoma	**1**
	Rhabdomyosarcoma	0

[121] The classification of orbita tumours may be confused here. In this assessment, information on orbita tumours can be found in the ear-nose-throat region.

[122] Region not specified in the identified studies: may include naso- or oropharynxcarcinoma.

	Indication	The frequency of clinical studies including pts with indication
Lung	**Non-small cell lung carcinomas (NSCLC)**[123]	**8**
	Mediastinal tumours (including thymoma)	0
	Pleural mesothelioma	0
Gastrointestinal Tumours	**Gastrointestinal tumours**	
	Esophageal carcinoma	**1**
	Pancreatic cancer	0
	Liver carcinoma	**2**
	Rectal carcinoma recurrence presacral	**1**
	Schwannomas/malignant schwannomas	0
	Ewing's sarcoma	0
Bone and Soft Tissue	**Bone and soft tissue**	
	Osteosarcoma	**2**
	Soft tissue sarcoma	**2**
	Sacral chordoma	1
	Sacral chondrosarcoma	**2**
	Spinal meningiomas	0
Prostate Cancer	**Prostate cancer**	**11**
Breast Cancer	Breast cancer (left, young, patient)	0
Kidney	Nephroblastoma	0
Nervous System	**Neuroblastoma**[124]	**0**
"Hematologic Cancer"	Non-Hodgkin's lymphoma (in exceptional cases)	0
	Hodgkin's lymphoma	0
Other	Solitary liver metastases in colorectal cancer	0
	Retroperitoneal metastases in controlled primary tumours	0
	Oligometastases in controlled primary tumours in selected indications[125]	1

Abbreviations: ENT – Ear-Nose-Throat; pts – patients;

[123] 8 studies with NSCLC patients and 1 further study [175] enrolled patients with oligo-recurrence in the lung in the sample. Therefore, 9 studies were identified for lung cancer in total.

[124] Only 1 study (n=35) [31] included 5 patients with olfactory neuroblastomas in their sample. For more information on this study, see the data extraction table for cancer in the ENT region (Table A-4).

[125] The identified study [175] enrolled patients with oligo-recurrence in the lung in the sample.

*Table A-19: **Skull base** tumours – identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT[126])*

Name of first author, year of publication	Study Design	Chordoma/ Chondro-sarcoma[127]	Meningioma Grade II/ Grad III or Grade I (complex)	Cranio-pharyngioma	Pituitary adenoma	Lacrimal gland tumours	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Combs, 2009 [162]	Case series	17					17	17
Combs, 2013 [163]	Case series		107	5	14		84	260
Combs, 2013 [164]	Case series		70				26	70
Debus, 2000 [165]	Case series	27	6				45	45
Mizoe, 2009 [44]	Case series	33					33	**33**
Mizoguchi, 2015[166]	Case series					21	21	21
Rieken, 2012 [167]	Case series		7				33	33
Schulz-Ertner, 2002 [168]	Case series	37					37	37
Schulz-Ertner, 2003 [169]	Case series	74					74	74
Schulz-Ertner, 2007 [43]	Case series	54					54	**54**
Takahashi, 2009 [170]	Case series	32					32	32
Uhl, 2014 [42]	Case series	25					25	**25**
Total		**299**	**190**	**5**	**14**	**21**	**481**	**701**

*Table A-20: Tumours in the **brain** region – identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT)*

Name of first author, year of publication	Study design	Glioma Grade II	Glioma Grade III	Glioblastoma	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Combs, 2013a [163]	Case series	51	26	29	84	260
Hasegawa, 2012 [69]	Case series	14			14	14
Mizoe, 2007 [68]	Case series		16	32	48	48
Rieken, 2012 [167]	Case series	5	3	18	26	33
Total		**70**	**45**	**79**	**172**	**355**

[126] The number of patients for specific tumour entities in those studies refers to the total number of patients enrolled in the clinical study and not to the CIRT patients. In Combs, 2013 [163], for instance, 84 out of 260 patients received CIRT.

[127] In total, 8 studies were identified for chordomas and chondrosarcomas. Some of the studies had only chordomas or chondrosarcomas in their sample. Due to practical reasons, those studies were summed up: Mizoe, 2009 [44] had only patients with chordomas in their sample and Schulz-Ertner, 2002 [168] had only patients with chondrosarcomas in their sample.

Table A-21: ***Prostate cancer*** *– identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT)*

Name of first Author and year of publication	Study Design	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Akakura, 2004 [159]	Case series	247	247
Habl, 2016 [132]	RCT	45	92
Ishikawa, 2006 [139]	Case series	175	175
Ishikawa, 2015 [133]	Before-After Study & case series study	76	76
Maruyama, 2017 [134][128]	Before-After Study		
Nikoghosyan, 2011 [136]	Case series	14	14
Nomiya, 2016 [138]	Multi-institutional observational studies/case series	2,157	2,157
Shimazaki, 2010 [160]	Case series	254	254
Shimazaki, 2006 [161]	Case series	37	37
Tsuji, 2005 [137]	Case series	201	201
Wakatsuki, 2008 [135][129]	Before-After Study		
Total		**3,206**	**3,253**

Abbreviations: CIRT – carbon ion radiotherapy

[128] 417 patients were included in this assessment to assess health related quality of life (HRQoL) before and after CIRT. However, those patients are assumed to be included in [138]. Thus, those patients were only counted once in this analysis.

[129] 194 patients were included in this assessment to assess health related quality of life (HRQoL) before and after CIRT. However, those patients are assumed to be included in [137]. Thus, those patients were only counted once in this analysis.

*Table A-22: **Lung cancer** region – identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT)*

Name of first Author and year of publication	Study Design	Indication	CIRT pts enrolled in the clinical study	Patients enrolled in the clinical study
Iwata, 2010 [100]	Case-control study	NSCLC	23	80
Iwata, 2013 [99]	Case-control study	NSCLC	27	70
Koto, 2004 [30]	Case series	NSCLC	81	81
Miyamoto, 2003[130] [29]	Case series	NSCLC		
Miyamoto, 2007a[102]	Case series	NSCLC	79	79
Miyamoto, 2007b [101]	Case series	NSCLC	50	50
Takahashi, 2015 [98]	Case series	NSCLC	62	62
Yamamoto, 2013 [175]	Case series	Oligo-recurrence in the lung	91	91
Yamamoto, 2017 [97]	Case series	NSCLC	218	218
Total patients			**631**	**731**

Abbreviations: CIRT – carbon ion radiotherapy; NSCLC – non-small cell lung cancer

*Table A-23: Cancer in the **Ear-Nose-Throat (ENT) region** – identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT)*

Name of first author and year of publication	Study design	Tumours in the nasal cavity and paranasal sinus	Maxillary sinus carcinomas	Pharynx carcinoma[131]	adenoid cystic salivary gland tumours	Sarcomas in the head and neck region	Orbita	CIRT patients	Patients enrolled in the clinical study
Jingu, 2012 [86]	Case series	11				27		27	27
Mizoe, 2004 [32]	Case series	10	2	7	4			36	36
Mizoe, 2012 [33]	Case series	116	2	23	15		20	236	236
Schulz-Ertner, 2005 [87]	Case-control study				63			29	63
Shirai, 2017 [31]	Case series	18	9	4	6			35	35
Yanagi, 2009 [172]	Case series	60						72	72
Jensen, 2015 [85]	Case series				54			54	54
Total		**215**	**13**	**34**	**142**	**27**	**20**	**489**	**523**

[130] 2 studies [29, 30] are assumed to have reported on the same 81 patients in their studies. It was found out considerably late in the assessment and both of the studies were excluded for the qualitative synthesis because of high risk of bias. Therefore, those patients were only counted once in the analysis.

[131] Region not specified in the identified studies: may include naso- or oropharynxcarcinoma.

*Table A-24: Cancer in the **bone and soft tissue area** – identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT)*

Name of first author and year of publication	Study design	Soft Tissue Sarcoma	Osteosarcoma	Sacral Chordoma	Sacral Chondrosarcoma	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Kamada, 2002 [176]	Case series	16	15	11	6	57	57
Sugahara, 2012[126]	Case series	13	3		1	17	17
Total		**29**	**18**	**11**	**7**	**74**	**74**

*Table A-25: Cancer in the **gastrointestinal** region – identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT)*

Name of first Author and year of publication	Study design	Oesophagus carcinoma	Liver carcinoma	Rectal carcinoma	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Akutsu, 2012 [106]	Case series	31			31	31
Kasuya, 2017 [173]	Case series		124		124	124
Kato, 2004 [174]	Case series		24		24	24
Yamada, 2016 [107]	Case series			184	184	184
Total		**31**	**148**	**184**	**363**	**363**

*Table A-26: Cancer in the **eye region** identified studies according to study design, sample size and specific indications according to the list of potential indications for carbon ion radiotherapy (CIRT)*

Name of first Author and year of publication	Study Design	Choroid Melanoma	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Tsuji, 2007 [171]	Case series	59	59	59

*Table A-27: Cancer in the **gynecologic region** – identified studies according to study design and sample size*

Name of first Author and year of publication	Study design	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Kato 2006 [179]	Case series	44	44
Nakano 2006 [180]	Case series	49	49
Nakano 1999 [181]	Case series	31	31
Wakatsuki 2015a [182]	Case series	26	26
Wakatsuki 2014a [184][132]	Case series		
Wakatsuki 2014b [185][133]	Case series		
Wakatsuki 2015b [183]	Case series	91	91
Total		**241**	**241**

*Table A-28: Cancer in the **skin** region – identified studies according to study design and sample size*

Name of first Author and year of publication	Study design	Number of patients enrolled in the clinical studies receiving CIRT	Number of patients enrolled in the clinical studies
Zhang 2012 [186]	Case series	45	45

[132] 22 patients were enrolled in this study. Those patients were also included in the dose-escalation, case series study of Wakatsuki 2015b [183]. None of the studies was excluded for research question 1, since different outcomes were measured. However, patients were only included once in the estimation of patients having been treated with CIRT in those clinical studies.

[133] 58 patients were enrolled in this study. Those patients were also included in the dose-escalation, case series study of Wakatsuki 2015b [183]. None of the studies was excluded for research question 1, since different outcomes were measured. However, patients were only included once in the estimation of patients having been treated with CIRT in those clinical studies.

Literature search strategies

Search strategy for Cochrane

Search Name: Carbon-Ions in Cancer Therapies	
Search Date: 07/09/2017	
ID	Search
#1	MeSH descriptor: [Heavy Ion Radiotherapy] explode all trees
#2	MeSH descriptor: [Ions] this term only and with qualifier(s): [Therapeutic use - TU]
#3	MeSH descriptor: [Heavy Ions] explode all trees and with qualifier(s): [Therapeutic use - TU]
#4	carbon ion* near (therap* or treat* or radiotherap* or radio-therap* or regimen* or program*) (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Neoplasms] explode all trees
#7	MeSH descriptor: [Carcinoma] explode all trees
#8	neoplasm* or cancer* or tumor* or tumour* or carcinoma* or oncolog* (Word variations have been searched)
#9	#6 or #7 or #8
#10	#5 and #9 in Trials
Total: 44 Hits	

Search strategy for CRD

Search Name: Carbon-Ion Therapy	
Search Date: 07/09/2017	
ID	Search
#1	MeSH DESCRIPTOR Heavy Ion Radiotherapy EXPLODE ALL TREES
#2	MeSH DESCRIPTOR Ions WITH QUALIFIER TU
#3	MeSH DESCRIPTOR Heavy Ions EXPLODE ALL TREES WITH QUALIFIER TU
#4	(carbon ion* NEAR (therap* OR treat* OR radiotherap* OR radio-therap* OR regimen* OR program*))
#5	#1 OR #2 OR #3 OR #4
Total: 11 Hits	

Search strategy for Embase

Search Name: Carbon-Ions in Cancer Therapies			
Search Date: 07/09/2017 18:01:40.183			
ID	Query results	Results	Date
#20	(('carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab) AND ('malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*))) AND ('clinical trial'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial'/de)) OR (('carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab) AND ('malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*))) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)) OR (('carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab) AND ('malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*))) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti))	282	7 Sep 2017
#19	(('carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab) AND ('malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*))) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti)	134	7 Sep 2017
#18	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,121,462	7 Sep 2017
#17	(('carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab) AND ('malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*))) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	63	7 Sep 2017
#16	(('carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab) AND ('malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*))) AND ('clinical trial'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial'/de)	172	7 Sep 2017
#15	('carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab) AND ('malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*))	1,872	7 Sep 2017

#14	'malignant neoplasm'/exp OR 'neoplasm'/exp OR 'carcinoma'/exp OR (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*)	5,525,971	7 Sep 2017
#13	neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR oncolog*	5,060,901	7 Sep 2017
#12	'carcinoma'/exp	1,040,879	7 Sep 2017
#11	'neoplasm'/exp	4,164,393	7 Sep 2017
#10	'malignant neoplasm'/exp	3,064,172	7 Sep 2017
#9	'carbon ion radiotherapy'/exp OR 'carbon ion radiation'/exp OR 'carbon ion irradiation'/exp OR 'ion therapy'/exp OR 'heavy ion radiation'/exp OR 'heavy ion'/exp/dd_dt OR 'ion'/mj/dd_dt OR ('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab	2,545	7 Sep 2017
#8	('carbon ion*' NEAR/3 (therap* OR treat* OR radiotherap* OR 'radio therap*' OR regimen* OR program*)):ti,ab	1,047	7 Sep 2017
#7	'ion'/mj/dd_dt	27	7 Sep 2017
#6	'heavy ion'/exp/dd_dt	68	7 Sep 2017
#5	'heavy ion radiation'/exp	715	7 Sep 2017
#4	'ion therapy'/exp	1,456	7 Sep 2017
#3	'carbon ion irradiation'/exp	17	7 Sep 2017
#2	'carbon ion radiation'/exp	39	7 Sep 2017
#1	'carbon ion radiotherapy'/exp	55	7 Sep 2017

Search strategy for Medline via OVID

Database:Ovid MEDLINE(R) <1946 to August Week 5 2017>, Ovid MEDLINE(R) Epub Ahead of Print <September 06, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 05, 2017>, Ovid MEDLINE(R) Daily Update <September 05, 2017	
Search Date: 05/09/2017 18:01:40.183	
ID	Search
1	exp Heavy Ion Radiotherapy/ (436)
2	*Ions/tu, th [Therapeutic Use, Therapy] (70)
3	exp *Heavy Ions/tu [Therapeutic Use] (205)
4	exp Heavy Ion Radiotherapy/ (436)
5	(carbon ion* adj3 (therap* or treat* or radio?therap* or regimen* or program*)).mp. (800)
6	1 or 2 or 3 or 4 or 5 (1165)
7	exp Neoplasms/ (3104407)
8	exp Carcinoma/ (597801)
9	(neoplasm* or cancer* or tumo?r* or carcinoma* or oncolog*).mp. (3644138)
10	7 or 8 or 9 (4011737)
11	6 and 10 (923)
12	limit 11 to clinical trial, all (125)
13	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (3693350)
14	11 and 13 (184)
15	12 or 14 (226)
16	remove duplicates from 15 (203)

Study selection process: exclusion of full-text studies

Table A-29: Excluded studies based on full-text evaluation with reasons

Name	Title	Exclusion reason
Akakura 2005 [187]	Heavy particle therapy for prostate cancer	Wrong language
Akakura 2004 [159]	Phase I/II clinical trials of carbon ion therapy for prostate cancer.[Erratum appears in Prostate. 2004 Sep 15;61(1):103]	High RoB
Akutsu 2012 [188]	Heavy ion radiotherapy for esophageal cancer – To further progress in multidisciplinary treatment	Wrong language
Akutsu 2012 [189]	A phase I/II clinical trial of preoperative short-course carbon-ion radiotherapy for patients with squamous cell carcinoma of the esophagus	Only abstract
Baba 2008 [190]	Carbon ion radiotherapy in hypofraction regimen for stage I non-small cell lung cancer	Wrong language
Blattmann 2010 [191]	Non-randomized therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with non-resectable osteosarcoma	Protocol
Castro 1980 [192]	Radiotherapy with heavy charged particles at Lawrence Berkeley Laboratory	Wrong intervention
Combs 2010 [193]	Carbon ion radiation therapy for high-risk meningiomas	≤10 pts
Combs 2011 [194]	Proton and carbon ion radiotherapy for primary brain tumors amd meningeomas delivered with active rasterscanning at the Heidelberg Ion Therapy Center (HIT): Initial treatment results and study concepts	Only abstract
Combs 2013 [164]	Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and 68Ga-DOTATOC-PET	High RoB
Combs 2010 [178]	Randomised phase I/II study to evaluate carbon ion radiotherapy versus fractionated stereotactic radiotherapy in patients with recurrent or progressive gliomas: the CINDERELLA trial	Protocol
Combs 2013b [14]	Treatment with heavy charged particles: systematic review of clinical data and current clinical (comparative) trials	HTA-Reports/ Systematic Reviews.
Combs 2010 [195]	Treatment of patients with atypical meningiomas Simpson grade 4 and 5 with a carbon ion boost in combination with postoperative photon radiotherapy: the MARCIE trial	Protocol
Combs 2013 [163]	Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base	High RoB
Combs 2012 [196]	Phase I/II trial evaluating carbon ion radiotherapy for the treatment of recurrent rectal cancer: the PANDORA-01 trial	Protocol
Combs 2010 [177]	Randomized phase II study evaluating a carbon ion boost applied after combined radiochemotherapy with temozolomide versus a proton boost after radiochemotherapy with temozolomide in patients with primary glioblastoma: the CLEOPATRA trial	Protocol
Combs 2009 [162]	Carbon ion radiotherapy for pediatric patients and young adults treated for tumors of the skull base	High RoB
Debus 2000 [165]	[Carbon ion irradiation of skull base tumors at GSI. First clinical results and future perspectives]	High RoB
Fagundes 2016 [197]	In Regard to Habl et al	Commentary
Grutters 2010 [12]	Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: A meta-analysis	HTA-Reports/ Systematic Reviews.
Habermehl 2012 [198]	Carbon ion therapy applied in raster scanning technique for hepatocellular carcinoma-first results from the Heidelberg Ion-Beam Therapy Center	Only abstract
Habl 2014 [157]	Ion Prostate Irradiation (IPI) – a pilot study to establish the safety and feasibility of primary hypofractionated irradiation of the prostate with protons and carbon ions in a raster scan technique	Protocol
Hasegawa 2010 [199]	Carbon ion radiotherapy for malignant head-and-neck tumors invading the skull base	Only abstract

Name	Title	Exclusion reason
Hasegawa 2014 [200]	Carbon ion radiotherapy for adenoid cystic carcinoma of the head and neck	Only abstract
Hasegawa 2011 [201]	Carbon ion radiotherapy for adenoid cystic carcinoma of the head and neck	Only abstract
Hasegawa 2016 [202]	Carbon ion radiotherapy for adenoid cystic carcinomas invading the skull base	Only abstract
Huybrechts 2007 [203]	Hadronthérapie. KCE reports vol. 67B	HTA-Reports/ Systematic Reviews.
Igaki 2017 [15]	A systematic review of publications on charged particle therapy for hepatocellular carcinoma	HTA-Reports/ Systematic Reviews.
Imada 2010 [204]	Comparison of efficacy and toxicity of short-course carbon ion radiotherapy for hepatocellular carcinoma depending on their proximity to the porta hepatis	Wrong study design
Imai 2010 [205]	Effect of carbon ion radiotherapy for sacral chordoma: results of Phase I-II and Phase II clinical trials	Wrong study design
Imai 2004 [206]	Carbon ion radiotherapy for unresectable sacral chordomas	Wrong study design
Ishikawa 2012 [207]	Carbon-ion radiation therapy for prostate cancer	Wrong study design
Ishikawa 2005 [208]	A phase II trial using carbon ion radiotherapy (C-ion RT) for prostate cancer	Only abstract
Ishikawa 2006 [209]	Clinical experience of carbon ion radiotherapy for malignant tumors	Wrong language
Jensen 2011 [210]	Phase II study of induction chemotherapy with TPF followed by radioimmunotherapy with Cetuximab and intensity-modulated radiotherapy (IMRT) in combination with a carbon ion boost for locally advanced tumours of the oro-, hypopharynx and larynx – TPF-C-HIT	Protocol
Jensen 2011 [211]	Carbon ion therapy for advanced sinonasal malignancies: feasibility and acute toxicity	Wrong study design
Jensen 2012 [212]	IMRT and carbon ion boost for malignant salivary gland tumors: interim analysis of the COSMIC trial	Double-Publication (same sample)[134]
Kamada 2002 [176]	Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas	published before 2005
Jensen 2011 [213]	Treatment of malignant sinonasal tumours with intensity-modulated radiotherapy (IMRT) and carbon ion boost (C12)	Protocol
Jensen 2010 [214]	Combined treatment of malignant salivary gland tumours with intensity-modulated radiation therapy (IMRT) and carbon ions: COSMIC	Protocol
Karasawa 2016 [215]	A study of radical intent apbi using carbon-ion radiotherapy for patients with stage i breast cancer	Only abstract
Karasawa 2014 [216]	Clinical trial of carbon ion radiotherapy for gynecological melanoma	Wrong study design
Karube 2015 [217]	Single fraction carbon ion radiotherapy for 80 year old and over patients with stage I peripheral NSCLC	Only abstract
Karube 2016 [218]	Single-Fraction Carbon-Ion Radiation Therapy for Patients 80 Years of Age and Older With Stage I Non-Small Cell Lung Cancer	Double-Publication (same sample)[135]
Kasuya 2017 [173]	Progressive hypofractionated carbon-ion radiotherapy for hepatocellular carcinoma: Combined analyses of 2 prospective trials	High RoB
Kato 2001 [219]	Charged particle (carbon-ion) therapy	Wrong language
Kato 2004 [174]	Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis	published before 2005
Kato 2005 [220]	Two-fraction carbon ion radiotherapy for hepatocellular carcinoma: Preliminary results of a phase I/II clinical trial	Only abstract
Kato 2009 [221]	Carbon Ion radiotherapy for Hepatocellular Carcinoma	Wrong language
Kato 2006 [179]	Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix	Wrong indication

[134] The sample of this study is judged to be included in [85].

[135] The sample of this study is judged to be included in [97].

Name	Title	Exclusion reason
Kong 2016 [222]	Phase I/II trial evaluating concurrent carbon-ion radiotherapy plus chemotherapy for salvage treatment of locally recurrent nasopharyngeal carcinoma	Protocol
Kong 2016 [223]	Phase I/II Trial Evaluating Carbon Ion Radiotherapy for Salvaging Treatment of Locally Recurrent Nasopharyngeal Carcinoma	Protocol
Koto 2004 [30]	Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy	High RoB
Leroy 2015 [19]	Hadron therapy in children – an update of the scientific evidence for 15 paediatric cancers. Synthesis.	HTA-Reports/ Systematic Reviews
Miyamoto 2002 [224]	Heavy ion therapy for lung cancer	Wrong language
Miyamoto 2002 [225]	Heavy-ion therapy for non-small cell lung cancer	Wrong language
Miyamoto 2003 [29]	Carbon ion radiotherapy for stage I non-small cell lung cancer	High RoB
Miyawaki 2009 [226]	Brain injury after proton therapy or carbon ion therapy for head-and-neck cancer and skull base tumors	Wrong study design
Mizoe 2005 [227]	Carbon ion radiotherapy for brain tumors	Wrong language
Mizoe 2004 [32]	Dose escalation study of carbon ion radiotherapy for locally advanced head-and-neck cancer	High RoB
Mizoguchi 2012 [228]	Carbon-ion radiation therapy for locally advanced primary or postoperative recurrent epithelial carcinoma of lacrimal gland: A phase I/II dose-escalation study	Only abstract
Mizoguchi 2015 [166]	Carbon-ion radiotherapy for locally advanced primary or postoperative recurrent epithelial carcinoma of the lacrimal gland	High RoB
Nakano 1999 [181]	The phase I/II clinical study of carbon ion therapy for cancer of the uterine cervix	Wrong indication
Nakano 2006 [180]	Carbon beam therapy overcomes the radiation resistance of uterine cervical cancer originating from hypoxia	Wrong indication
Nakayama 2017 [229]	Carbon-ion therapy of lung cancer	Only abstract
Nathan 1995 [230]	Weighing the benefits of heavy-ion therapy	Commentary
Nikoghosyan 2010 [231]	Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study	Protocol
Nikoghosyan 2010 [232]	Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study	Protocol
Nomiya 2013 [233]	Up-to-date results of a clinical trial of carbon-ion radiotherapy for prostate cancer: Analysis of 1,144 patients	Only abstract
Ogino 2002 [234]	Heavy charged particle radiation therapy for prostate cancers	Wrong language
Oonishi 2011 [235]	Outcomes after short-course carbon ion radiotherapy for patients with hepatocellular carcinoma according to tumor size	Only abstract
Pijls-Johannesma 2008 [11]	Particle therapy in lung cancer: where do we stand?	HTA-Reports/ Systematic Reviews
Pommier 2012 [236]	Medico-economical prospective randomized trials of carbon ions therapy	Only abstract
Ramaekers 2011 [13]	Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons	HTA-Reports/ Systematic Reviews
Ramaekers 2010 [237]	Radiotherapy with photons, carbon-ions and protons in various head and neck cancers: A review and metaanalysis of observational studies	Only abstract
Rieken 2012 [167]	Proton and carbon ion radiotherapy for primary brain tumors delivered with active raster scanning at the Heidelberg Ion Therapy Center (HIT): early treatment results and study concepts	High RoB
Schulz-Ertner 2002 [168]	Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions	High RoB
Schulz-Ertner 2004 [238]	Results of carbon ion radiotherapy in 152 patients	Wrong study design
Schulz-Ertner 2003 [169]	Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas of the skull base. Results in 67 patients	High RoB
Serizawa 2009 [239]	Carbon Ion Radiotherapy for Unresectable Retroperitoneal Sarcomas	Wrong study design

Name	Title	Exclusion reason
Shimazaki 2006 [161]	Monotherapy with carbon ion radiation for localized prostate cancer	High RoB
Shimazaki 2010 [160]	Carbon ion radiotherapy for treatment of prostate cancer and subsequent outcomes after biochemical failure	High RoB
Shinoto 2015 [240]	A phase II clinical trial of carbon-ion radiotherapy and concurrent S-1 chemotherapy for locally advanced pancreatic cancer	Protocol
Shinoto 2009 [241]	A phase I/II clinical trial of carbon ion therapy for patients with locally advanced pancreas cancer (protocol 0204, 12 fractions/3 weeks)	Only abstract
Sugane 2009 [242]	Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer	Double-Publication (same sample)[136]
Sulaiman 2014 [243]	Particle beam radiation therapy using carbon ions and protons for oligometastatic lung tumors	Wrong study design
Takagi 2014 [244]	Treatment outcomes of proton or carbon ion radiation therapy for chordoma of the skull base	Only abstract
Takagi 2013 [245]	Treatment outcomes of proton or carbon ion radiation therapy for adenoid cystic carcinoma of the head and neck	Only abstract
Takahashi 2009 [170]	Skull base chordomas: efficacy of surgery followed by carbon ion radiotherapy	High RoB
Takahashi 2016 [246]	Changes in pulmonary function after single-fraction carbon-ion radiotherapy for stage I NSCLC	Only abstract
Takahashi 2014 [247]	Prospective phase 1/2 trial of carbon ion radiation therapy for locally advanced non-small cell lung cancer (NSCLC)	Only abstract
Tian 2016 [248]	Proton and Carbon ion for stage I non-small cell lung cancer: A meta analysis	Only abstract
Tsuji 2007 [171]	Carbon-ion radiotherapy for locally advanced or unfavorably located choroidal melanoma: a Phase I/II dose-escalation study	High RoB
Tsujii 1999 [249]	Current status of heavy ion beam therapy at NIRS	Wrong language
Tsujii 1997 [250]	Preliminary results of phase I/II carbon-ion therapy at the National Institute of Radiological Sciences	Wrong study design
Tsujii 2004 [251]	Overview of clinical experiences on carbon ion radiotherapy at NIRS	Wrong study design
Tuan 2013 [252]	Initial clinical experience with scanned proton beams at the Italian National Center for Hadrontherapy (CNAO)	Wrong intervention
Uhl 2014 [253]	Randomized phase II trial of hypofractionated proton versus carbon ion radiation therapy in patients with sacrococcygeal chordoma-the ISAC trial protocol	Protocol
Uhl 2014 [254]	High control rate in patients with chondrosarcoma of the skull base after carbon ion therapy: first report of long-term results	Wrong study design
Uhl 2015 [255]	Carbon ion beam treatment in patients with primary and recurrent sacrococcygeal chordoma	Wrong study design
Vitolo 2016 [256]	Chordoma of the skull base: Initial results in a series of patients treated by particle therapy at the italian national center for oncological hadron therapy (CNAO)	Only abstract
Wakatsuki 2013 [257]	Carbon ion radiation therapy for locally-advanced adenocarcinoma of the uterine cervix	Only abstract
Wakatsuki 2012 [258]	Carbon ion radiotherapy for locally advanced adenocarcinoma of the uterine cervix	Only abstract
Wakatsuki 2015 [182]	Clinical trial of prophylactic extended-field carbon-ion radiotherapy for locally advanced uterine cervical cancer (protocol 0508).[Erratum appears in PLoS One. 2015;10(11):e0143301; PMID: 26565701]	Wrong indication
Wakatsuki 2014 [184]	Dose-escalation study of carbon ion radiotherapy for locally advanced squamous cell carcinoma of the uterine cervix (9902)	Wrong indication
Wakatsuki 2014 [185]	Clinical outcomes of carbon ion radiotherapy for locally advanced adenocarcinoma of the uterine cervix in phase 1/2 clinical trial (protocol 9704)	Wrong indication

[136] The study used a fraction of patients (elderly) enrolled in other included studies [101, 102].

Name	Title	Exclusion reason
Wakatsuki 2015 [183]	Difference in distant failure site between locally advanced squamous cell carcinoma and adenocarcinoma of the uterine cervix after C-ion RT	Wrong indication
Wang 2016 [259]	The preliminarily results of carbon ion radiotherapy in 60 patients	Only abstract
Wang 2016 [260]	The clinical study on oligometastases from different tumors treated with carbon ions	Only abstract
Wild 2015 [261]	[Hadron therapy in children: evidence synthesis for 15 paediatric tumours. Report based on Belgian (KCE) HTA report]	HTA-Reports/ Systematic Reviews
Wild 2013 [9]	[Hadron therapy: proton and carbon ion therapy – a review of clinical evidence of efficacy, ongoing research and reimbursement]	HTA-Reports/ Systematic Reviews
Yamada 2005 [262]	Phase I/II trial of carbon-ion therapy for patients with locally recurrent rectal cancer	Only abstract
Yamada 2009 [263]	[Current status and perspective of heavy ion beam therapy for patients with pelvic recurrence after primarily resected rectal cancer]	Wrong language
Yamamoto 2013 [175]	Carbon ion radiotherapy for oligo-recurrence in the lung	High RoB
Yamamoto 2010 [264]	[Particle therapy--carbon ion radiotherapy for non-small cell lung cancer]	Wrong language
Yamamoto 2009 [265]	Particle radiotherapy for malignant gliomas	Wrong language
Yanagi 2007 [266]	Concomitant chemoradiotherapy with carbon ion beams for hypopharyngeal carcinoma – Preliminary report	Wrong language
Yanagi 2009 [172]	Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy	High RoB
Yanagi 2003 [267]	[Heavy charged particles radiotherapy--mainly carbon ion beams]	Wrong language
Zhang 2012 [186]	Results of carbon ion radiotherapy for skin carcinomas in 45 patients	Wrong indication
Zhang 2016 [268]	Meta analysis of carbon ion therapy prostatic cancer	Only abstract
Zhang 2016 [269]	Carbon ion radiotherapy for stage I non-small cell lung cancer: A Meta-analysis of 369 patients	Only abstract

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