HTA Austria
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Stereotactic radiotherapy, proton therapy and irreversible electroporation for the treatment of localised prostate cancer

Systematic Review

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Stereotaktische Strahlentherapie, Protonentherapie und irreversible Elektroporation zur Behandlung des lokalisierten Prostatakarzinoms

Systematischer Review

Wien, Juli 2024

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List of Abbreviations

ACR ..... American College of Radiology
ADT ..... Androgen deprivation therapy
AS ..... Active surveillance
ASSERT ..... Androgen Suppression With Stereotactic Body or External Beam Radiation Therapy
ASTRO ..... American Society for Radiation Oncology
AUA ..... American Urological Association
AWMF ..... Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
BCFFS ..... Biochemical failure-free survival
BF ..... Biochemical failure
BT ..... Brachytherapy
CGE ..... Cobalt Grey Equivalent
CI ..... Confidence interval
CIRT ..... Carbon ion radiotherapy
CTCAE ..... Common Terminology Criteria for Adverse Events
DKG ..... Deutsche Krebsgesellschaft e. V.
DKH ..... Deutsche Krebshilfe
EAU ..... European Association of Urology
EBRT ..... External beam radiotherapy
ECOG ..... Eastern Cooperative Oncology
EORTC ..... European Organisation for Research and Treatment of Cancer
EORTC QLQ ..... European Organisation for Research and Treatment of Cancer Quality of Life Group
EPIC ..... Expanded Prostate Cancer Index Composite
FU ..... Follow-Up
GI ..... Gastrointestinal
GU ..... Genitourinary
Gy ..... Gray
GyE ..... Gray Equivalent
HDR ..... High dose rate
HIFU ..... High intensity focused ultrasound
HRQOL ..... Health related quality of life
HTA ..... Health Technology Assessment
IGRT ..... Image guided radiotherapy
IIEF-5 ..... International Index of Erectile-Function-5
IMRT ..... Intensity modulated radiation therapy
IPSS ..... International Prostate Symptom Score
IQR ..... Interquartile Range
IRE ..... Irreversible electroporation
ISUP ..... International Society of Urological Pathology
KG ..... Kontrollgruppe
KPS ..... Karnofsky
LDR ..... Low dose rate
MD ..... Mean difference
N ..... Noduli

n ..... Number
NCCN ..... National Comprehensive Cancer Network®
NHS ..... National Health Service
PCa ..... Prostate cancer
PCSI ..... Prostate Cancer Symptom Indices
PICO ..... Population, Intervention, Comparator(s), Outcome(s)
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA ..... Prostate specific antigen
PSPT ..... Passively scattered proton therapy
PT ..... Proton therapy
QoL ..... Quality of life
RCT ..... Randomised controlled trial
RoB ..... Risk of bias
RR ..... Risk ratio
RTOG ..... Radiation Therapy Oncology Group
SBRT ..... Stereotactic body radiation therapy
SD ..... Standard deviation
SSPT ..... Spot scanning proton therapy
TNM ..... Primary tumour (T), regional lymph nodes (N), Distant metastasis (M)
TURP ..... Transurethral resection of the prostate
WHO ..... World Health Organization
WW ..... Watchful waiting

Zusammenfassung

Einführung

Gesundheitsproblem und therapeutisches Ziel

Prostatakarzinom (PCa) zählt zu häufigsten Tumorerkrankungen

lokalisiertes Tumorstadium hat günstige Prognose und mehrere Behandlungsmethoden stehen zur Verfügung

Das Prostatakarzinom (PCa) zählt zur häufigsten Tumorerkrankung bei Männern in Industrieländern und mit einer Inzidenz von fast 30 % auch zur häufigsten Krebserkrankung der österreichischen Männer. Prostatakrebs ist die häufigste Tumorerkrankung bei Männern in Industrieländern. Im Jahr 2022 war Prostatakrebs für etwa 13% Krebstodesfällen verantwortlich, obwohl die Sterblichkeitsraten seit ihrem Höchststand im Jahr 1999 erheblich gesunken sind. Früherkennung bedeutet auch, dass 50% aller neuen Diagnosen in einem lokalisierten Tumorstadium erfolgen, das im Allgemeinen eine sehr günstige Prognose hat. Es stehen mehrere Methoden zur Verfügung, um lokalisierte Tumoren zu behandeln. Dazu gehören Methoden zur Zerstörung oder Entfernung des Tumors mittels chirurgischer oder radiotherapeutischer Techniken, obwohl bei Patienten mit einem niedrigen Risikoprofil auch eine aktive Überwachung in Betracht gezogen werden kann.

Beschreibung der Technologien

3 Technologien zur Behandlung werden bewertet: irreversible Elektroporation (IRE),

stereotaktische Strahlentherapie (SBRT),

Protonentherapie (PT)

Die in diesem Bericht betrachteten drei Interventionen sind:

Irreversible Elektroporation (IRE, NanoKnife®) ist eine Art fokaler Therapie, die bei den Elektroden verwendet wird, um kurze, wiederholte elektrische Impulse abzugeben und die Krebszellen zu zerstören.

Stereotaktische Radiotherapie (SBRT) ist eine Art der externen Bestrahlung, bei der eine höhere Strahlendosis in einer geringeren Anzahl von Fraktionen im Vergleich zur konventionellen oder moderat fraktionierten Strahlentherapie verabreicht wird.

Protonentherapie (PT) ist eine Form der externen Strahlentherapie, die Protonenstrahlen anstelle von Röntgenstrahlen oder Photonen verwendet.

Forschungsfrage und Projektziel

Update des 2018 Berichtes

Wirksamkeit und Sicherheit von IRE, SBRT, PT

Der vorliegende Bericht handelt sich um die Aktualisierung einer Bewertung aus dem Jahr 2018 und soll die folgende Forschungsfrage beantworten: Sind irreversible Elektroporation (IRE), stereotaktische Strahlentherapie (SBRT) oder Protonentherapie (PT) wirksamer und sicherer bei der Behandlung von Patienten mit lokalisiertem Prostatakrebs (PCa) im Vergleich zu anderen Behandlungsoptionen für lokalisierten PCa in Bezug auf die definierten Endpunkte?

Methoden

systematische Literatursuche in 4 Datenbanken nach

randomisierte kontrollierte Studien (RCTs) für Wirksamkeit und Beobachtungsstudien für Sicherheit

Die Literaturrecherche wurde in vier Datenbanken durchgeführt und durch eine manuelle Suche ergänzt. Die Suche beschränkte sich auf Studien, die zwischen Februar 2018 und Februar 2024 auf Deutsch oder Englisch veröffentlicht wurden. Die Studienauswahl, Datenextraktion und Qualitätsbewertung der eingeschlossenen Studien wurden von zwei unabhängigen Wissenschaftlerinnen durchgeführt. Die Vertrauenswürdigkeit der Evidenz wurde nach dem GRADE-Schema (Grading of Recommendations Assessment, Development and Evaluation) bewertet. Die festgelegten Wirksamkeits- und Sicherheitsendpunkte umfassten Überleben, Lebensqualität (QoL), Vermeidung einer Prostatektomie sowie Akut- und Spättoxizitäten. Zur Bewertung

der Wirksamkeit wurden nur RCTs als Evidenz herangezogen. Zur Bewertung der Toxizität wurden auch prospektiven Beobachtungsstudien mit über 50 Patienten bei IRE und PT sowie über 200 Patienten bei SBRT berücksichtigt. Der Grund für die Abweichung in der minimal erforderlichen Patientenzahl für die prospektiven Beobachtungstudien lag darin, dass die Evidenz aus RCTs für SBRT robuster war, wodurch die Notwendigkeit zur Einbeziehung kleiner Beobachtungsstudien verringert wurde.

Ergebnisse

nur für SBRT wurden RCTs identifiziert, für IRE und PT nur Beobachtungsstudien

Nach dem Entfernen von Duplikaten wurden 1.039 Publikationen gescreent. RCTs konnten nur für SBRT identifiziert werden. Für IRE und PT wurden nur Beobachtungsstudien einbezogen. Daher wurde die Wirksamkeit ausschließlich für SBRT analysiert.

IRE: keine RCTs in 2018 oder im aktuellen Update, 5 Beobachtungsstudien (n=846)

Die Evidenz zur **IRE** (NanoKnife®) ist nach wie vor begrenzt. Trotz einer umfassenden Literatursuche konnten weder im 2018 Bericht noch in diesem Update RCTs identifiziert werden. Wir fanden nur fünf große Beobachtungsstudien mit insgesamt 846 Patienten, wobei viele Patienten im Verlauf der Studien verloren gingen, was die Robustheit der Studienergebnisse beeinträchtigt. Definitive Aussagen zur Wirksamkeit sind nicht möglich, und die Vertrauenswürdigkeit der Evidenz in Bezug auf die Toxizität bleibt sehr gering bis gering.

allgemeiner Trend zu abnehmender Toxizität über Zeit

hohe Variabilität bei Grad-1- und Grad-2-Akuttoxizitäten zwischen Studien

Dennoch zeigen die Ergebnisse einen allgemeinen Trend zur abnehmenden Toxizität im Laufe der Zeit. Besonders bemerkenswert ist die erhebliche Variabilität bei Grad-1- und Grad-2-Toxizitäten zwischen den Studien. Innerhalb von drei Monaten wurde eine Grad-1-Toxizität zwischen 0.5% und 47.2% und eine Grad-2-Toxizität zwischen 0.8% und 12.3% berichtet. Nach 24 Monaten berichtete nur eine Beobachtungsstudie über eine minimale Inzidenz von 0.6% bei Grad-2-Toxizität, und nach 48 Monaten wurden keine Toxizitätsereignisse verzeichnet.

SBRT: 3 neue RCTs (n=2.138) und 2 Beobachtungsstudien (n=460)

Zur **SBRT** wurden im 2018 Bericht keine RCTs identifiziert, aber das aktuelle Update hat drei neue RCTs (n=2.138) und zwei Beobachtungsstudien (n=460) gefunden. Evidenz von moderater Vertrauenswürdigkeit aus einer Nicht-Unterlegenheits-RCT zeigt, dass die Überlebensraten über zwei und fünf Jahre hinweg in der Kontrollgruppe geringfügig höher waren, obwohl diese Unterschiede keine statistische Signifikanz erreichten (HR 1,11; 95% CI 0,73 bis 1,69). Die krankheitsspezifische Überlebensrate war nach zwei Jahren zwischen den Gruppen konsistent, zeigte jedoch nach fünf Jahren bessere Ergebnisse in der Kontrollgruppe (98,2% vs. 99,8%, p-Wert nicht berichtet). Das metastasenfreie Überleben bevorzugte zunächst die Kontrollgruppe nach zwei Jahren, verschob sich jedoch leicht zugunsten der Interventionsgruppe nach fünf Jahren (98,7% vs. 98,3%, p-Wert nicht berichtet). Das biochemische Rezidiv-freie Überleben zeigte nach fünf Jahren keine signifikanten Unterschiede zwischen den Gruppen (HR 1,00; 95% CI 0,76 bis 1,32). Diese Ergebnisse deuten auf subtile Unterschiede hin, aber keine statistisch signifikanten Unterschiede in den Überlebensraten, was darauf hindeutet, dass SBRT hinsichtlich des Überlebens bei niedrig- und mittlerem Risiko nicht schlechter ist als die konventionelle Fraktionierung (CFRT).

1 Nicht-Unterlegenheits-RCT zu Überleben: n.s. Unterschiede, SBRT nicht unterlegen gegenüber CFRT in niedrig- und mittlerem Risiko PCa

heterogene Ergebnisse zur Lebensqualität

In Bezug auf die Lebensqualität (QoL) Endpunkten variierten die Ergebnisse der drei RCTs in verschiedenen Bereichen (Harn- und Darmsyteme, sexuelle Funktion und hormonelle Symptome) mit unterschiedlicher Vertrauenswürdigkeit der Evidenz (für die Harnsymptomen war es niedrig, für die anderen Bereiche moderat).

Harnsymptomen zeigen sich kurzfristig keine Unterschiede,

langfristig gemischte Ergebnisse mit SBRT

Die Ergebnisse zu Harnsymptomen zwischen SBRT und CFRT zeigten gemischte Ergebnisse. Kurzfristige Ergebnisse zeigten typischerweise keine signifikanten Unterschiede zwischen den beiden Behandlungen. Langfristige Nachbeobachtungen wiesen jedoch auf eine signifikante Verschlechterung der Harninkontinenz bei Patienten hin, die mit SBRT behandelt wurden, während CFRT keine solche Veränderung zeigte. Beide Behandlungsgruppen zeigten im Laufe der Zeit signifikante Verbesserungen der Harnobstruktionssymptome. Lebensqualitätsbewertungen bezüglich Harnsymptome (IPSS QoL) nahmen auch langfristig bei SBRT signifikant zu, was auf ausgeprägtere Harnsymptome hinweist. Insgesamt kann SBRT zu einer Verschlechterung spezifischer Harnsymptome im Vergleich zu CFRT führen, insbesondere über längere Zeiträume.

unterschiedliche Ergebnisse für Darmsymptome, sexuelle Funktion und hormonelle Symptome besser mit SBRT

Die Ergebnisse für Darmsymptome waren variabel; einige Studien berichteten über vergleichbare Verbesserungen in beiden Gruppen, während andere bessere Ergebnisse in der Kontrollgruppe zeigten. Im Gegensatz dazu waren sexuelle Funktion und hormonelle Symptome in der Interventionsgruppe tendenziell besser. Es ist bemerkenswert, dass keine der Studien die Vermeidung einer Prostatektomie als Endpunkt definiert haben.

GI-Toxizität: wenigere Grad ≥1 Akuttoxizität mit SBRT, Unterschied bleibt nach einem Jahr, kein Unterschied nach zwei Jahren (1 RCT, n=64)

Beobachtungsstudien: keine oder meist Grad 1 Akuttoxizität

Zur Bewertung der Toxizität wurden zusätzlich zu den RCTs zwei größere Beobachtungsstudien (>200 Patienten) einbezogen. Die Vertrauenswürdigkeit der Evidenz war für kurzfristige Ergebnisse niedrig und für zwei- und fünfjährige Ergebnisse moderat. Evidenz aus einer einzigen RCT (n=64) zeigt, dass die kumulativen Grad ≥1 GI-Toxizität am Ende der Behandlung in der SBRT-Gruppe signifikant niedriger war als in der Kontrollgruppe (35% vs. 87%, p<0,0001). Dieselbe RCT zeigte, dass dieser Unterschied nach einem Jahr bestehen blieb (64% vs. 84%, p=0,033). Evidenz von moderater Vertrauenswürdigkeit zeigt keinen Unterschied nach zwei Jahren. Einarmige Studien bestätigten diese Ergebnisse, indem sie zeigten, dass Patienten entweder keine oder hauptsächlich Grad 1 Toxizität innerhalb von 30 Tagen und bis zu 3 Monate nach der Behandlung erlebten (mit Grad 2 oder höheren Toxizitäten bei weniger als 6% der Patienten).

GU-Toxizität: statistisch signifikant (s.s.) weniger Grad ≥1 Akuttoxizität mit SBRT, Unterschied nach einem Jahr nicht signifikant (n.s.), s.s. mehr Grad ≥2 nach einem Jahr (n=1.200) und kumulative Grad ≥2 Toxizität mit SBRT nach zwei Jahren (n=874)

Beobachtungsstudien: weniger Akuttoxizitäten

Für GU-Toxizitäten war die Vertrauenswürdigkeit der Evidenz ebenfalls niedrig für Akuttoxizitäten und für Toxizititäten nach einem Jahr, zwei sowie fünf Jahren moderat. Die kumulativen Grad ≥1 Toxizität war in der SBRT-Gruppe signifikant niedriger (87% vs. 100%, p=0,04) in der akuten Phase, obwohl der Unterschied nach einem Jahr nicht mehr statistisch signifikant war. Grad ≥2 Toxizitäten waren in der SBRT-Gruppe nach einem Jahr höher waren als in der Kontrollgruppe (6% vs. 2%, p=0,0037) in einer RCT (n=1.200). Ebenso zeigte eine andere RCT (n=874) nach zwei Jahren, dass die kumulativen Grad ≥2 Toxizität in der Interventionsgruppe höher war (18,3% vs. 10,6%; HR 1,80; 95% CI 1,25 bis 2,61; log-rank p=0,0015). Die Beobachtungsstudien berichteten über weniger akute GU-Toxizitäten innerhalb von 30 Tagen (ungefähr 50% erlebten keine GU-Toxizität oder nur Grad 1 Toxizität) als RCTs, aber nach 3 Monaten stimmten sie mit den RCT-Ergebnissen überein (ungefähr 90% erlebten keine Toxizität oder nur Grad 1 Toxizität).

PT: keine neuen RCTs, 8 Beobachtungsstudien (n=5.514)

keine Schlussfolgerungen zu Lebensqualität und Überleben möglich

Akuttoxizität: GU häufiger als GI (mehr Grad 1 und 2, weniger Patienten ohne Toxizitäten); Grad 3 ist bei beiden selten

Spättoxizität: anfänglich hohe Frequenz von GU-Toxizitäten verringerte sich, GI-Toxizitäten blieben bestehen

zunehmende Inzidenz von Grad 2 Toxizitäten im Zeitverlauf bei Patienten, die Komplikationen entwickeln

Zur **PT** konnten in diesem Update keine neuen RCTs identifiziert werden. Der 2018 Bericht schloss zwar RCTs ein, jedoch wurde die Evidenz aus diesen RCTs kritisiert, da sie PT nicht allein mit traditionellen Therapien (wie Prostatektomie, Androgendeprivationstherapie, Brachytherapie) verglichen und die Evidenz in Bezug auf Überleben und Lebensqualität unzureichend war. Da keine neuen RCTs verfügbar sind, können weiterhin keine Schlussfolgerungen zur Wirksamkeit gezogen werden. Zur Sicherheitsbewertung wurden acht Beobachtungsstudien einbezogen (n=5.514). Evidenz von geringer Vertrauenswürdigkeit deutet auf unterschiedliche Trends bei GI- und GU-Toxizitäten hin. Innerhalb von drei Monaten nach der Behandlung erlebten 85% der Patienten keine GI-Toxizität im Vergleich zu nur 26% bei GU-Toxizität, wobei Grad 1 und Grad 2 Toxizitäten bei GU (45% und 28%) häufiger auftraten als bei GI (13% und 5%). Grad 3 Toxizität war für beide selten und lag im Durchschnitt bei weniger als 1%.

Über einen längeren Nachbeobachtungszeitraum von bis zu 48 Monaten nahm die anfänglich hohe Häufigkeit der GU-Toxizität ab, wobei 62% der Patienten keine GU-Toxizität erlebten, was eine Verbesserung gegenüber der kurzfristigen Nachbeobachtung zeigt. Umgekehrt zeigte die langfristige Nachbeobachtung, dass 31% der Patienten keine GI-Toxizität erlebten, was auf eine anhaltende Präsenz von GI-Symptomen im Laufe der Zeit hinweist. Grad 1 und Grad 2 GI-Spättoxizitäten traten bei 25% bzw. 6,6% der Patienten auf. Dies deutet auf anhaltende, aber allgemein milde GI-Symptome hin. Bei GU-Toxizitäten zeigten kumulative Studienergebnisse einen konstanten Anstieg der Inzidenz von Grad 2 Toxizitäten von 12% nach sechs Monaten auf 32% nach 48 Monaten. Dieser Trend deutet darauf hin, dass, während die Gesamthäufigkeit jeglicher GU-Toxizitäten abnehmen mag, die Schwere oder Persistenz dieser Toxizitäten bei betroffenen Patienten sich verschlimmern oder im Laufe der Zeit deutlicher werden kann. Diesen allmählichen, aber signifikanten Anstieg der Inzidenz schwerer GU-Toxizitäten betont das langfristig ansteigende Risiko und hebt die Notwendigkeit einer verlängerten Überwachung hervor.

Schlussfolgerung

unzureichende Evidenz für IRE, SBRT, PT als Ersatz für radikale Verfahren

SBRT bei niedrigem bis mittlerem Risiko nicht unterlegen gegenüber konventioneller Fraktionierung

weitere Forschung zur Langzeitwirksamkeit und Sicherheit nötig

Die Ergebnisse dieses Reviews stimmen mit den aktuellen klinischen Praxisrichtlinien und anderen jüngsten systematischen Reviews überein. Die Evidenz für alle drei Therapien ist unzureichend, um schlussfolgern zu können, ob IRE, SBRT und PT radikal invasive Verfahren wie die Prostatektomie ersetzen oder verhindern können oder ob diese Therapien einen signifikanten Vorteil für die Patienten in Bezug auf verbesserte Lebensqualität oder Überleben bieten. Die aktuelle Evidenz deutet jedoch darauf hin, dass SBRT in Bezug auf Überlebensraten bei Patienten mit niedrigem bis mittlerem Risiko nicht schlechter ist als die konventionelle Fraktionierung. Weitere qualitativ hochwertige Forschung ist erforderlich, um die langfristige Wirksamkeit und Sicherheit dieser Therapien im Vergleich zu Standardbehandlungen nachzuweisen. Derzeit laufen mehrere Studien, darunter auch einige RCTs, die Vergleiche mit konventionellen Technologien beinhalten und somit Aussagen zur Wirksamkeit und Sicherheit ermöglichen sollten.

Executive Summary

Introduction

This report is an update of a 2018 assessment on the effectiveness and safety of three procedures for treating localised prostate cancer (PCa): irreversible electroporation (IRE), stereotactic radiation therapy (SBRT), and proton therapy (PT).

update of a 2018 report

Health problem

Prostate cancer (PCa) is the most common cancer among men in industrialised countries, accounting for 30% of cancer cases in Austrian men. In 2022, PCa was responsible for about 13% of all cancer deaths, although mortality rates have significantly decreased since their peak in 1999. Early detection has led to 50% of all new diagnoses occurring in a localised tumour stage, which generally has a very favourable prognosis.

prostate cancer (PCa) is the most common cancer among men

localised PCa in 50% of all new diagnoses

Description of the technologies

The three assessed therapies have been suggested as alternatives to more radical treatments like prostatectomy due to their more targeted, less invasive nature. IRE (NanoKnife®) is a type of focal therapy which delivers short repetitive electrical pulses to destroy the cancer cells. SBRT is a type of external beam radiation therapy (EBRT) in which a higher radiation dose is delivered in a reduced number of fractions. PT is another type of EBRT which uses high doses of ionising rays directed at the tumour.

3 potential treatment options for localised PCa: irreversible electroporation (IRE), stereotactic body radiation therapy (SBRT), proton therapy (PT)

Methods

A systematic literature search was conducted in four databases for studies published in English and German language between February 2018 to February 2024. This was supplemented by a manual search to ensure completeness. Two researchers independently performed study selection, data extraction and quality-assessment of included studies. The certainty of evidence was assessed according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme.

systematic search in 4 databases

study selection, extraction and quality assessment

The following effectiveness and safety endpoints were defined a priori: survival, quality of life (QoL), avoidance of prostatectomy, and acute and late toxicities. To assess effectiveness, only RCTs were considered. To assess toxicity, evidence from prospective observational studies with over 50 patients with IRE and PT and over 200 patients for SBRT are also considered. The reason for the deviation in the minimum required patient number for the prospective observational cohort studies was that the RCT evidence was more robust for SBRT, reducing the need for the inclusion of small observational studies.

effectiveness endpoints: survival, quality of life (QoL), avoidance of prostatectomy

safety endpoints: acute and late toxicities

Results

After removing duplicates, 1039 publications were screened. We could identify RCTs only for SBRT. For IRE and PT, only observational studies were included. Hence, effectiveness was analysed solely for SBRT.

RCTs only for SBRT included, for IRE and PT observational studies

IRE: no RCTs, 5 observational studies (n=846)

considerable variability in grade 1 and 2 toxicities across studies

decreasing toxicity incidences over time

IRE (NanoKnife®) has been subject to limited research, primarily featuring in small, inconclusive observational cohort studies. Despite an exhaustive literature search, no RCTs were identified either in the initial 2018 report or in this update. The current review found only five larger observational studies involving 846 patients, although many were lost to follow-up, compromising the robustness of the study findings. In lack of RCTs, no definitive conclusions on efficacy are feasible, and the certainty of the evidence regarding toxicity remains very low to low. Nonetheless, toxicity assessments indicate a general trend of decreasing toxicity over time. Notably, the variability in grade 1 and 2 toxicities was significant across studies. Initially, at three months, grade 1 toxicity was reported between 0.5% and 47.2%, and grade 2 toxicity ranged from 0.8% to 12.3%. By 24 months, only a single cohort study reported a minimal 0.6% incidence of grade 2 toxicity, and by 48 months, no events of toxicity were recorded.

SBRT: 3 RCTs (n=2,138), 2 observational studies (n=460)

survival outcomes: reported in 1 non-inferiority RCT, n.s. difference between groups, hence SBRT is non-inferior to CFRT in low and intermediate risk PCa

For **SBRT**, no RCTs were identified in the 2018 review, but the current update has identified three new RCTs (n=2,138) and additionally two larger observational studies (n=460) for assessing toxicity. Moderate certainty evidence from one non-inferiority RCT indicates that over two and five years, overall survival rates were marginally higher in the control group, although these differences did not reach statistical significance (HR 1.11, 95% CI, 0.73 to 1.69). Disease-specific survival was consistent between the two groups at the two-year follow-up but showed divergence at five years, with better outcomes in the control group (98.2% vs. 99.8%, p-value not reported). Metastases-free survival initially showed a preference for the control group at two years but shifted slightly in favour of the intervention group by the five-year mark (98.7% vs. 98.3%, p-value not reported). Biochemical failure-free survival demonstrated no significant differences between the groups after five years (HR 1.00, 95% CI 0.76 to 1.32). These findings suggest subtle variations but no statistically significant differences in survival rates, hence SBRT was found to be non-inferior in terms of survival to the conventional fractionation radiation therapy (CFRT) in low and intermediate risk cancer.

QoL outcomes: heterogeneous findings across different domains

urinary symptoms show no difference short-term, long-term mixed results with SBRT

mixed results for bowel symptoms across studies, sexual function and hormonal symptoms were better with SBRT

avoidance of prostatectomy was not reported

In terms of QoL endpoints, findings from the three RCTs varied across different domains, each supported by different evidence certainty. The urinary domain was assessed with low certainty evidence, while evidence for the other domains was of moderate certainty. Findings on urinary symptoms between SBRT and CFRT have shown mixed results. Short-term outcomes typically reveal no significant differences between the two treatments. However, longer-term follow-ups indicate a significant worsening in urinary incontinence for patients treated with SBRT, while CFRT shows no such change. Both treatment groups show significant improvements in urinary obstructive symptoms over time. Quality of life scores related to urinary symptoms (IPSS QoL) also tend to increase significantly for SBRT in the long term, suggesting more pronounced urinary symptoms. Overall, SBRT may lead to some worsening in specific urinary symptoms compared to CFRT, particularly over extended periods.

The results for bowel symptoms were variable; some studies reported comparable improvements across groups, while others suggested superior outcomes in the control group. In contrast, sexual function and hormonal symptoms tended to be better in the intervention group. It is noteworthy that none of the studies included measures for the avoidance of prostatectomy.

For toxicity results, two larger observation studies (>200 patients) were included additionally to the RCTs. The certainty of evidence was low for the shorter-term outcomes and moderate for two- and five-year outcomes. Low certainty evidence from a single RCT (n=64) indicates that the cumulative grade ≥1 GI toxicity at the end of treatment was significantly lower in the SBRT group compared to the control group (35% vs. 87%, p<0.0001). The same RCT showed that a difference persisted at one year (64% vs. 84%, p=0.033). Moderate certainty evidence indicates no difference beyond two years. Single-arm studies corroborated these findings, showing that patients experienced either no toxicity or primarily grade 1 toxicity within 30 days and up to 3 months post-treatment (with grade 2 or higher toxicities observed in less than 6% of patients). For GU toxicities, similarly, low certainty evidence indicates that the cumulative grade ≥1 toxicities were significantly lower in the SBRT group (87% vs. 100%, p=0.04) at the acute phase, although the difference at one year did not remain statistically significant. Moderate certainty evidence from one RCT (n=1,200) shows that grade ≥2 toxicities were higher in the SBRT group than in the control group (6% vs. 2%, p=0.0037) at one-year. Similarly, at the two-year follow-up another RCT (n=874) showed that cumulative grade ≥2 was higher in the intervention group (18.3% vs. 10.6%; HR 1.80 (95% CI, 1.25 to 2.61); log-rank p=0.0015). Single-arm observational studies reported fewer acute GU toxicities within 30 days (approximately 50% experienced no GU toxicity or only grade 1 toxicity) than RCTs, but at the 3-month mark, they aligned with the RCT findings (approximately 90% experienced no toxicity or only grade 1 toxicity).

GI toxicity:
significantly fewer cumulative grade ≥1 acute toxicity with SBRT, difference persisted at 1 year, no difference beyond 2 years (1 RCT, n=64), mainly mild or no toxicities in observational studies

GU toxicity:
significantly fewer cumulative grade ≥1 acute toxicity with SBRT, difference n.s. at 1 year (1 RCT, n=64), significantly more grade ≥2 at 1 year (1 RCT, n=1,200), and cumulative grade ≥2 with SBRT (1 RCT, n=874) at 2 years

For **PT**, no new RCTS could be identified in this update. The 2018 report included RCTs, however, the evidence coming from those RCTs was criticised because they did not compare PT alone with any of the traditional therapies (like prostatectomy, androgen deprivation therapy or brachytherapy) and the evidence was inconclusive on survival and QoL outcomes. With no new RCTs available, effectiveness conclusions still cannot be drawn. For safety assessment, eight observational studies were included (n=5,514). Low certainty evidence suggests differing trends in GI and GU toxicities. Within three months of treatment, 85% of patients experienced no GI toxicity compared to only 26% for GU, with grade 1 and grade 2 toxicities also being more frequent in GU (45% and 28%) than in GI (13% and 5%). Grade 3 toxicity was rare for both, averaging less than 1%. Over a longer follow-up period of up to 48 months, the initial high frequency of GU toxicity decreased, with 62% of patients experiencing no GU toxicity, showing an improvement from the short-term follow-up. Conversely, the long-term follow-up revealed that 31% of patients experienced no GI toxicity, indicating a persistent presence of GI symptoms over time. The rates for late grade 1 and grade 2 GI toxicities were 25% and 6.6%, respectively, suggesting sustained but generally mild GI symptoms. For GU toxicity, cumulative study results indicated a consistent increase in the incidence of grade 2 toxicities from 12% at six months to 32% at 48 months. This trend suggests that while the overall frequency of any GU toxicities may decline, the severity or persistence of these toxicities in affected patients can worsen or become more pronounced over time. This gradual but significant rise in the incidence of severe GU toxicities underscores the long-term accumulating risk and the need for prolonged monitoring.

PT: no new RCTs, 8 observational studies (n=5,514)

acute toxicity:
GU is more frequent than GI (more grade 1 and 2 toxicities and less patients with no toxicities), grade 3 is rare for both

long-term toxicity:
initial high frequency of GU toxicities decreased; GI toxicities persisted

increasing incidence of grade 2 toxicity over time among patients who develop complications

Conclusion

results align with current clinical guidelines and SRs

inconclusive evidence on the ability of SBRT, IRE and PT to replace radical procedures, SBRT non-inferior to CFRT in low/intermediate-risk PCa

need for high-quality research on long-term efficacy and safety

The results of this review are in line with the current clinical practice guidelines and other recent SRs. There is a limited and inconclusive body of evidence for all three therapies: SBRT, PT and IRE so it cannot be determined whether IRE, SBRT, and PT can replace or prevent radically invasive procedures such as prostatectomy, or whether these therapies provide a significant benefit to patients in terms of improved QoL or survival chances. However current evidence does indicate that SBRT is non-inferior to conventional fractionation in terms of survival outcomes for low-to intermediate-risk cancer patients. Further high-quality research is required to demonstrate the long-term efficacy and safety of these therapies in comparison with standard treatments. Currently, several studies are underway, including a few RCTs that involve comparisons with conventional technologies and thus should enable statements on efficacy and safety.

Summary of Report 2018

Introduction

3 Technologien zur Behandlung wurden bewertet

The report in 2018 [1] addressed the research question if irreversible electroporation, stereotactic radiotherapy and proton therapy was more effective and safer for the treatment of localised prostate cancer – in terms of predefined outcome parameters – in comparison with other treatment options for this condition.

Description of the technologies

irreversible Elektroporation (IRE)

Irreversible electroporation (IRE, NanoKnife®) is a type of focal therapy which has been suggested as an alternative to radical treatment. It typically uses 3 to 5 electrodes which deliver short repetitive electrical pulses to destroy the cancer cells.

stereotaktische Strahlentherapie (SBRT)

Stereotactic radiotherapy (stereotactic body radiation therapy or SBRT) is a type of external radiation (external beam radiation therapy or EBRT) in which a higher radiation dose is delivered in a reduced number of fractions as is the case with conventional or moderately fractionated radiation therapy.

Protonentherapie (PT)

Proton therapy (PT) is a further type of external radiation therapy which uses high doses of ionizing rays directed at the tumour. In contrast to standard radiation, PT uses proton beams rather than x-rays or photons.

Health Problem

Prostatakarzinom (PCa) zählt zu häufigsten Tumorerkrankungen

Prostate cancer (PCa) is one of the most prevalent cancers among men in industrialised countries and, with an incidence of 23%, is also one of the most common cancer forms among Austrian men. The choice of specific treatment depends on various factors such as the patient's age, health status at the time of diagnosis, co-morbidity profile, life expectancy, individual patient preferences as well as clinical and pathological information such as tumour stage, PSA levels and Gleason score. The effectiveness and safety of three potential technologies (IRE, SBRT, PT) for the treatment of localised PCa was assessed in this report.

Methods

Methoden: Literatursuche und Review

Search: To answer the research question, a systematic search in five bibliographic databases was conducted, together with a hand search. Where applicable, experts were also contacted. The literature selection process was conducted by two reviewers working independently of each other. Data extraction and GRADE assessments was performed by one reviewer and checked by the second reviewer.

Endpunkte: Überleben und Lebensqualität

Sicherheit (Toxizität)

Critical endpoints and study designs: Survival and quality of life were used as patient-relevant endpoints for the assessment of effectiveness. Only randomized controlled trials (RCTs) were defined as appropriate study designs for assessing these endpoints so only effectiveness data from these types of studies were used. The endpoint safety (toxicity) was also included. In assessing toxicity, evidence from prospective studies with 50 or more participants was permitted, in addition to evidence from RCTs.

Results

keine RCTs zu IRE, SBRT
5 RCTS zu PT

Available evidence: Only one observational study with more than 50 participants could be identified for IRE; there were no RCTs available for this

intervention. Twenty-five prospective observational studies (in 30 publications) were identified for SBRT; again there were no available RCTs for this technology. There was more evidence available for PT: five RCTs and twelve prospective non-controlled studies were identified.

keine Aussagen zur Wirksamkeit von IRE und SBRT möglich

Clinical Effectiveness: Due to a lack of RCT evidence, no conclusions regarding the effectiveness (impact on survival and quality of life) of IRE or SBRT were possible. The five RCTs of PT were based on differing clinical questions, which effectively meant there was only one study available pro specific subquestion. In addition to which, the RCTs were methodologically flawed. Only one RCT compared PT to an alternative therapy; a second RCT compared a combined proton-photon therapy with an alternative. The three remaining RCTs were comparisons of differing dosage schedules or fractions. No effect could be seen (there is moderate strength of evidence for this assessment) regarding the endpoint overall survival. There were conflicting results regarding the endpoint biochemical relapse-free survival, for this reason the strength of evidence was classed as very low. There was generally no evidence to suggest that varying doses and fractions of PT conferred any advantages regarding quality of life, particularly in terms of genitourinary (GU) and gastrointestinal (GI) symptoms. Only one statistically significant result was reported for sexual functioning and that was in the comparison between hypofractionated PT (worse) compared to standard fractionated PT. As the results were similarly inconsistent, the quality of evidence was considered to be moderate to low.

nur 1 RCT mit relevanter Kontrollintervention

kein Unterschied bei Gesamtüberleben

rezidivfreies Überleben: inkonsistent

kein Unterschied: Lebensqualität

Sicherheit von IRE: 1 Beobachtungsstudie

Safety: There was only one available observational study on IRE; this study reported only on acute toxicity and found grade 1 GU toxicity among 24% of patients and grade 2 GU toxicity among 11%.

urogenitale (GU) Akuttoxizität Grad 1 bei fast 50% der Patienten, gastrointestinale (GI) Akuttoxizität Grad 1 bei über 1/3 der Patienten

PT and SBRT showed similar frequencies of toxicity: GU toxicity grade 1 occurred in around half of the patients and GI toxicity in around one-third (it should be noted that the RCT studies on PT reported considerably higher toxicities than the observational studies on PT). Grade 2 GU acute toxicity occurred in around one-quarter of PT-treated patients and around 18% of SBRT-treated patients (whereby grade 2 GI was again reported much less frequently in the PT observational studies than the PT RCT studies).

Spättoxizität nach einer PT-Behandlung sehr hoch

Late toxicity was generally less frequently observed than acute toxicity except for GI toxicity for PT which was more prevalent in the late phase than in the acute phase. According to the RCT results, late toxicity after PT occurred frequently: GU grade 1 was observed among around one-third of patients and GI grade 1 in around 50% (again the observational studies reported much lower frequencies).

Evidenz aus den Fallserien „sehr niedrig" Evidenz aus den RCTs zu PT „niedrig"

Due to the uncontrolled nature of the observational studies and the inconsistency of the results (the range of reported toxicity incidences was large), the quality of evidence from the observational studies was considered to be very low. Even the evidence from the RCTs of PT could only be considered as low evidence in the GRADE assessment since the toxicity rates were very different, indicating inconsistency.

Conclusion

unzureichende Evidenz für verbesserte Outcomes von IRE, SBRT und PT hinsichtlich Überleben, Lebensqualität und Vermeidung von radikal invasiven Verfahren

Evidence was inadequate and insufficient to show that IRE, SBRT and PT have either a positive impact on survival and quality of life or the ability to prevent or delay prostatectomy. It was concluded that high-quality comparative studies were urgently needed. In total 39 ongoing studies could be identified for these technologies. However, relatively few of these clinical studies provided the type of comparisons and data which addressed the review question posed in the report, although the following could be singled out as particularly noteworthy:

laufende Studien

- A registry of IRE patients running until December 2024, to provide data on toxicity (NCT02255890).
- An international RCT comparing prostatectomy or conventional radiotherapy with SBRT (NCT01584258); results expected in September 2026. Furthermore, one RCT comparing SBRT with conventionally fractionated radiotherapy (NCT02339701), two RCTs comparing SBRT with moderately fractionated radiotherapy (NCT03367702, NCT02361515) and one study comparing SBRT with ADT and EBRT with ADT (NCT02594072).
- One study comparing PT with IMRT (NCT01617161) and one study comparing a combined radiotherapy (including PT) with and without ADT (NCT01492972).

1 Background

1.1 Epidemiology

Prostatakarzinom (PCa) zählt zu häufigsten Tumorerkrankungen

Inzidenz: 30% in Österreich

Mortalitätsrate: starker Rückgang von 1999

Früherkennung bedeutet eine bessere Prognose (lokalisiertes PCa)

Prostate cancer (PCa) is the most common tumour disease among men in industrialised countries. It also remained the most common cancer among Austrian men in 2022, with an incidence of nearly 30%. In 2022, PCa accounted for about one in eight cancer deaths (13%) in men [2]. The incidence rate spiked between 1993 and 2003, then sharply declined until 2013. Since 2015, the incidence rate has risen again and stabilised for the last years (age-adjusted incidence around 150 per 100,000 men). The increase in the incidence rate was largely attributed to increased PSA screening, facilitating very early diagnosis. Although the absolute number of new cancer cases has increased over the past two decades, cancer mortality has decreased. Earlier diagnoses and new treatment methods have contributed to prolonged survival for cancer patients in Austria [3]. Mortality rates have significantly decreased from their peak in 1999 of 66.1 to 38.1 in 2022 [2]. Early detection means also that 50% of all new diagnoses are in a localised tumour stage, which generally has a very favourable prognosis [3].

Risikofaktoren: Alter, Veranlagung, Ethnizität sowie Ernährung

The development of PCa is not yet fully understood, but there are several risk factors that can promote its occurrence. Age, African origin, and a family history of PCa are well-established risk factors. Various environmental factors are associated with PCa risk and progression from latent to clinical PCa, but no effective preventative dietary or pharmacological interventions are currently known [4].

Symptome erst bei fortgetschrittenem Verlauf

Many cases of PCa have a slow progression if left untreated. However, many men die with PCa rather than because of it. In its early stages, clinically localised PCa is usually asymptomatic. As the disease progresses, problems with urination such as pain, burning, weak urine stream, and blood in the urine can occur. Prostate cancer can be diagnosed based on these symptoms in combination with a physical examination, PSA level determination, and a biopsy [4].

1.2 Diagnosis

Diagnose durch eine digitale rektale Tastuntersuchung sowie durch die Bestimmung des PSA-Wertes endgültige Diagnose durch Biopsie

Various diagnostic tools, including digital rectal examination (DRE), prostate-specific antigen (PSA), and transrectal ultrasound (TRUS), can be used separately or in combination to indicate the need for a prostate biopsy. PSA is a better independent predictor of cancer than DRE or TRUS, but optimal PSA thresholds for detecting clinically significant PCa are not established. Elevated PSA levels should be confirmed under standardised conditions before further testing [4].

ultraschallgezielte Prostatabiopsie als Standard

Risk calculators and PSA density (PSA-D; serum PSA divided by prostate volume) can reduce unnecessary testing, with PSA-D being particularly predictive in smaller prostates. Multiparametric magnetic resonance imaging (mpMRI) is crucial for biopsy optimisation, demonstrating high sensitivity and specificity in detecting significant cancers. Combining PSA-D and MRI further improves biopsy decision-making [4].

CT, MRT & PET als weiterführende Untersuchungen

The Stockholm3 test, incorporating clinical variables and blood biomarkers, reduces clinically insignificant cancer diagnoses and the need for mpMRI scans. Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) or PSMA PET/magnetic resonance imaging (MRI) can also target biopsies, improving sensitivity but reducing specificity compared to MRI alone [4].

PSA-Screening: Testintervalle, Alter, Lebenserwartung-Kriterien

The diagnostic pathway for PCa aims to detect significant cases early while minimizing the detection of insignificant cases, balancing accuracy with the burden on patients and healthcare providers. Screening for PCa remains controversial. The optimal intervals for PSA testing are not well defined, but a two-year interval is suggested for men at increased risk, while it can be extended to up to eight years for those not at risk. The age to stop early diagnosis should be based on individual life expectancy, considering comorbidity as important as age. Men with less than 15 years of life expectancy are unlikely to benefit from early diagnosis. Despite improvements, overdiagnosis remains a risk, and decoupling diagnosis from compulsory active treatment is key to reducing overtreatment while maintaining the benefits of early diagnosis for those who request it [4].

1.3 Staging/Grading

Beurteilung des Tumorstadiums durch TNM-Klassifikation (tumor, node, metastasis) und Risikoklassifizierung bezüglich der Entwicklung eines Rezidivs

The 2017 TNM classification from the Union for International Cancer Control (8th edition) is recommended for staging PCa. The clinical T (cT) stage, traditionally based on DRE, is now influenced by advanced imaging techniques such as MRI and PSMA PET imaging, which may cause shifts in risk group distribution and affect treatment decisions. The European Association of Nuclear Medicine (EANM) has proposed a molecular imaging TNM (miTNM) classification using PSMA PET/CT, which is more sensitive than conventional methods and may offer better prognostic information [4]. The TNM classification is presented in Table 1.3.1.

Table 1.3-1: TNM classification

Abbreviation	Definition
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T_1	Clinically inapparent tumour that is not palpable
T_{1a}	Tumour incidental histological finding in 5% or less of tissue resected
T_{1b}	Tumour incidental histological finding in more than 5% of tissue resected
T_{1c}	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T_2	Tumour that is palpable and confined within the prostate
T_{2a}	Tumour involves one half of one lobe or less
T_{2b}	Tumour involves more than half of one lobe, but not both lobes
T_{2c}	Tumour involves both lobes
T_3	Tumour extends palpably through the prostatic capsule
T_4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
M_x	Metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis
M_{1a}	Non-regional lymph node(s)
M_{1b}	Bone(s)
M_{1c}	Other site(s)

Source: EAU guideline [4]

Gleason Score als Bewertungssystem für das Prostatakarzinom:

Einteilung in 5 Grades

The ISUP 2005 Gleason score (and its 2014 and 2019 updates) remains the standard for grading PCa. This system involves assigning a Gleason grade based on biopsy results and reporting an overall Gleason score for carcinoma-positive biopsies. Recent modifications introduced grade groups to distinguish clinical differences between various Gleason score combinations more clearly [4]. One Gleason grade is assigned to the most predominant pattern in your biopsy and a second Gleason grade to the second most predominant pattern. The two grades will then be added together to determine the Gleason score. A Gleason score of 6 is low grade, 7 is intermediate grade, and a score of 8 to 10 is high grade cancer [4, 5].

weitere Klassifikationssysteme nach... D'Amico,

The D'Amico risk group classification (see Table 1.3-2), which categorizes patients by their risk of biochemical recurrence (BCR) post-treatment, now includes a useful subdivision for intermediate-risk disease. The Cambridge Prognostic Groups, a five-tier model incorporating ISUP grade groups, PSA levels, and cT stage, has shown superior discriminative performance for predicting PCa-specific mortality compared to the traditional three-tier risk groups [4].

EAU,

The EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, combines clinical information on tumour extent, PSA and pathology from systematic biopsy (see Table 1.3-3) [4].

NCCN

Stratification of risk according to the NCCN guidelines is also reported in some of the studies we include in this report. The NCCN Guidelines subdivide intermediate-risk disease into favourable and unfavourable intermediate-risk, with unfavourable features including ISUP grade group 3, and/or ≥ 50% positive systematic biopsy cores and/or at least two intermediate-risk factors (see Table 1.3-4) [4].

Table 1.3-2: D'Amico risk group classification

D'Amico	Low risk	Intermediate risk	High risk
Tumour stage	T1c-T2a	T2b	≥T2c
Gleason Score	≤6	7	≥8
PSA	≤10 ng/ml	10-20 ng/ml	>20 ng/ml

Source: EAU guideline [4]

Table 1.3-3: EAU risk classification

EAU Risk groups	lokal begrenztes PCa	Low risk	Intermediate risk	High risk	Locally advanced PCa	High risk
Tumour stage		T1-T2a	T2b	T2c		T3-T4
Gleason Score		<7	7	>7		any
PSA		<10 ng/ml	10-20 ng/ml	>20 ng/ml		any

Source: EAU guideline [4]

Table 1.3-4: NCCN risk classification

NCNN	Very low risk	Low risk	Moderate risk	High risk	Very high risk
Tumour stage	T1c	T1-T2a	T2b-T2c	T3a	T3b-4
Gleason Score	≤6	≤6	7	8-10	5 or >4 biopsy cores with Gleason Score between 8-10
PSA	<10 ng/ml	<10 ng/ml	10-20 ng/ml	>20 ng/ml	

Source: EAU guideline [4]

1.4 Therapy

zahlreiche Faktoren sind bei der Wahl der geeigneten Therapie zu berücksichtigen

Therapy decisions should be made in a multidisciplinary team (including urologists, radiation oncologists, medical oncologists, pathologists, and radiologists), and using a shared care approach to balance of benefits and side effects of each therapeutic modality together with the patients' views and preferences. Individual life expectancy, health status, frailty, and co-morbidity, not only age, should be central in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of ten years is most commonly used as a threshold for benefit of local treatment [4].

primäre Therapien

The risk group of the cancer will determine which type of treatment is most appropriate. Options for PCa include watchful waiting, active surveillance, radical prostatectomy (surgical removal of the prostate gland), radiotherapy, brachytherapy, focal therapy and hormone therapy [6].

andere Therapieformen bei nicht-metastasierten Tumoren oder geringem Risikoprofil:

kurative Therapie, aktive Überwachung

Localised tumours can be treated with methods to destroy or remove the tumour [7]. For patients with a low risk profile, active surveillance can be considered although an active treatment is not excluded [7-10]. If active surveillance is not suitable or PSA values increase, the surgical or radiotherapy options can be considered [7, 9, 10]. Surgery can be recommended for all types of locally restricted PCa [7, 10]. Radiation therapy can be accompanied by an androgen deprivation treatment before, during or after the course of radiation. This is designed to reduce the amount or even size of the cancer cells, thus increasing the effectiveness of the radiation therapy. [7-10].

1.5 Description of the interventions

1.5.1 Irreversible electroporation (IRE)

irreversible Elektroporation (IRE) soll Krebszellen durch kurze, wiederholende, nicht-thermische, hochenergetische Impulse von ins Krebsgewebe eingeführten Elektrodennadeln zerstören

Irreversible electroporation (IRE, NanoKnife®) is an alternative treatment method to radical therapies, typically involving the insertion of three to five electrode needles into and around the carcinoma tissue. The goal of the treatment is to destroy the cancer cells through short, repeated, non-thermal, high-energy electrical impulses delivered over several minutes. The electrodes can be repositioned to expand the reach of electroporation until the entire tumour, along with a sufficient safety margin, can be ablated. This process creates multiple pores in the cell membrane, which disrupts the homeostatic mechanism of the cells, ultimately leading to cell death. This procedure is performed under general anaesthesia and lasts two to four hours. A neuromuscular blocker is used to prevent uncontrolled severe muscle contractions that can be triggered by the electric current. Cardiac resynchronization is used to regulate the delivery of electrical impulses within the refractory period, thereby minimising the risk of arrhythmias [11].

Guideline recommendations for IRE

2018 und 2022: keine AUA/ ASTRO Leitlinie-Empfehlung für IRE in den USA

In the 2018 report we referenced joint guidelines from the American Urological Association (AUA) and American Society for Radiation Oncology (ASTRO) [12] that did not specifically refer to IRE but there were general references to focal therapy. The recommendation was that patients offered focal therapy should be informed that this type of therapy cannot be seen as a conventional therapy, due to a lack of comparative studies. The latest

AUA/ASTRO guideline published in 2022 reiterates that clinicians should inform patients with intermediate-risk PCa considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. This recommendation is based on expert opinion and covers all types of focal therapy, not just IRE [13].

2018 und 2021: keine AWMF-Empfehlung für IRE bei lokal fortgeschrittenem PCa in Deutschland

The S3 Leitlinie from the „Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF), Deutschen Krebsgesellschaft (DKG) and Deutschen Krebshilfe (DKH)“ recommended that IRE should not be used as a therapy for locally advanced PCa [8, 14]. The latest S3 guideline (from 2021) confirmed that there is still not enough data to assess the effectiveness or safety of IRE [15].

2017 EAU-Leitlinie: fokale Therapie nur in klinischen Studien

The European Association of Urology (EAU) guideline (from 2017) [4] does not refer specifically to IRE but mentions that focal therapy more generally should be performed only within the context of a clinical trial setting or a well-designed prospective registry.

1.5.2 Stereotactic radiotherapy (SBRT)

stereotaktische Strahlentherapie (SBRT) als Form der externen Strahlentherapie (EBRT),

bei der eine hohe Strahlendosis in weit weniger Fraktionen als bei konventioneller oder moderat fraktionierter Bestrahlung üblich ist, verabreicht wird

Unlike many other cancers, PCa cells are believed to have a low alpha/beta ratio, making them more sensitive to hypofractionated radiation compared to an equivalent dose given over multiple fractions. Stereotactic body radiation therapy (SBRT) is a form of external beam radiation therapy (EBRT) that delivers high doses in fewer fractions than conventional or moderately fractionated radiation. It is often called extremely hypofractionated or ultra-hypofractionated radiation therapy. With standard EBRT 1.8-2 Gray (Gy) per day up to 74-80 Gy is administered, while with SBRT up to 10 Gy is delivered per day over fewer days or weeks, with a total dose of 35-50 Gy typically in five or fewer fractions, but up to eight fractions can still be considered extreme hypofractionation [16]. There is no clear definition of SBRT in the literature; for this analysis, radiotherapy was classified as SBRT if ≤8 units with >4 Gy per fraction were used. SBRT is mainly performed using intensity-modulated radiotherapy (IMRT) with Cyberknife® or a linear accelerator (LINAC). Cyberknife® treatments typically involve five units, each lasting 45-60 minutes.

Guideline recommendations for SBRT

Leitlinienempfehlungen in 2018: SBRT als experimentell gekennzeichnet, nur in klinischen Studien

In 2018, several institutions (ASTRO/AUA, NCCN, AWMF, NHS) [4, 12, 14, 16, 17] which issued guidelines about the use of SBRT highlighted its experimental nature, advised the use in experienced centres, in the framework of clinical trials because evidence was limited to demonstrate the equivalence of SBRT (<5 fractions) to existing standard treatments. Therefore, further well-designed clinical trials were urged.

2022 AUA/ ASTRO Leitlinie: positive Empfehlung

aber dennoch mehr Langzeitergebnisse zur Beurteilung notwendig

In recent years, two of these guidelines have been updated to incorporate more recent findings. The 2022 ASTRO/AUA guideline [13] expressed positive approach towards SBRT. The guideline states that clinicians may offer ultra-hypofractionated EBRT to patients with low- or intermediate risk PCa who elect EBRT (conditional recommendation; evidence level: B). In patients with low- or favourable intermediate-risk PCa electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment (strong recommendation;

evidence level: B). Currently, data on long-term control with ultra-hypofractionated compared to moderate hypofractionation is less well documented; however, data to date support the use of hypofractionated EBRT [13].

2018 und 2024 AWMF-Leitlinie: extreme Hypofraktionierung nur in klinischen Studien

The other updated guideline, the „S3 Leitlinie Prostatakarzinom" from AWMF only reiterated its 2018 statements. Specifically, it maintains that extreme hypofractionation should only be conducted within controlled clinical trials (recommendation level: A) [15].

2024 EAU-Leitlinie: positive Upflung

The EAU guideline from 2024 [4] recommends offering ultra-hypofractionated IMRT/image guided radiotherapy (IGRT) or SBRT, using either 36.25 Gy (40 Gy to the prostate) in 5 fx or 42.7 Gy in 7 fx delivered on alternate days for intermediate risk PCa (week recommendation).

1.5.3 Proton therapy (PT)

bei Protonentherapie (PT) wird die Bestrahlung mittels Ionen-Teilchen statt Röntgenstrahlen durchgeführt

PT ist daher eine weitere Art der EBRT, bei der hochdosierte ionisierende Strahlungen an den Tumor abgegeben werden

External beam radiotherapy (EBRT) can be performed using either photons or protons. Proton therapy (PT or proton beam therapy) involves the use of particle beams instead of X-rays and thus is another form of EBRT, where high-dose ionising radiation is delivered to the tumour. PT is administered in fractions using a cyclotron or synchrotron and aims to reduce radiation exposure to the surrounding healthy tissue. Protons have the physical advantage of being able to release almost all their energy within the tumour, sparing healthy tissue from damage; this could theoretically reduce the risk of side effects [12{Tambas, 2022 #35]}. PT can be delivered through two methods: first, using a three-dimensional conformal technique (the older method), and second, using pencil-beam scanning (PBS), which is similar to IMRT [18]. Like SBRT, there is a discussion about hypofractionation in PT. However, the technical effort required to generate and direct the proton beam is enormous, and this therapy is offered in only a few centres worldwide [19].

Guideline recommendations for PT

2018 Übereinstimmung in Leitlinien: zu wenig Evidenz für PT, vorerst nur in klinischen Studien empfohlen

The guideline summary in the report 2018 referred to several guidelines (ASTRO/AUA, American College of Radiology (ACR), NCCN and the AWMF S3 guideline) [12, 14, 17, 20], which all concurred that there was insufficient evidence to recommend proton therapy as a standard therapy for PCa and the AWMF guideline went further, stating that treatment should only take place within the context of a clinical trial.

2022 AUA/ASTRO Leitlinie: Behandlungsoption, aber anderen Radiotherapien nicht überlegen

The updated AUA/ASTRO guideline (part III) recommends that clinicians can advise patients with PCa that proton therapy is a treatment option, but that it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (Conditional Recommendation; Evidence Level: Grade C) [21].

2024 NCCN und AWMF: keine Überlegenheit gegenüber IMRT

AWMF: nur in klinischen Studien

The updated NCCN Panel recommendation [22] states that there is no clear evidence to support a benefit or decrement to proton therapy over intensity-modulated radiation therapy for either treatment efficacy or long-term toxicity. Similarly, the S3 AWMF guideline [15] finds no patient-relevant advantage for proton therapy in comparison with IMRT for patients with localised PCa and repeats its recommendation from earlier that the therapy should only be delivered within the context of a clinical trial (recommendation A, level of evidence 4).

EAU: keine Erwähnung

The updated EAU guideline [4] does not mention proton therapy.

2 Methods

2.1 Research question

The present report aims to update the 2018 report [1] with evidence published after its search period and answer the following research question:

Forschungsfrage: Vergleich der IRE, SBRT und PT zu anderen Therapieotionen

Are irreversible electroporation (IRE), stereotactic radiation therapy (SBRT), or proton therapy (PT) more effective and safer for treating patients with localised prostate cancer (PCa) in terms of the defined outcome parameters (see PICO framework in Table 2.2 1) compared to other localised PCa treatment options?

2.2 Inclusion criteria

Einschlusskriterien relevanter Studien

The inclusion criteria for relevant studies are summarized in Table 2.2 1. Since various treatment options for localised PCa exist, the nature of the control was left open, i.e., any type of comparison was considered in the analysis.

Table 2.2-1: Inclusion criteria (PICO scheme)

Population	Men with primary or localised (stage 1 or stage 2) prostate cancer
Intervention	1. Intervention: Irreversible electroporation (IRE) 2. Intervention: Stereotactic radiotherapy (SBRT) 3. Intervention: Proton therapy (PT) as primary treatment. Studies that use the intervention as a boost or salvage therapy were not included.
Control	■ Active surveillance ■ Watchful waiting ■ Radical prostatectomy ■ Internal radiotherapy (brachytherapy) ■ Other types of external radiotherapy (EBRT) ■ Androgen deprivation therapy (ADT) ■ Focal therapy (like high-intensity focused ultrasound)
Outcomes	*Effectiveness:* Survival and disease control: ■ Overall survival ■ Disease-specific survival ■ Metastasis-free survival ■ Biochemical recurrence-free survival (BCRFS) Patient-reported health status/quality of life (QoL): ■ Urinary incontinence ■ Urinary symptoms (urinary incontinence, urge to urinate, problems with bladder emptying) ■ Bowel complaints ■ Sexual functioning ■ Hormonal symptoms Other: Avoidance of prostatectomy *Safety:* ■ Toxicity (acute and late: grade 0 to 5)
Study type	For effectiveness: ■ Systematic reviews (SRs) & health technology assessment (HTA) reports ■ Randomised controlled trials (RCTs) For safety: ■ All above mentioned and ■ Non-controlled prospective studies with ≥ 50 patients for PT and IRE and ≥ 200 patients for SBRT

systematische Literatursuche in Datenbanken

The systematic literature search to identify relevant studies was conducted in February 2024 in the following databases (the detailed search strategy can be found in Appendix 8.1):

- Cochrane CENTRAL
- CRD (DARE-, NHS-EED-, HTA databases)
- Embase
- Medline via Ovid

Ein- und Ausschlusskriterien

Studies in English and German were included. The search spanned from February 2018 to February 2024, as it is an update of the literature search. Studies were mainly excluded due to differing study designs, insufficient numbers of participants, and failing to report on endpoints of our interest. When relevant SRs and HTAs included retrospective studies, they were excluded from our analysis. However, we meticulously verified whether any prospective studies were included in the identified HTAs and SRs. Through this rigorous snowballing process, we were able to identify an additional seven references.

Screening von Referenzlisten

Bewertung der Wirksamkeit ausschließlich durch randomisierte kontrollierte Studien (RCTs) als Evidenz

The patient-relevant endpoints of survival and quality of life (QoL) were defined a priori. To assess effectiveness, only RCTs were included as evidence, i.e., Chapter 3 exclusively refers to RCT results. In Chapter 4 (Toxicity), evidence from prospective observational studies with over 50 patients with IRE and PT and over 200 patients for SBRT are also considered. The reason for the deviation in the minimum required patient number for the prospective observational cohort studies was that the RCT evidence was more robust for SBRT, reducing the need for the inclusion of small observational studies.

insgesamt konnten über 1.000 Publikationen zu den 3 Therapieformen gefunden werden

In total, over 1,000 publications on the three therapy forms were found through database and manual search. After removing duplicates, 1039 publications were screened. The literature selection process is depicted in Figure 2.2-1.

Literatur-auswahlverfahren

The literature selection was conducted by two independent researchers. The abstract screening was performed by IR and LS, and the full texts were subsequently screened by JE and LS. In case of discrepancies, a consensus was reached through discussion, or the opinion of a third person was sought.

Suche nach laufenden Studien

Additionally, a search for relevant ongoing clinical studies was conducted in the ClinicalTrials.gov database. The potential hits were screened and selected by the author and checked by the co-author. The same selection criteria as for the published study selection were applied, except that SBRT studies were included only if they were RCTs, given the extensive number of ongoing studies and already published RCTs.

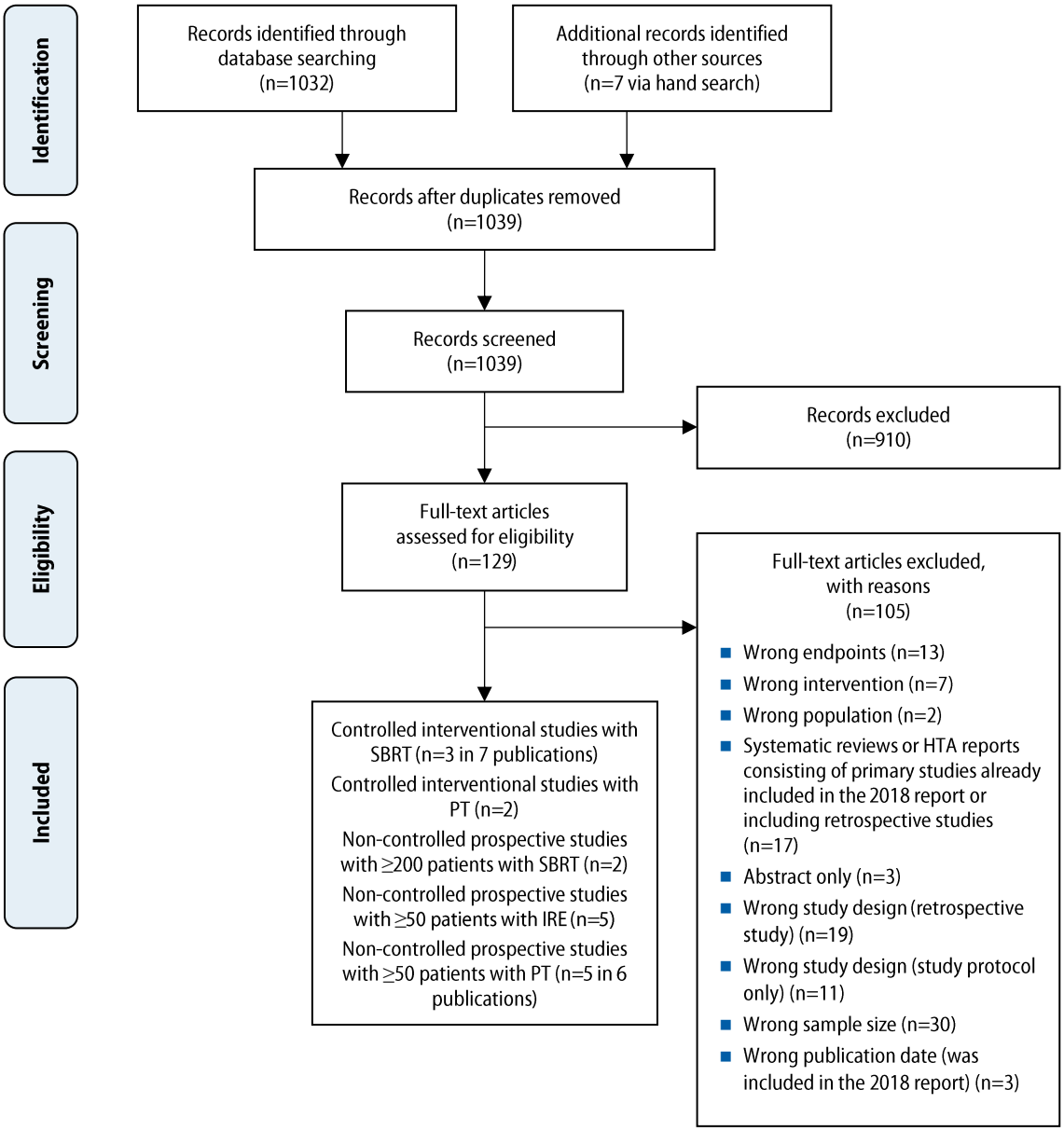

Figure 2.2-1: Selection process (PRISMA flow diagram)

2.3 Data extraction and analysis

Datenextraktion und Datenkontrolle durch Erst- und Zweitautorin

The data from the included studies were extracted by the author (JE) and verified by the co-author (LS). The extracted data regarding the respective interventions are presented in tabular form. The data extraction tables for ongoing studies identified in the ClinicalTrials.gov database are located in the appendix (Table 8.3-1, Table 8.3-2, Table 8.3-3). To facilitate the presentation and interpretation of the results, unweighted mean values were calculated for occurrences of toxicity. These calculations were performed by the author (JE) and verified by the co-author (LS). Additionally, the range of the toxicity occurrences was presented.

2.4 Risk of bias assessment of the included studies

Bewertung der Studienqualität für RCTs anhand des Cochrane RoB 2.0 Tools und für einarmige Beobachtungsstudien anhand des IHE Checkliste

The assessment of the internal validity of all included studies was performed independently by the authors (JE, LS) for RCTs using the Cochrane Risk of Bias (RoB) 2.0 Tool [23] and for single-arm observational cohort studies, the Institute of Health Economics (IHE) Checklist [24, 25]. The risk of bias for individual RCTs is displayed in Table 4.3-1 for effectiveness outcomes, and in Table 4.3-1 for the safety outcomes. The risk of bias assessments of single-arm studies are displayed in the appendix in Table 8.2-1 for SBRT, Table 8.2-2 for PT and Table 8.2-3 for IRE.

The certainty of evidence for patient-relevant endpoints was evaluated by the author (JE) using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [26] by summarizing all relevant study results for each endpoint and subsequently assessing the certainty of the evidence. The review of the GRADE tables was conducted by the co-author (LS). Discrepancies were resolved through discussion and consensus.

Bewertung Patientenrelevanter Endpunkte nach GRADE

The GRADE approach classifies the certainty of evidence into levels:

- *High certainty*: Further research is very unlikely to change our confidence in the estimate of the treatment effect.
- *Moderate certainty*: Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
- *Low certainty*: Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
- *Very low certainty*: There is very high uncertainty in the treatment effect estimate.

3 Effectiveness

3.1 Endpoints

Survival (overall and biochemical recurrence-free)

Endpunkte Gesamtüberleben und rezidivfreies Überleben

In addition to overall survival, biochemical recurrence-free survival (BCRFS) according to ASTRO (“Phoenix definition”) was also analysed, which are briefly described below.

nach ASTRO-Definition handelt es sich um ein PSA-Rezidiv, wenn der PSA-Wert nach primärer Strahlentherapie mindestens 2 ng/ml über den Nadir steigt

The latest ASTRO definition, also known as the "Phoenix definition," is considered more sensitive and specific than former definitions from ASTRO. According to this definition, a PSA recurrence occurs when the PSA level rises at least 2 ng/ml above the nadir after primary radiation therapy. The dating of the recurrence is done at the documented time of exceeding the threshold ("at call") [27].

Quality of life

Endpunkt Lebensqualität

In the included studies, the endpoints regarding QoL were measured using the following instruments:

Bewertung nach EORTC QLQ-C30 Fragebogen:

umfasst 30 Fragen über 10 Subskalen und dient zur Beurteilung der Lebensqualität onkologischer PatientInnen

The multidimensional *EORTC QLQ-C30* questionnaire, developed by the European Organisation for Research and Treatment of Cancer Quality of Life Group, comprises 30 questions across 10 subscales and is used to assess the QoL of cancer patients. As it is a non-disease-specific (generic) questionnaire, additional modules have been developed for the QLQ-C30 depending on the type of cancer, such as the prostate-specific QLQ-PR25, which is predominantly used in Europe. Neither of the included studies used this prostate-specific instrument, although it would capture the general side effects after radiation therapy concerning obstruction, continence, potency, and subjective well-being. In the QLQ-C30 the scoring ranges from 0 to 100. A higher score indicates better function and QoL. However, in the subscales, higher points indicate more symptoms [28].

der Prostate Cancer Symptom Indices (PCSI) besteht aus 4 Domänen und 29 Items

The *Prostate Cancer Symptom Indices* (PCSI) consists of four domains and assesses urinary incontinence, urinary tract irritation/obstruction, digestive complaints, and sexual dysfunction following PCa treatment. This questionnaire comprises 29 items and is scored on a scale from 0 to 100, where 0 represents "no symptoms." The response options are based on a four- or five-point Likert scale [29].

der American Urological Association Symptom Index Score (AUA Score) erhebt die Symptome einer Prostatahyperplasie und besteht aus 7 Fragen

The *American Urological Association Symptom Index Score (AUA Score)* assesses the symptoms of benign prostatic hyperplasia and consists of seven questions. The responses relate to the frequency of the symptoms and are based on a six-point Likert scale. The score has a maximum of 35 points, where 0 to 7 points indicate mild symptoms, 8 to 19 points moderate symptoms, and 20 to 35 points severe symptoms. Based on the number of points, the most suitable treatment method is then selected [30].

der Expanded Prostate Cancer Index Composite (EPIC) ist ein Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität

The *Expanded Prostate Cancer Index Composite (EPIC)* is a questionnaire used to measure health-related QoL in patients with PCa. It covers four domains related to urinary, gastrointestinal, sexual, and hormonal symptoms, comprising a total of 50 questions. The maximum score is 100 points, with lower scores indicating worse outcomes [31].

Avoidance of radical prostatectomy

Vermeidung von radikal invasiven Eingriffen

Another endpoint that was defined as an important endpoint was the extent to which the interventions led to the avoidance of radically invasive procedures (e.g., surgical procedures such as prostatectomy). None of the included studies measured this outcome.

3.2 Irreversible electroporation (IRE)

3.2.1 Included studies

keine RCTS zu IRE

We could not identify any RCTs comparing IRE with any of the comparators of our interest.

3.2.2 Results

keine Ergebnisse zur Wirksamkeit

In the absence of RCTs, we cannot describe the effectiveness of IRE.

3.2.3 Certainty of evidence

keine Beurteilung der Vertrauenswürdigkeit der Evidenz möglich

In the absence of RCTs, the certainty of evidence is not applicable for effectiveness outcomes.

3.3 Stereotactic body radiotherapy (SBRT)

3.3.1 Included studies

3 RCTs zu SBRT: SBRT vs. CFRT

Three RCTs (in seven publications) [32-38] could be identified, each comparing SBRT to conventionally fractionated radiotherapy (CFRT). While one of the clinical trials, PACE-B [32, 36, 37] used various terms to describe the control intervention (moderately or conventionally fractionated, and intensity-modulated fractionated radiotherapy (IMRT)), whereas other trials uniformly referred to CFRT as the comparator. The types of comparisons are presented in Table 3.3-1. There were other RCTs too, but they compared two types of SBRT, therefore we handled them as single-arm prospective cohort studies and considered their results applicable only in the safety analysis (see chapter 4.3 Toxicity).

Table 3.3-1: Types of comparisons in RCTs

Intervention vs. Comparator	Study name (publications)
SBRT vs. conventionally or moderately fractionated radiotherapy (CFRT/MFRT)[1]	**PACE-B** (Brand 2019 [32], Tree 2022 [37], Ratnakumaran 2023 [36])
Ultra-hypofractionated (i.e. SBRT) vs. CFRT	**HYPO-RT-PC** (Widmark 2019 [38], Rasmusson 2020 [35], Fransson 2021 [33])
SBRT vs. CFRT	**Poon 2021** [34]

Study characteristics

Two RCTs (PACE-B [32, 36, 37] and HYPO-RT-PC [33, 35, 38]) were phase 3, open-label, multicentre, non-inferiority studies, one RCT [34] was a phase 2 single-centre study. The HYPO-RT-PC trial [33, 35, 38] was conducted in European centres only, PACE-B [32, 36, 37] was conducted in Europe and Canada and the third one [34] in China. One RCT [32, 36, 37] was funded by the health technology developer, one RCT [34] reported no funding and the third study reported funding from diverse research grants [33, 35, 38]. HYPO-RT-PC randomised 1200 patients and the per protocol population included 1178. PACE-B randomised 874 patients, the per protocol population included 848 patients. The third RCT [34] randomised and included 64 patients.

2 multizentrische, offene Nicht-Unterlegenheits-studien,
1 Überlegenheitsstudie

insgesamt 2.138 Patienten randomisiert, 2.090 analysiert

In two RCTs (PACE-B and Poon et al.), the applied SBRT was 36.25 Gy in five fractions over one to two weeks. The control intervention, CFRT was delivered as 76-78 Gy in 38-39 fractions over 7.5 to 7.8 weeks or 62 Gy in 20 daily fractions over 4 weeks. In another RCT (HYPO-RT-PC), SBRT was delivered as 42.7 Gy in seven fractions, three days per week for 2.5 weeks. The control group received 78 Gy in 39 fractions, five days per week for eight weeks. Only HYPO-RT-PC reported survival and QoL outcomes, the other two RCTs reported only QoL outcomes.

SBRT-Fraktionierung: in 2 RCTs gleich, in 1 RCT leicht abweichend, Kontrollintervention: gleiche Fraktionierung in den Studien

The follow-up period ranged from 12 weeks to five years. Losses to follow-up were reported in all studies and varied depending on the measured endpoint and the cut-off points. In the PACE-B trial, at 12 weeks [32], 26 drop-outs were reported, due to not having received the treatment per protocol (received less fractions). At 24-month follow-up [37], five patients were lost to follow-up, died or were excluded for having received both SBRT and CFRT (two vs. three). The HYPO-RT-PC study for the survival outcome reported that ten patients withdrew before treatment (six vs. four), ten were excluded from the ITT analysis (three vs. seven) [38], and for the QoL outcomes, the loss was 15 due to non-completed or late-completed questionnaires (nine vs. six) [35]. In the third study [34], no one dropped out during the time of delivering the interventions but three patients in both study arms were excluded from the one-year analysis and two vs. 10 patients were excluded at two years.

Nachbeobachtung:
12 Wochen bis 5 Jahre

„Losses to Follow-up" in allen Studien, variierend aus verschiedenen Gründen (Protokollabweichungen, Todesfälle usw.)

[1] The publications name these as intensity-modulated fractionated radiotherapy (IMFR) too.

Patient characteristics

Einschlusskriterien (WHO-Status, ADT, PSA-Level) waren ähnlich in 2 RCTs (HYPO-RT-PC, PACE-B)

Risikoprofil: niedrig- bis mittleres Risiko (PACE-B, Poon); mittleres bis hohes Risiko (HYPO-RT-PC)

The inclusion criteria of two studies (HYPO-RT-PC and PACE-B) show similarities in terms of requirements for WHO performance status (0-2), exclusion of patients who are receiving ADT, and upper limit of PSA at ≤ 20 ng/ml. Two studies (PACE-B and Poon et al.) focused on patients with low- or intermediate-risk PCa (stages T1-T2), the third study (HYPO-RT-PC) targeted men with intermediate-to-high-risk PCa, including stage T3 and Gleason scores of at least 7. All three studies required no evidence of lymph node involvement or distant metastases. Two studies (PACE-B and Poon et al.) had a lower age limit of 18 years and no upper limit, while the third study (HYPO-RT-PC) had an upper age limit of 75 years and did not specify a lower age limit. Detailed study and patient characteristics are presented in Table 3.3-2.

Table 3.3-2: Study characteristics (RCTs) with SBRT

Author, Year, Reference	Brand 2019 [32] PACE-B	Tree 2022 [37] PACE-B	Ratnakumaran 2023 [36] PACE-B	Widmark 2019 [38] HYPO-RT-PC	Fransson 2021 [33] HYPO-RT-PC	Rasmusson 2020 [35] HYPO-RT-PC	Poon 2021 [34]
Country	UK, Ireland, and Canada			Sweden and Denmark			China
Intervention (I) vs. Comparator (C)	Stereotactic body radiation therapy (SBRT) vs. conventionally fractionated or moderately hypofractionated radiotherapy (CFRT/MFRT)			Ultra-hypofractionation (UHF) vs. CFRT			SBRT vs. CFRT
Funding / conflicts of interest (CoI)	Funder and sponsor until 2014 Accuray, after 2014 the Royal Marsden NHS Foundation Trust. Various level of support (direct funding, coordination and facilitation): Cancer Research UK, National Institute for Health Research (NIHR) Cancer Research Network, Cancer Trials Ireland, Prostate Cure Foundation, NIHR Biomedical Research Centre, UK's Comprehensive Local Research Networks. CoI: approx. 50% of the authors report research support from the health technology developers			Funding: Nordic Cancer Union, the Swedish Cancer Society and the Swedish Research Council CoI: none declared.			Funding: none CoI: none declared
Setting, Time period	Phase 3, open-label, randomised, non-inferiority trial at 37 centres[2] in three countries, recruitment completed with follow-up ongoing; data snapshot as of May 2019.			Phase 3, open-label, randomised, non-inferiority trial at 12 centres in two countries, recruitment completed			Phase 2, single-centre, prospective, randomised trial
Details of the interventions (number of fractions, total dose, equipment)	SBRT: 36.25 Gy in 5 fractions/1–2 weeks. Initially CyberKnife (Accuray) was mandatory, after sponsorship change conventional linear accelerators were allowed. CFRT/MFRT: 78 Gy in 39 daily fractions or 62 Gy in 20 daily fractions			UHF: 42.7 Gy in 7 fractions, 3 days/week for 2.5 weeks CFRT: 78.0 Gy in 39 fractions, 5 days/week for 8 weeks Radiotherapy was delivered with 3D CRT, IMRT, or VMAT with use of fiducial markers in both arms. Image-guided radiotherapy technique: BeamCath technique was initially used but was subsequently replaced by implanted gold fiducial markers in both arms.			SBRT: 36.25Gy/5 fractions/ 2 weeks CFRT: 76Gy/38 fractions/7.5 weeks
Follow-up period	Up to 12 weeks	Up to 24 months	Up to 24 months (secondary analysis of the 24-month toxicity data)	Median 5 years	Median 4 years	Median 5 years (secondary analysis of relationship between absorbed dose and erectile dysfunction)	Median 2.2 vs. 2.4 years (for toxicity 5 year follow-up)
Toxicity classification	Radiation Therapy Oncology Group (RTOG) and Common Terminology Criteria for Adverse Events (CTCAE)			RTOG	NA	NA	RTOG

[2] Tree and Ratnakumuran reported 35 centres.

Author, Year, Reference	Brand 2019 [32] PACE-B	Tree 2022 [37] PACE-B	Ratnakumaran 2023 [36] PACE-B	Widmark 2019 [38] HYPO-RT-PC	Fransson 2021 [33] HYPO-RT-PC	Rasmusson 2020 [35] HYPO-RT-PC	Poon 2021 [34]
Method for measuring survival and quality of life	QoL: EPIC tool, Vaizey questionnaire, IPSS, IIEF-5			Survival: Failure-free survival, Biochemical disease-free survival, Clinical disease-free survival, Prostate cancer specific survival, Overall survival	QoL: PCSS, EORTC QLQ-C30, IIEF-5	QoL: Time to ED	QoL: EPIC
Inclusion criteria	Patients suitable for radical radiotherapy (RT), but not willing to have or not suitable for radical prostatectomy (RP), aged ≥18 years, WHO performance status 0–2, with low- or intermediate-risk prostate cancer (PCa), Gleason score ≤ 3+4, T1c –T2c, N0-X, M0-X, prostate-specific antigen (PSA) ≤ 20 ng/ml, not receiving androgen deprivation therapy (ADT).			Men aged ≤ 75 years, WHO performance status 0-2, with intermediate-to-high-risk PCa, T1c–T3a, N0, M0 with one or two of the following risk factors: stage T3a, Gleason score ≥7, or PSA ≥ 10 and ≤ 20 ng/mL and not receiving ADT.			Men aged ≥18 years with NCCN low- or intermediate-risk (T1-2, Gleason score ≤7 and PSA < 20 ng/mL) localized PCa. Zubrod performance status < 2, N0, M0, and no prior bilateral orchiectomy, chemotherapy, RT, cryosurgery, or RP.
Number of patients	874 randomised			1200 randomised			64 randomised
	Per protocol population: 848 SBRT: 416 CFRT/MFRT: 432	Per protocol population: 849 SBRT: 416 CFRT: 433	Per protocol population: 842 SBRT: 414 CFRT: 428	Per protocol population: 1180 UHF: 589 CFRT: 591	Per protocol population: 1165 UHF: 583 CFRT: 582	Per protocol population: 673 UHF: 343 CFRT: 330	Per protocol population: 64 SBRT: 31 CFRT: 33
Patient charateristics (age in years– average and range, ADT in %), I vs. C	Age: 69.6 (65.3–73.8) vs. 69.7 (65.6–73.9) ADT was not permitted.			Age: 68 (64–72) vs. 69 (65–72) ADT was not permitted.		Age: 68 (51-76) vs. 68 (54-76) ADT was not permitted.	Age: 69.4 (53–78) vs. 69 (55–81) ADT: 13 vs. 18
Tumor classification (T1-T3) (% of patients), I vs. C	T1c: 18 vs. 18 T2a: 25 vs. 30 T2b: 20 vs. 13 T2c: 37 vs. 39			T1c: 53 vs. 49 T2: 43 vs. 47 T3a: 4 vs. 5		T1c: 54 vs. 51 T2: 41 vs. 45 T3a: 4 vs. 4	T1a: 3 vs. 0 T1c: 51 vs. 45 T2a: 22 vs. 30 T2b: 16 vs. 9 T2c: 6 vs. 15
Gleason Score (% of patients), I vs. C	3+3: 15 vs. 19 3+4: 85 vs. 81			5: 1 vs. <1 6: 17 vs. 18 7: 76 vs. 75 8: 6 vs. 6 9: 1 vs. <1		≤6: 17 vs. 16 7: 77 vs. 78 ≥8: 6 vs. 7	5: 9 vs. 0 6: 51 vs. 66 7: 38 vs. 33

Author, Year, Reference	Brand 2019 [32] PACE-B	Tree 2022 [37] PACE-B	Ratnakumaran 2023 [36] PACE-B	Widmark 2019 [38] HYPO-RT-PC	Fransson 2021 [33] HYPO-RT-PC	Rasmusson 2020 [35] HYPO-RT-PC	Poon 2021 [34]
Risik status of patients e.g. - D'Amico, NCCN (% of patients), I vs. C	*NCCN* Low risk: 7 vs. 9 Intermediate risk: 93 vs. 91			*TNM* Intermediate risk: 89 vs. 89 High risk: 11 vs. 11		Intermediate risk: 90 vs. 89 High risk: 11 vs. 11	*NCCN* Low risk: 51 vs. 48 Intermediate risk: 48 vs. 51
Loss to follow-up (FU)	26 drop-outs (not received ≥1 fraction of therapy) 1 patient had both treatments and was excluded; 2 crossed over to SBRT and 9 crossed over to the control	3 patients in the CFRT group (2 lost-to-FU, 1 died) 2 patients in the SBRT group (1 lost-to-FU, 1 had both treatments and was excluded)	NA	20 drop-outs (10 withdrew before treatment (6 vs. 4), 10 excluded from ITT analysis (3 vs. 7))	15 (9 patients in the UHF group and 6 patients in the CFRT group due to completed questionnaires dated outside the acceptable time intervals or no completed QOL assessments at all)	NA	0 drop-outs At 1-year FU: 3 vs. 3 excluded from analysis At 2-year FU: 2 vs. 10

Abbreviations: ADT: androgen deprivation therapy; C: control; CFRT: conventionally fractionated radiotherapy; FU: follow-up; I: intervention; ITT: intention-to-treat; MFRT: moderately hypofractionated radiotherapy; NCCN: National Comprehensive Cancer Network; PSA: prostate specific antigen; SBRT: stereotactic body radiotherapy; TNM: TNM Staging System includes the extent of the tumor (T), extent of spread to the lymph nodes (N), and presence of metastasis (M); UHT: ultra-hypofractionation therapy;

Risk of bias assessment

RoB: niedrig für Überleben "some concerns" und hoch für Lebensqualität

The risk of bias assessment for each effectiveness outcome reported in the studies is presented in Table 3.3-3. The overall risk of bias indicated some concerns for QoL outcomes in two RCTs [33-35, 38] and was assessed as high in one RCT [32, 36, 37], while it was assessed as low for survival outcomes [38]. The primary reasons for the concerns include the open-label nature of the studies and the fact that the outcome assessors were not blinded to the treatments received by the patients. Additionally, in the PACE-B trial [32, 36, 37], deviations from the initial treatment allocations were noted; notably, four cases involved patients assigned to SBRT who received CFRT/MFRT instead. These deviations were not evenly distributed across the groups. In the study by Poon et al. [34], there was a lack of information regarding allocation concealment, contributing to uncertainties regarding bias arising from the randomisation process.

Table 3.3-3: Risk of bias (RCTs) with SBRT

Study	Endpoint	Bias arising from randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
PACE-B [32, 36, 37]	QoL	Low	High[3]	Low	Some concerns[4]	Low	High
HYPO-RT-PC [33, 35, 38]	QoL	Low	Low	Low	Some concerns[5]	Low	Some concerns
HYPO-RT-PC [38]	Survival	Low	Low	Low	Low[6]	Low	Low
Poon 2021 [34]	QoL	Some concerns[7]	Some concerns[8]	Low	Some concerns[9]	Low	Some concerns

Abbreviations: QoL: quality of life

[3] Participants and researchers were not masked to treatment assignment. In 11 cases the patients received a treatment different from what they were initially allocated. Some deviations appear that the reason might have been the trial context. Notably, of these deviations, four involved patients who were allocated to SBRT but, according to protocol deviations, received CFMHRT instead. The deviations were therefore not balanced between the two groups.

4 For patient-reported outcomes like QoL, patients themselves are the outcome assessors. In this study, patients were not blinded to their treatment. Additionally, unblinded clinicians may have been influenced by their knowledge of the treatments when interacting with patients, potentially affecting their management of symptoms and interpretation of patient feedback during follow-up visits. However, the instruments used for measuring the outcome were validated questionnaires, which are designed to minimize measurement errors and bias.

[5] Same as footnote PACE-B.

[6] Although the study was open-label design but for the survival outcomes the assessors were blinded.

[7] No information was available about the allocation concealment, nor about details on the methods e.g. inclusion criteria.

[8] Participants and researchers were not masked to treatment assignment. It was not reported if deviations occurred or not occurred.

[9] Same as footnote PACE-B.

3.3.2 Results

Survival, QoL and other effectiveness outcomes (i.e. avoidance of prostatectomy) were considered in the effectiveness results. The detailed effectiveness results are presented in Table 3.3-4.

Survival

Endpunkt: Überleben (Gesamtüberleben, krankheitsspezifisches, metastasenfreies und biochemisches rezidivfreies Überleben): 1 RCT (n=1.200)

One study (HYPO-RT-PC) [38] (n=1,200) reported survival outcomes as part of their pre-defined outcomes. Another RCT (PACE-B) [32] mentioned overall survival in their reporting, but the study was not designed to assess the survival outcomes and therefore no statistical tests were planned and conducted for this outcome. Therefore, this data was not included in the quantitative evidence synthesis. Overall survival, disease-specific survival and metastases-free survival were measured at two and five years each. Biochemical failure-free survival was measured as percentage and events.

Gesamtüberleben nach 2 und 5 Jahren: 99,0% vs. 98,6%; 96,4% vs. 93,7% HR: 1,11 (95% CI; 0,73–1,69), kein signifikanter Unterschied

Survival outcomes show varying results between the intervention and control groups. Both at the two- and the five-year follow-up, **overall survival** was slightly higher in the control group (99.0%; 95% CI, 98.2−99.8 and 96.4%; 95% CI, 94.6−98.1) compared to the intervention group (98.6%; 95% CI, 97.7−99.6 and 93.7%; 95% CI, 91.7−96.2), with a hazard ratio (HR) of 1.11 (95% CI, 0.73−1.69), suggesting no significant difference.

krankheitsspezifisches Überleben nach 2 Jahren: kein Unterschied, nach 5 Jahren: 98,2% vs. 99,8%

Disease-specific survival rates were identical at the two-year follow-up for both groups at 99.8% (95% CI, 99.5−100.0). However, by the five-year follow-up, the control group maintained a slightly higher survival at 99.8% (95% CI, 99.5−100.0) compared to 98.2% (95% CI, 96.9−99.6) in the intervention group, indicating better long-term disease-specific outcomes, although there is no statistical significance reporting.

metastasenfreies Überleben nach 2 Jahren: 99,5% vs. 99,7% nach 5 Jahren: 98,7% vs. 98,3%

Metastases-free survival at two years was slightly higher in the control group at 99.7% (95% CI, 99.2−100.0) versus 99.5% (95% CI, 98.9−100.0) in the intervention group. This trend reversed at five years, where the intervention group showed a slightly better outcome at 98.7% (95% CI, 97.6−99.8) compared to 98.3% (95% CI, 97.2−99.5) in the control group.

biochemisches rezidivfreies Überleben nach 5 Jahren: kein Unterschied

Biochemical failure-free survival at the five-year follow-up demonstrated no difference between the groups, with both recording a rate of 84% (95% CI 80−87). The HR was 1.002 (95% CI, 0.760–1.320), and the log-rank p-value was 0.99, indicating no statistically significant difference. The number of events of biochemical or clinical failure was nearly identical, with 100 events in the intervention group and 102 in the control group.

Quality of life

Lebensqualität: Harn-, Darm-, sexuelle und hormonelle Symptome

All three studies [32-38] measured and reported QoL outcomes. Urinary symptoms, bowel complaints, sexual function were assessed in all three studies, hormonal symptoms were assessed in two of the RCTs [32, 34, 36, 37].

Harnsymptome:
1. RCT: nach 12 Wochen: kein Unterschied, nach 24 Monate: Verschlechterung der Harninkontinenz in der SBRT-Gruppe, kein Unterschied in IPSS Subscores, IPSS-Gesamtscore besser in der SBRT-Gruppe
2. RCT: kein Unterschied in Harninkontinenz (53% vs. 47%) nach 1 Jahr
3. RCT: minimale Unterschiede nach 6 Jahren, außer in Blasenentleerung mit statistisch signifikanter (s.s.) Verbesserung in der SBRT-Gruppe

In terms of **urinary symptoms**, PACE-B [32, 36, 37] (n=874) analysed multiple urinary symptoms at 12-week and 24-month follow-up points. None of the 12-week results were statistically significant. On the EPIC-26 urinary incontinence subdomain at the 12-weeks, there was no difference between the groups (MD 0 vs. 0, p=0.72), however there was a significant worsening at 24-month in the intervention group and no change in the control group (MD -6.2 vs. 0, p=0.007). The IPSS QoL subscore and the IPSS total score showed minor differences between the groups at 12 weeks (MD 0 vs. -1 and -0.5 vs. 0, respectively), neither result being statistically significant. At the 24-month mark, however, in both groups a significant increase was observed in the IPSS QoL subscore (MD +1 vs. +1, p=0.002) and in the IPSS total score also showed a significant increase in the intervention group (MD +1 vs. 0, p=0.007). In the EPIC-26 urinary obstructive subdomain the intervention group reached higher scores at 12 weeks, but the result was non-significant (MD 0 vs. +6.3, p=0.28). However, at 24 months, both groups improved significantly (MD +6.3 vs. +6.3, p=0.02). The second RCT (n=64) [34] focused on the EPIC urinary incontinence subdomain, comparing baseline and 1-year outcomes. This trial reported that 53% of patients in the intervention group achieved a greater than 2-point score reduction at 1 year versus 47% in the control group, although this was not found to be statistically significant. The third RCT, HYPO-RT-PC [33, 35, 38] (n=1,200) assessed several aspects of urinary dysfunction using the PCSS at six years after treatment. The findings revealed minor differences in overall bother from urinary symptoms (28% vs. 33%) and urinary incontinence (29% vs. 30%), suggesting modest impacts on these symptoms. There were slightly larger differences in the urgency subdomain (31% vs. 36%) and urge incontinence (35% vs. 33%). However, the only statistically significant improvement was reported in problems with the ability to empty the bladder subdomain, with 16% vs. 32% (p<0.05), indicating that less patients had a problem in the intervention group compared to the control group.

Darmsymptome:
1. RCT: kein Unterschied
2. RCT: klinisch signifikante Verbesserung in 40% vs. 47%
3. RCT: weniger tägliche Beschwerden in der SBRT-Gruppe

Similarly, all three RCTs [32-38] measured **bowel symptoms.** Two of them used the EPIC bowel questionnaire to measure the outcome [32, 34, 36, 37]. While PACE-B [32, 36, 37] (n=874) indicates an equivalent improvement in both groups (MD -4.2 vs. -4.2), the second RCT [34] (n=64) shows a slightly better outcome for the control group in achieving clinically significant symptom reduction (meaning at least 5 points) (40% vs. 47%). The third RCT, HYPO-RT-PC [33, 35, 38] (n=1,200) underscores better management of bowel symptoms in the intervention group, as reflected in lower percentages of patients reporting daily activity limitations and bother (24 and 28% vs. 32 and 33%, respectively).

sexuelle Funktion:
1. RCT: besser in der SBRT-Gruppe nach 12 Wochen, nach 24 Monaten kein Unterschied
2. RCT: signifikante Verbesserung nach 1 Jahr: 30% vs. 25%
3. RCT: mehr Beschwerden in der Kontrollgruppe

Sexual function was also measured in all three RCTs [32-38] and all of them showed better outcomes for the intervention group in terms of sexual health. PACE-B [32, 36, 37] (n=874) indicates that the control group experienced more significant declines in sexual health as measured by the EPIC-26 and IIEF-5 at 12 weeks (MD -4.2 vs. -8.3 and MD -1.5 vs. -4, respectively) although at the 24-month follow-up point the difference was less pronounced and was not statistically significant. Another RCT [34] (n=64) reported slightly higher percentage of patients who experienced a significant improvement or less deterioration in sexual symptoms (>11-point reduction on the EPIC sexual subdomain at 1 year compared to baseline) in the intervention group (30% vs. 25%). Finally, HYPO-RT-PC [33, 35, 38] (n=1,200) shows a higher percentage of the control group with more bother from sexual dysfunction and

greater difficulty achieving erection without aid, indicating worse outcomes for sexual function in this group.

hormonelle Symptome: bessere Ergebnisse in der SBRT-Gruppe

Hormonal symptoms were assessed in two RCTs [32-35]. Both studies show that the intervention group experienced more favourable outcomes in terms of hormonal health. In one RCT [32, 33, 35] (n=874), the intervention group maintained stability in their condition, whereas the control group experienced deterioration (MD 0 vs. -2.5). In the other RCT [34] (n=64), the intervention group achieved significant improvements more frequently than the control group (>3-point reduction on the EPIC hormonal subdomain at 1 year versus baseline in 43% vs. 25%).

Other effectiveness outcomes

Vermeidung der Prostatektomie: nicht berichtet

Avoidance of prostatectomy was not measured in any of the included studies.

Table 3.3-4: Effectiveness results (RCTs) with SBRT: Survival and QoL

Author, Year, Reference	PACE-B [32, 36, 37]	HYPO-RT-PC [33, 35, 38]	Poon 2021 [34]
Effectiveness outcomes			
Survival, I vs. C			
Overall survival, %	At 12-week FU: 100 vs. 100 At 24-month FU: 98.5 vs. 99.3[10]	At 2 year-FU: 98.6 (97.7–99.6) vs. 99.0 (98.2–99.8) At 5 year-FU: 93.9 (91.7–96.2) vs. 96.4 (94.6–98.1), HR 1.11 (95% CI, 0.73–1.69)	NR
Disease-specific survival, %	NR	At 2 year-FU: 99.8 (99.5–100.0) vs. 99.8 (99.5–100.0) At 5 year-FU: 98.2 (96.9–99.6) vs. 99.8 (99.5–100.0)	NR
Metastasis-free survival, %	NR	At 2 year-FU: 99.5 (98.9–100.0) vs. 99.7 (99.2–100.0) At 5 year-FU: 98.7 (97.6–99.8) vs. 98.3 (97.2–99.5)	NR
Biochemical recurrence-free survival, %	NR	At 5 year-FU: Failure-free survival 84% (95% CI 80–87) vs. 84% (80–87); HR 1·002 (95% CI 0·760–1·320), log-rank p=0.99 At 5-year FU: Biochemical or clinical failure (events): 100 vs. 102	NR
Quality of life, I vs. C			
Urinary incontinence	*EPIC-26*[11] *urinary incontinence subdomain* Baseline median score: 100 vs. 100 12-week FU median score: 100 vs. 100 (p=0.72) 24-month FU median score: 93.8 vs. 100 (p=0.07) *IPSS total score* Baseline median score: 6 vs. 6 12-week FU median score: 6.5 vs. 6 24-month FU median score: 7 vs. 6 (**p=0.007**) *IPSS QoL subscore* Baseline median score: 2 vs. 2 12-week FU median score: 2 vs. 1 24-month FU median score: 1 vs. 1 (**p=0.002**)	*PCSS overall bother from urinary symptoms subdomain* (%): At 6-year FU: 28 vs. 33, MD 5.1 (-4.4 to 14.6), p=0.38 *PCSS urinary incontinence subdomain* (%): At 6-year FU: 29 vs. 30, MD 0.6 (0.6 to 10), p=0.91	EPIC urinary subdomain: >2-point score reduction at 1 year compared with baseline: 53% vs. 47% of patients (SBRT, p = 0.07; CFRT, p = 0.21)
Urge to urinate or problems with bladder emptying	*EPIC-26 urinary obstructive subdomain:* Baseline median score: 87.5 vs. 87.5 12-week FU median score: 87.5 vs. 93.8 (p=0.28) 24-month FU median score: 93.8 vs. 93.8 **(p=0.02)**	*PCSS urgency subdomain* (%): At 6-year FU: 31 vs. 36, MD 5 (-4.8 to 14.8), p=0.40 *PCSS urge incontinence subdomain* (%): At 6-year FU: 35 vs. 33, MD -2.4 (-12.3 to 7.4), p=0.68 *PCSS emptying bladder subdomain* (%)*: At 6-year FU: 16 vs. 32, MD 15.8 (7.1 to 24.5), **p=0.0036**	NR

[10] In Tree et al. 2022 [37] it is stated that 9 patients died between radiotherapy and the 24-month follow-up (6 in the SBRT and 3 in the CFRT group), hence this overall survival result was calculated by the review authors (410/416 vs. 429/432). Nor Brand et al. [32] or Tree et al. [37] was designed to assess the survival outcomes and therefore no statistical tests were planned and conducted for this outcome. Therefore, this will be not included in the quantitative evidence synthesis.

[11] EPIC-26 MCID subdomain score: urinary incontinence 8 points, urinary obstruction 6 points, bowel 5 points, sexual 11 points, and hormonal 5 points.

*Mean difference between the groups was statistically significant only for this outcome of all side effects/patient reported health status outcomes of the HYPO-RT-PC study.

Author, Year, Reference	PACE-B [32, 36, 37]	HYPO-RT-PC [33, 35, 38]	Poon 2021 [34]
Effectiveness outcomes			
Bowel complaints	EPIC-26 bowel subdomain: Baseline median score: 100 vs. 100 12-week FU median score: 95.8 vs. 95.8 (p=0.61) 24-month FU median score: 100 vs. 95.8 (p=0.1) *Vaizey total score* Baseline median score: 1 vs. 1 12-week FU median score: 2 vs. 2 24-month FU median score: 2 vs. 2 (p=0.75)	*PCSS overall bother from all bowel symptoms subdomain* (%): At 6-year FU: 28 vs. 33, MD 5.7 (-3.8 to 15.2), p=0.33 *PCSS limitation in daily activity caused by bowel symptoms subdomain* (%): At 6-year FU: 24 vs. 32, MD 10.9 (1.3 to 20.5), p=0.065	EPIC bowel subdomain: >5-point reduction at 1 year compared with baseline: 40% vs. 47% of patients (SBRT, p = 0.28; CFRT, p = 0.08)
Sexual functioning	*EPIC-26 sexual subdomain:* Baseline median score: 48.7 vs. 52.8 12-week FU median score: 44.5 vs. 44.5 (p=0.63) 24-month FU median score: 34.7 vs. 36.2 (p=0.28) *IIEF-5 score* Baseline median score: 14 vs. 16 12-week FU median score: 12.5 vs. 12 24-month FU median score: 10 vs. 12 (p=0.29)	*PCSS overall bother from sexual function subdomain* (%): At 6-year FU: 50 vs. 60, MD 9.1 (-1.4 to 19.6), p=0.15 *PCSS erection without aid subdomain* (%): At 6-year FU: 66 vs. 74, MD 7.2 (-2.6 to 17.1), p=0.23 Post-hoc analysis: ED during FU: 92 (27%) vs. 89 (27%) patients ED at 12 months: 37 (5%) vs. 37 (5%) ED at 24 months: 52 (8%) vs. 53 (8%)	EPIC sexual subdomain: >11-point reduction at 1-year compared with baseline: 30% vs. 25% (SBRT, p=0.28; CFRT, p=0.12)
Hormonal symptoms	EPIC-26 hormonal subdomain: Baseline median score: 95 vs. 97.5 12-week FU median score: 95 vs. 95 (p=0.11) 24-month FU median score: 95 vs. 97.5 (p=0.11)	NR	EPIC hormonal subdomain: >3-point reduction at 1-year compared with baseline: 43% vs. 25% (SBRT, p=0.27; CFRT, p=0.06)
General QoL scores	NR	*QLQ-C30 Global health/QoL subdomain* (%): At 6-year FU: 37 vs. 42, MD 5.0 (-5.0 to 15), p=0.41	NR
Avoidance of prostatectomy	NR	NR	NR

Abbreviations: CFRT: conventional fractionation radiotherapy; ED: erectile dysfunction; EPIC-26: Expanded Prostate Cancer Index Composite-26 items; IIEF: International Index of Erectile Function; FU: follow-up; NR: not reported; PCSS: Prostate Cancer Symptom Scale; SBRT: stereotactic body radiotherapy, QLQ-C30: Quality-of-Life Questionnaire–Core 30

3.3.3 Certainty of evidence

Vertrauenswürdigkeit der Evidenz „hoch" für Überleben

"moderat" für Lebensqualität

The certainty of evidence was rated high for all but one survival outcome (survival at 5 years), which was rated to be moderate. The reason for the moderate certainty was that the confidence interval for the hazard ratio was wide. The certainty of the evidence for the QoL outcomes was rated to be mostly moderate. The only QoL outcome for which the certainty was rated to be low was the urinary symptoms outcome. The reason for the moderate certainty was a serious risk of bias of the included studies due to some concerns regarding the risk for bias resulting from measurement of the outcome, in one study deviations from intended interventions occurred, which were imbalanced between the intervention and control groups and in one study there was no information about allocation concealment. For the low certainty the reason was additionally to the above mentioned, that results are inconsistent depending on the outcome measure.

Detailed description of the evidence profile for survival outcomes is presented in Table 3.3-5, and that for QoL outcomes is presented in Table 3.3-6.

Table 3.3-5: Evidence profile of SBRT: Survival

№ of studies/ Patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates	Certainty
Outcome: Survival at 2 years								
1/1180	RCT	Not serious	Not serious	Not serious	Not serious	None	98.6 (97.7–99.6) vs. 99.0 (98.2–99.8)	High
Outcome: Survival at 5 years								
1/1180	RCT	Not serious	Not serious	Not serious	Serious[a]	None	93.7 (91.7–96.2) vs. 96.4 (94.6–98.1), HR 1.11 (95% CI, 0.73–1.69)	Moderate
Outcome: Disease-specific survival at 2 years								
1/1180	RCT	Not serious	Not serious	Not serious	Not serious	None	99.8 (99.5–100.0) vs. 99.8 (99.5–100.0)	High
Outcome: Disease-specific survival at 5 years								
1/1180	RCT	Not serious	Not serious	Not serious	Not serious	None	98.2 (96.9–99.6) vs. 99.8 (99.5–100.0)	High
Outcome: Biochemical recurrence-free survival								
1/1180	RCT	Not serious	Not serious	Not serious	Not serious	None	84 (80–87) vs. 84 (80–87)	High
Outcome: Metastases-free survival at 2 years								
1/1180	RCT	Not serious	Not serious	Not serious	Not serious	None	99.5 (98.9–100.0) vs. 99.7 (99.2–100.0)	High
Outcome: Metastases-free survival at 5 years								
1/1180	RCT	Not serious	Not serious	Not serious	Not serious	None	98.7 (97.6–99.8) vs. 98.3 (97.2–99.5)	High

[a]: *Wide CI for the HR.*

Table 3.3-6: Evidence profile of SBRT: Quality of life

№ of studies/ patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates	Certainty
QoL outcomes: Urinary symptoms (urinary incontinence, urge to urinate, problems with bladder emptying)								
3/2138	RCT	Serious[a]	Serious[b]	Not serious	Not serious	The improvement was above the MCID threshold for the urinary obstructive subdomain for the control group in one RCT, however statistically non-significant result.	1. RCT: At 12-week FU EPIC-26 urinary incontinence subdomain: MD 0 vs. 0 IPSS QoL subscore: MD 0 vs. -1 IPSS total score: MD -0.5 vs. 0 EPIC-26 urinary obstructive subdomain: MD 0 vs. +6.25 At 24-month FU: EPIC-26 urinary incontinence subdomain: MD -6.2 vs. 0 **(p=0.007)** IPSS QoL subscore: MD +1 vs. +1 (**p=0.002**) IPSS total score: MD +1 vs. 0 (**p=0.007**) EPIC-26 urinary obstructive subdomain: MD +6.3 vs. +6.3 (**p=0.02**) 2. RCT: EPIC urinary incontinence subdomain >2-point score reduction at 1 year vs. baseline: 53% vs. 47% of patients 3. RCT: At 6-year FU: PCSS overall bother from urinary symptoms subdomain: 28% vs. 33% PCSS urinary incontinence subdomain: 29% vs. 30% PCSS urgency subdomain: 31% vs. 36% PCSS urge incontinence subdomain: 35% vs. 33% PCSS emptying bladder subdomain: 16% vs. 32% **(p<0.05)**	Low
QoL outcome: Bowel complains								
3/2138	RCT	Serious[a]	Not serious	Not serious	Not serious	1 RCT shows deteriorations above the MCID threshold (>5-point reduction in EPIC). Results were statistically non-significant.	1 RCT: EPIC-26 bowel subdomain: MD -4.2 vs. -4.2, Vaizey total score: MD +1 vs. +1 1 RCT: >5-point reduction on EPIC bowel subdomain at 1 year vs. baseline: 40% vs. 47% of patients 1 RCT: PCSS overall bother from all bowel symptoms subdomain: 28% vs. 33% PCSS limitation in daily activity caused by bowel symptoms subdomain: 24% vs. 32%	Moderate

№ of studies/ patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates	Certainty
QoL outcome: Sexual functioning								
3/2138	RCT	Serious[a]	Not serious	Not serious	Not serious	1 RCT shows deteriorations above the MCID threshold (>11-point reduction in EPIC). Results were statistically non-significant.	1 RCT: EPIC-26 sexual subdomain: MD -4.2 vs. -8.3 IIEF-5 score: MD -1.5 vs. -4 1 RCT: >11-point reduction on EPIC sexual subdomain at 1-year vs. baseline: 30% vs. 25% 1 RCT: PCSS overall bother from sexual function subdomain: 50% vs. 60% PCSS erection without aid subdomain: 66% vs. 74%	Moderate
QoL outcome: Hormonal symptoms								
2/938	RCT	Serious[a]	Not serious	Not serious	Not serious	1 RCT shows deteriorations above the MCID threshold (>3-point reduction in EPIC). Results were statistically non-significant.	1 RCT: EPIC-26 hormonal subdomain: MD 0 vs. -2.5 1 RCT: >3-point reduction on EPIC hormonal subdomain at 1-year vs. baseline: 43% vs. 25%	Moderate
QoL outcome: Avoidance of prostatectomy								
0	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: EPIC: Expanded Prostate Cancer Index Composite, MD: mean difference; PCCS: Prostate Cancer Symptom Scale, RCT: randomised controlled trial, QoL: quality of life

[a]: Studies were open-label, patients were aware of their received intervention. As in case of QoL outcomes, the outcome assessor is the patient, there were some concerns regarding the risk for bias resulting from measurement of the outcome. In one study deviations from intended interventions occurred, which were imbalanced between the intervention and control groups. In one study there was no information about allocation concealment, and it was not clear if deviations from intended intervention occurred.

[b]: Results are inconsistent as depending on the outcome measure, the intervention group shows better, or worse results compared to the control group.

3.4 Proton therapy (PT)

3.4.1 Included studies

keine RCTs zu PT

We could not identify any RCTs comparing PT with any of the comparators of our interest.

3.4.2 Results

keine Ergebnisse zur Wirksamkeit

In the absence of RCTs, we cannot describe the effectiveness of IRE.

3.4.3 Certainty of the evidence

keine Beurteilung der Vertrauenswürdigkeit der Evidenz möglich

In the absence of RCTs, the certainty of evidence is not applicable for effectiveness outcomes.

4 Safety (toxicity)

4.1 Endpoints

Toxicity

Toxizität: Nebenwirkungen nach Klassifikationskriterien nach CTCAE (Common Terminology Criteria for Adverse Events) und RTOG (Radiation Therapy Oncology Group)

To assess acute and late radiogenic side effects, the included studies used one or both of the following classification criteria: the Common Terminol-ogy Criteria for Adverse Events (CTCAE) [32] or the Radiation Therapy Oncology Group criteria (RTOG) [33]. Depending on the severity of the ad-verse effects, these are classified from grade 1 to grade 5 according to both CTCAE and RTOG (see Table 2.3 1). Included studies that used the RTOG classification criteria were marked with an "*" in the corresponding tables for the endpoint of safety (toxicity). The definition of acute and late toxicities varied across studies, being determined at the discretion of each study's authors. For the purposes of synthesizing results, we defined acute toxicity as occurring within the first three months post-treatment, while late toxicity was classified as occurring after this period. To provide a clearer understanding of trends over the long term, we have presented late toxicities in a more detailed manner, breaking down the data to high-light specific trends across extended follow-up periods. For acute toxicity, where data permitted, we further delineated the analysis by presenting additional cut-off points within the initial three-month period to provide a more nuanced view of early toxicity trends. In instances where studies did not provide explicit definitions of acute or late toxicity, we classified the da-ta as acute or late according to our predefined criteria.

Table 4.1-1: CTCAE und RTOG criteria

Grade	CTCAE	RTOG
0	Not defined	None
1	Minor; Asymptomatic or mild symptoms; only clinical or diagnostic observations; intervention not indicated	Mild, slight
2	Moderate; Minimal, local or non-invasive intervention indicated; limitation of age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothing, using the telephone, handling money, etc.)	Moderate, significant
3	Severe; Medically significant but not immediately life-threatening; hospitalisation or extension of hospital stay indicated; disabling; limitation of self-care activities of daily living (bathing, dressing, and undressing, eating independently, using the toilet, taking medication, and not being bedridden)	Severe
4	Life-threatening effects; urgent intervention indicated	Life-threatening or associated with disability
5	Death associated with an unexpected event	Side effect with fatal outcome

Source: [39, 40]

4.2 Irreversible electroporation (IRE)

5 Studien: 3 Beobachtungsstudien, 1 RCT (die 2 Formen der IRE analysiert), und 1 Propensity-Score-Matching-Studie

One RCT comparing focal and extended IRE [41], three single-arm observational studies [42-44] and a propensity score matched study [45] could be identified. As the RCT [41] compared the intervention of our interest in two forms (focal and extended) rather than a control group consisting of another treatment, we included it in the safety analysis only, as a single-arm study. The propensity score matched study [45] was similarly analysed as single-arm study, taking into consideration the IRE arm only.

4.2.1 Included studies

Study characteristics

Teilnehmeranzahl: 50 bis 411 Patienten

Nachbeobachtung: 3 bis 48 Monate

Clavien-Dindo-Klassifikation, CTCAE-Kriterien

The number of participants in the included studies varied substantially, ranging from 50 to 411. The studies took place in European countries, China, Australia and one study included centres from all the previously mentioned countries. The majority of the studies were multi-centre [41, 43-45], with only one being single-centre [42]. All studies report funding received from research grants. Two of the studies declared no conflicts of interests [41, 44], three studies had authors who declared having received fees from technology developers of the product used in the study [42, 43, 45]. The range of follow-up periods varied from three to 48 months. Three studies used Clavien-Dindo classification for reporting safety outcomes [42, 43, 45]. Two studies used the CTCAE classification criteria [41, 44].

Variationen in Führungstechniken, Sicherheitsprotokolle, Zusatzmaßnahmen

In terms of the intervention, all studies utilised high-voltage IRE techniques, with three of the studies [41, 42, 44] specifically mentioning the use of AngioDynamics Inc.'s NanoKnife System. Each of these studies delivered 90 pulses at 1500 V/cm under general anaesthesia. The direct current range is between 20 and 50 amperes in three studies [41, 42, 44], indicating a standard parameter for the electrical output in most of the studies. Variations exist in guidance techniques, safety protocols, and adjunctive measures like muscle relaxants and antibiotics. One study [43] utilised a different electroporation system, termed a composite steep-pulse therapeutic apparatus from Remedicine Co. One study [45] focused on electrode placement in relation to MRI-identified lesions but lacks detailed procedural specifics.

Patient characteristics

Alter: Ø 64 bis 68 Jahre
Gleason Score: ≤7 niedrig- bis mittleres Risiko
Tumorstadien: vorherrschend T1c und T2a, ein Teil T3 in einer Studie

The average or median ages across studies generally ranged from 64 to 68 years. In the three studies that report it, Gleason scores were consistently ≤7, indicating a focus on low- to intermediate-grade PCa [41-43]. The most prevalent tumour stages were T1c and T2a, though a subset of patients reached T3 in one study [44]. Risk stratification was conducted using D'Amico and NCCN guidelines, with a notable majority of the patients classified into the intermediate-risk category in the two studies where it was reported [42, 43]. Deatiled study and patient characteristics of the studies are presented in Table 4.2-1and Table 4.2-2.

Table 4.2-1: Study characteristics with IRE (prospective cohort studies) (part I)

Author, Year, Reference	de la Rosette 2022 [41]	Blazevski 2020 [42]	Wang 2022 (NCT03838432) [43]
Country	Five European countries (not individually named)	Australia	China
Funding / conflict of interest	Funding: Clinical Research Office of the Endourological Society. CoI: none.	Funding: the Australian Commonwealth Department of Health and Ageing and the St. Vincent's Prostate Cancer Centre. CoI: one author received consulting fees from Angiodynamics and fees for training surgeons in IRE. The remaining authors had nothing to disclose.	Funding: Remedicine Co, grant 2019YFC0119100 from the National Key Research and Development Program of China, grant 81602220 from the National Natural Science Foundation of China, grant PWRd2020-17 from the Shanghai Pudong New District Health System Medical Talents Training Plan, China, grant PKX2020-S11 from the Fund of Development on Science and Technology of Shanghai Pudong New District, China, and grant 18441910900 from the Shanghai "Action Plan of Technological Innovation." CoI: authors received grants from Remedicine Co.
Study design	Multicentre, randomised, single-blind study, comparing focal and extended IRE	Single-centre prospective database of patients undergoing primary IRE	Prospective observational study
Setting, time period	5 European centres in 5 countries, from July 2015 to February 2020	Single centre, between February 2013 and August 2018	4 medical centres, from May 2018 to March 2019
Description of intervention	Focal irreversible electroporation (IRE) using the AngioDynamics Inc. NanoKnife System. Up to 6 IRE electrode needles were placed into the ablation zone under ultrasound image guidance. 90 consecutive 1,500 V/cm pulses were delivered with a direct current between 20 and 50 A.	All patients underwent standardised IRE procedure using Nanoknife™ device (Angiodynamics, Inc., Queensbury, New York). All patients underwent a general anaesthetic with full muscle paralysis and also received IV antibiotics at induction. The IRE device was programmed to deliver 90 pulses of 1500 V/cm with a direct current between 20 and 40 A.	High-frequency irreversible electroporation (H-FIRE) was performed using a composite steep-pulse therapeutic apparatus (Remedicine Co) under general anaesthesia. Electrode needles were placed into the target lesion through a 5-mm brachytherapy template grid under the guidance of a biplanar transrectal ultrasound probe.
Follow-up period	3 months (for the toxicity outcomes)	12 months	6 months
Toxicity classification	CTCAE	Clavien-Dindo classification	Clavien-Dindo classification
Inclusion criteria	Pca with a clinical stage T1c-T2b, Gleason sum score 6 or 7, PSA <15 ng/mL or PSA >15 ng/mL (counselled with caution) and life expectancy of >10 years	Low (high-volume > 4 mm)- to intermediate risk PCa (D'Amico), Gleason score ≤ 7 (ISUP ≤ 3), unilateral or midline anterior/posterior index tumour, allowing single targeted ablative therapy, PSA ≤ 15 ng/ml, life expectancy ≥ 10 years, no previous treatment for PCa, no previous androgen suppression treatment for PCa, minimum 12-months follow up and multiple lesions which can be encompassed in one treatment.	Low- or intermediate-risk PCa, verified by biopsy. Age 40 to 85 years; PSA level less than 20 ng/mL, clinical stage of T2c or less; and Gleason score of 7 or less, no prior radical prostatectomy, hormonal therapy, or radiotherapy; no prostatic calculus greater than 5 mm; no history of epilepsy; no cardiac pacemaker or any metal implant between L1 and mid-femur level; and no other malignant tumour.
Number of patients	106	170 treated 126 had >12-month follow-up 123 met consensus guidelines for focal therapy and had 12-month follow-up	109
Patient characteristics (Age in years/range, ADT in %)	Focal IRE vs. extended IRE Age: 64 (IQR 58-67) vs. 64 (IQR 57-68) ADT: NR	Age: 68 (IQR 62–73) ADT was not allowed.	Age: mean 67 (SD 8) ADT was not allowed.

Author, Year, Reference	de la Rosette 2022 [41]	Blazevski 2020 [42]	Wang 2022 (NCT03838432) [43]
Tumour stage (% of patients)	cT1c: 88.7 cT2a: 11.3	ISUP grade 1: 9.7, ISUP grade 2: 71.5 ISUP grade 3: 18.7	T1c: 29.4 T2a: 56.9 T2b: 5.5 T2c: 8.3
Gleason score (% of patients)	3+3: 56.6 3+4: 39.6 4+3: 3.8	3+3: 9.8 3+4: 71.5 4+3: 18.7	3 + 3: 43.1 3 + 4: 41.3 4 + 3: 15.6
Risk classification (% of patients)	NR	*D'Amico risk classification* Low: 9 Intermediate: 91	*NCCN* low: 24.8 intermediate: 75.2
Loss to follow-up	0 (up to 3 months)	44 of the original 170 patients	0 for the safety outcomes

Abbreviations: A: amper; ADT: androgen deprivation therapy; CoI: conflict of interest; CTCAE: Common Terminology Criteria for Adverse Events; H-FIRE: high-frequency irreversible electroporation; IRE: irreversible electroporation; ISUP: International Society of Urological Pathology; IQR: interquartile range; NCCN: National Comprehensive Cancer Network; NR: not reported; PCa: prostate cancer; PSA: prostate specific antigen; SD: standard deviation

Table 4.2-2: Study characteristics with IRE (prospective cohort studies) (part II)

Author, Year, Reference	Zhang 2024 [44] (NCT02255890)	Scheltema 2018 [45]
Country	Australia, Germany, France	NR[12]
Funding / conflict of interest	Funding: Open access funding provided by the Scientific and Technological Research Council of Türkiye (TÜBİTAK). CoI: none.	Funding: Australian Commonwealth Department of Health and Ageing and the St Vincent's Prostate Cancer Centre CoI: one author was consultant to AngioDynamics.
Study design	International prospective observational multi-center study	Patients receiving single-ablative unifocal IRE following the consensus guidelines were propensity score pair-matched to patients who received nerve-sparing RARP
Setting, time period	5 centres, from July 2015 to April 2020	No information on centres, from February 2013 to July 2016
Description of intervention	The AngioDynamics Inc. NanoKnife™ System was used to deliver IRE. 90 consecutive high-voltage pulses (1500 V/cm) with a direct current between 20 and 50 A were delivered. Patients received muscle relaxants. The whole procedure was performed under general anaesthesia.	The tumour was ablated using 3-6 electrodes, ensuring a minimum 5-mm safety margin around the visible magnetic resonance imaging (MRI) lesion. No further details.
Follow-up period	Median 24 months (IQR 15–36), up to 48 months for safety outcomes	6 months
Toxicity classification	CTCAE	Clavien-Dindo classification
Inclusion criteria	Patients with histologically confirmed PCa who were treated with IRE. In order to capture real-world data, there were no specific exclusion criteria.	Patients with clinical stage T1c–T2b, low- to intermediate-risk PCa (ISUP 1–3), written informed consent for QoL evaluation, minimum of 6 months follow-up and completion of all baseline questionnaires and matching criteria.
Number of patients	411	50
Patient characteristics (Age in years/range, ADT in %)	Age: mean 67.3 (SD 7.4) ADT: NR	Age: 67 (62–73) ADT: NR
Tumour stage (% of patients)	cT1c: 46.8 cT2a: 26.0 cT2b: 9.5 cT2c: 16.7 cT3a: 0.8 cT3b: 0.3	T1c: 74 T2a: 24 T2b: 2
Gleason score (% of patients)	NR	NR
Risk classification (% of patients)	NR	NR
Loss to follow-up	At 3 months: 28 At 6 months: 112 At 12 months: 147 At 24 months: 253 At 48 months: 363	0

Abbreviations: ADT: androgen deprivation therapy; CoI: conflict of interest; CTCAE: Common Terminology Criteria for Adverse Events; IRE: irreversible electroporation; ISUP: International Society of Urological Pathology; IQR: interquartile range; MRI: magnetic resonance imaging; NR: not reported; PCa: prostate cancer; PSA: prostate specific antigen; QoL: quality of life; SD: standard deviation; TÜBITAK: Technological Research Council of Türkiye.

[12] Contributing authors' affiliations in Australia and the Netherlands.

4.2.2 Results

5 Studien, 846 Patienten

Verschiedene Klassifikationssysteme (CTCAE, Clavien-Dindo)

Akuttoxizität (bis 3 Monate)
Spättoxizität (bis 6, 12, 24 und 48 Monate)

Five studies with a total of 846 patients treated, reported various types of toxicity, utilising different classification systems: two of them employed the CTCAE classification, while three used the Clavien-Dindo classification for adverse events. None of the studies separately reported GU and GI toxicities. In terms of follow-up data, one study [41] provided only acute toxicity data, two studies [43, 45] reported data for up to six months post-treatment, one study [42] covered up to 12 months, and one study [44] comprehensively reported on multiple timepoints including three, six, 12, 24, and 48 months. Additionally, two studies [42, 44] reported results based on per protocol analysis only. Detailed results are presented in Table 4.2-3.

Toxicity at ≤ 3 months follow-up

2 Studien, 517 Patienten
Grad 1: 0,5% bis 47,2%
Grad 2: 0,8% bis 12,3%
Grad 3: sehr selten, 0% bis 0,3%
Grad 4: 0,3% bis 1%

The data were pooled from two prospective cohort studies [41, 44], involving a total of 517 patients. Grade 1 toxicity was observed in 0.5% to 47.2% of patients (unweighted mean: 13.5%). Grade 2 toxicity was reported in a range from 0.8% to 12.3% (unweighted mean: 3.3%). Grade 3 occurrences were very rare, with a reported range of 0% to 0.3% (unweighted mean: 0.2%). Grade 4 toxicity was reported in a range between 0.3% and 1% (unweighted mean: 0.4%).

Toxicity at ≤ 6 months follow-up

3 Studien, 570 Patienten
Grad 1: 0,3% bis 30,3%
Grad 2: 0,3% bis 14%
Grad 3: 0,9%

Over a follow-up period of up to 6 months, toxicity data were collated from three studies [43-45], involving 570 patients in total. The data indicated that grade 1 toxicity affected 9.8% of patients (unweighted mean), with individual study results varying widely from 0.3% to 30.3%. Grade 2 toxicity was reported in 3.2% of the cohort (unweighted mean), spanning from 0.3% to 14%. Grade 3 was reported only by one of the three studies [43], and it was noted in 0.9% of patients.

Toxicity at ≤ 12 months follow-up

2 Studien, 581 Patienten
Grad 1: 0% bis 22%
Grad 2: 0% bis 9%
Grad ≥3: 0%

Analyses from two prospective cohort studies [42, 44] encompassing 581 patients, revealed that grade 1 toxicity at up to 12 months post-treatment was reported in 11% of patients (unweighted mean), with a variation range from 0% to 22%. Grade 2 events were less common, observed in a range of 0% to 9% (unweighted mean: 4.5%), and there were no reported events of grade 3 or higher.

Toxicity at ≤ 24 months follow-up

1 Studie, 411 Patienten
Grad 2: 0,6%

Long-term toxicity up to 24 months was assessed in a single prospective cohort study involving 411 patients [44]. The only toxicity reported was grade 2, affecting 0.6% of the patients.

Toxicity at ≤ 48 months follow-up

1 Studie, 411 Patienten
keine Toxizitätsereignisse

Long-term toxicity at 48 months was assessed in the same cohort of 411 patients [44], with no events of toxicity reported.

Table 4.2-3: Safety results (prospective cohort studies) with IRE

Endpoint: Toxicity					
Author, Year, Reference	**De la Rosette 2022 [41]**	**Wang 2022 [43]**	**Blazevski 2020 [42]**	**Zhang 2024 [44]**	**Scheltema 2018 [45]**
Complications (CTCAE-classification), ≤ 3-months FU	Grade 1: 50/106 (47.2%) Grade 2: 13/106 (12.3%) Grade 3: 0/106 (0) Grade 4: 1[13]/106 (1%)	NR	NR	Total: 7/383 (1.8%) Grade 1: 2/383 (0.5%) Grade 2: 3/383 (0.8%) Grade 3: 1/383 (0.3%) Grade 4: 1/383 (0.3%)	NR
Complications (CTCAE-classification), *Clavien-Dindo classification, ≤ 6 months FU	NR	No. of patients experiencing complications: 29/109 (26.6%, 95% CI, 18.6% to 35.9%) *Clavien-Dindo toxicity*:* No. of events: 41 (37.6%, 95% CI, 28.5% to 47.4%) Grade 1: 33/109 (30.3%, 95% CI, 21.8 to 39.8%) Grade 2: 7/109 (6.4%, 95% CI, 2.6 to 12.8%) Grade 3: 1/109 (0.9%, 95% CI, 0 to 5%)	NR	Total: 2/299 (0.7%) Grade 1: 1/299 (0.3%) Grade 2: 1/299 (0.3%)	*Clavien-Dindo toxicity*:* Grade 1: 11/50 (22%) Grade 2: 7/50 (14%)
Complications (CTCAE-classification), *Clavien-Dindo classification, ≤ 12 months FU	NR	NR	*Clavien-Dindo toxicity*:* Grade 1: 27/123 (22%) Grade 2: 11/123 (9%) Grade 3: 0 (0) Grade 4: 0 (0) Grade 5: 0 (0)	Total: 0/264 (0)	NR
Complications (CTCAE-classification), *Clavien-Dindo classification, ≤ 24 months FU	NR	NR	NR	At 24 months: 1/158 (0.6%) Grade 2: 1/158 (0.6%) At 48 months: 0/48 (0)	NR

Abbreviations: CI: confidence interval; FU: follow -up; NR: not reported

[13] The publication reported 9 patients in Table 2, however, the percentage number and the paragraph in the publication about the adverse events at 3 month follow-up made it clear that the correct number is 1.

4.2.3 Certainty of the evidence

Vertrauenswürdigkeit der Evidenz: „niedrig" und „sehr niedrig" für Sicherheit (Toxizität)

The certainty of the evidence presented across the various follow-up periods in the studies ranges from very low to low. The very low certainty ratings primarily at the shorter follow-up intervals (≤ 3 months, ≤ 6 months, and ≤ 12 months) are influenced by serious risks in study design and execution, variability in effect estimates and inconsistencies across study results. In contrast, the longer-term follow-up outcomes (≤ 24 months and ≤ 48 months) are rated as low certainty, primarily due to notable issues with imprecision arising from the evidence being derived from only one study that included a limited number of patients. Detailed evidence profile is displayed in Table 4.2-4.

Table 4.2-4: Evidence profile of IRE: Safety

Nº of studies/ patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Effect estimates	Certainty
Outcome: Toxicity at ≤ 3 months								
2/517 [41, 44]	Prospective cohort study	Serious[a]	Serious[b]	Not serious	Serious[c]	1 study (Zhang) reports per protocol results.	Grade 1: 13.5% (range 0.5% to 47.2%) Grade 2: 3.3% (range 0.8 to 12.3%) Grade 3: 0.2% 1(range 0 to 0.3%) Grade 4: 0.4% (range 0.3% to 1%)	Very low
Outcome: Toxicity at ≤ 6 months								
3/570 [43-45]	Prospective cohort study	Serious[a]	Serious[b]	Not serious	Serious[c]	Other classification systems used in the studies. 1 study (Zhang) reports per protocol results.	Grade 1: 9.8% (range 0.3% to 30.3%) Grade 2: 3.2% (range 0.3% to 14%) Grade 3: 0.9%	Very low
Outcome: Toxicity at ≤ 12 months								
2/581 [42, 44]	Prospective cohort study	Serious[a]	Serious[b]	Not serious	Serious[c]	Other classification systems, 1 study reported only aggregated results (0 toxicity at 12 months). The studies report per protocol results.	Grade 1: 11% (range 0% to 22%) Grade 2: 4.5% (range 0% to 9%) Grade ≥3: 0% (range 0% to 0%)	Very low
Outcome: Toxicity at ≤ 24 months								
1/411 [44]	Prospective cohort study	Serious[a]	Not serious	Not serious	Serious[c]	The study reports per protocol results.	Grade 2: 0.6%	Low
Outcome: Late toxicity at ≤ 48 months								
1/411 [44]	Prospective cohort study	Serious[a]	Not serious	Not serious	Serious[c]	The study reports per protocol results.	No event occurred.	Low

[a]: *Observational study design, studies were rated to have moderate risk of bias.*

[b]: *There is a wide range of variation, especially in grade 1 and grade 2 toxicity outcomes.*

[c]: *The number of patients and events was low.*

4.3 Stereotactic radiotherapy (SBRT)

4.3.1 Included studies

5 Studien: 3 RCTs und 2 Beobachtungsstudien

In addition to the RCTs included for efficacy outcomes (see Table 3.3-1), we identified two prospective cohort studies [46, 47]. Although one of these studies [47] was conducted as a randomised study of two treatment regimens (36.25 Gy in 5 fractions or 51.6 Gy in 12 fractions) and each arm of the study was compared against historical control data rather than directly against each other. Hence, the study essentially composed of two single-arm phase 2 studies accruing patients in parallel. Consequently, we treated it as a single cohort study for analysis purposes. The detailed characteristics of the studies and included patients are presented in Table 3.3-2 for the RCTs and in Table 4.3-2 table for the prospective observational studies.

Study characteristics

RCT-Beschreibung in Kapitel 3.2.1

2 Beobachtungsstudien: Nachbeobachtung bis 2 Jahre

Beide Studien mit Cyberknife®

Klassifizierungssyteme: RTOG und CTCAE

The description of the RCTs can be found in chapter 3.3.1. One of the prospective cohort studies took place in Europe [46], the other one in Canada [47]. The Canadian study received funding from diverse grants and authors did not declare any conflicts of interest. The European study authors also did not have any conflicts of interest, neither reported any funding. Both studies were single centre. The follow-up periods ranged from eight months to two years. Both studies used Cyberknife®. The European study used different treatment approaches for low-risk and intermediate to high-risk patients [46]. In low-risk patients 7.5–8 Gy was delivered to the prostate gland by each fraction. For intermediate- and high-risk patients a dose of 7.5–8 Gy was delivered to the prostate and 6–6.5 Gy to the seminal vesicles by each fraction with a simultaneous integrated boost technique. A total of 5 fractions (total dose 37.5–40 Gy) were given on every second working day. In the Canadian study [47] five or 12 fractions were given in two study arms (36.25 and 51.6 Gy, respectively). One study used RTOG [46], the other one [47] CTCAE criteria for toxicity classification. Losses to follow-up were reported in one study [47] at the two-year follow-up mark, by that time 12 patients died, two withdrew consent and 86 were not analysable due to questionnaire non-compliance.

Patient characteristics

insg. 460 Patienten

Alter relativ ähnlich zwischen 64 und 73 Jahren

T1-T2 Tumorstadium in der Mehrheit

The description of patients included in the RCTs can be found in chapter 3.3.1. The two prospective cohort studies included in total 460 patients (205 [46] and 255 [47] each, however from the latter study 15 patients dropped out). The study, which described two single-arm cohorts presented the mean age separately for the two cohorts (64 and 66 years) [47]. In the other study the mean age was 73 years [46]. In the European study the majority of patients had low- and intermediate-risk cancer (approx. 70%) and 30% had high-risk cancer. The Canadian study did not report D'Amico or NCCN risk classes. The European study included 80% of T1-T2 stages and approximately 20% T3 and the majority of patients had 7 or higher Gleason scores (70%), while the Canadian study included only patients with T1-T2 stages.

Risk of bias

The overall risk of bias of two RCTs was rated to be high (PACE-B and Poon et al.) and one RCT raised some concerns regarding risk of bias (HYPO-RT-PC). The high risk was awarded mainly because of the open-label nature of the studies and data handling issues. Detailed assessment of the RCTs is presented in Table 4.3-1. The risk of bias of the prospective cohort studies was rated to be moderate. Detailed assessment is presented in the appendix (Table 8.2-1).

2 RCTs: hohes Risiko
1 RCT: einige Bedenken hinsichtlich Biasrisiko

Beobachtungsstudien: moderates Risiko

Table 4.3-1: Risk of bias assessment (RCTs) with SBRT

Study	Endpoint	Bias arising from randomisation process	Bias due to deviations from intended interventions	Bias due to missingoutcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
PACE-B [36, 37]	Toxicity	Low	High[14]	High[15]	Some concerns[16]	Low	High
HYPO-RT-PC [38]	Toxicity	Low	Low	Low	Some concerns[17]	Low	Some concerns
Poon 2021 [34]	Toxicity	Some concerns[18]	Some concerns[19]	Low	Some concerns[20]	Low	High

[14] Participants and researchers were not masked to treatment assignment. In 11 cases the patients received a treatment different from what they were initially allocated. Notably, of these deviations, four involved patients who were allocated to SBRT but, according to protocol deviations, received CFMHRT instead. The deviations were therefore not balanced between the two groups. According to the protocol, the analyses of outcome data was planned to be ITT and therefore include all patients randomised into each arm. However, randomised patients who have not received at least one fraction of radiotherapy (or did not receive surgery if allocated to that group) were planned to be excluded from the toxicity analyses.

[15] At 12 weeks follow-up, for the various toxicity endpoints there were some missing data. No information was provided for the reason of the missing data. The protocol planned for standard algorithms to derive scores from and handle missing data in quality-of-life questionnaires only, so for the safety outcomes it was planned that patients with missing data will be excluded from the analysis.

[16] RTOG and CTCAE are clinician-administered questionnaires. Although unblinded clinicians might be influenced by their knowledge of the treatments during follow-up visits, the standardised and objective nature of these questionnaires reduces the likelihood of significant bias in reporting outcomes. This minimises the potential for differential reporting based on treatment expectations or perceptions.

[17] Same as footnote in PACE-B.

[18] No information was available about the allocation concealment.

[19] Participants and researchers were not masked to treatment assignment. It was not reported if deviations occurred or not occurred.

[20] Same as footnote PACE-B.

Table 4.3-2: Study characteristics (prospective cohort studies) with SBRT

Author, year, reference	Jorgo 2021	Lukka 2018 NRG Oncology RTOG 0938 trial (NCT01434290)
Country	Hungary	Canada
Funding / conflicts of interest (CoI)	Funding: NR CoI: none.	Funding: Grant UG1CA189867 (NCI Community Oncology Research Program), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology Statistics and Data Management Center), and U24CA180803 (Imaging and Radiation Oncology Core) CoI: none.
Study type	Prospective observational study	Randomised phase 2 study (2 single-arm phase 2 studies accruing patients in parallel)
Setting, time period	1 centre in 1 country, from February 2018 to August 2019	1 centre, from September 2011 to February 2014
Details of the interventions (number of fractions, total dose, equipment)	SBRT with CyberKnife M6 linear accelerator. In low-risk patients: 7.5–8 Gy by each fraction. In intermediate- and high-risk patients: 7.5–8 Gy to the prostate and 6–6.5 Gy to the seminal vesicles by each fraction with a simultaneous integrated boost technique. A total of 5 fractions (total dose 37.5–40 Gy) delivered on every second working day.	SBRT in 5 (7.25 Gy in 2 weeks, total 36.25 Gy) or 12 fractions (UHRT, 4.3 Gy in 2.5 weeks, total 51.6 Gy) and could be treated using CyberKnife, IMRT/VMAT techniques, or protons, as long as the protocol-specified dosimetry criteria were met.
Follow-up period	Median 8 months	NR for toxicity outcomes (2 years for QoL outcomes)
Toxicity classification	RTOG	CTCAE v4.0
Inclusion criteria	Histologically confirmed, low-, intermediate- and high-risk Pca. No lymph node or distant metastasis and previous pelvic irradiation.	Gleason score >2 and <6, cT1-2a, PSA <10 ng/mL. Patients undergoing active surveillance who were re-biopsied and confirmed to have low-risk disease were eligible for enrollment within 1 year of the repeat biopsy. Ineligibility criteria: prior or concurrent invasive malignancy, lymphomatous or hematogenous malignancy, distant metastases; regional lymph node involvement; previous prostatectomy; cryosurgery; HIFU; pelvic irradiation; brachytherapy; bilateral orchiectomy, hormonal therapy, previous or concurrent cytotoxic chemotherapy, use of finasteride within 30 days or dutasteride within 90 days before registration and severe active comorbidities.
Number of patients	205	255 randomised (5-fraction: 127 vs. 12-fraction: 128) 240 received treatment (5-fraction: 119 vs. 12-fraction: 121)
Patient characteristics (age in years– average and range, ADT in %)	Age: 73 (54–85) ADT: 57.1	Age: 64 (48-77) vs. 66 (50-79) for 5-fraction vs- 12-fraction (for the total study cohort: NR) ADT: was not allowed
Tumour classification (T1-T3) (% of patients)	T1: 22 T2a: 17.1 T2b: 25.3 T2c: 28.3 T3a: 3.4 T3b: 3.9	T1a: 2 T1c: 81.7 T2: 0.4 T2a: 17
Gleason Score (% of patients)	≤6: 29.3 7: 52.7 ≥8: 17	NR
Risk status of patients (D'Amico or NCCN) (% of patients)	*D'Amico*: Low risk: 11.2 Intermediate risk: 58.6 High risk: 30.2	NR
Loss to follow-up (FU)	0 (3 patients required a therapeutic interruption due to radiotherapy-related adverse events and did not complete radiation therapy at the planned dose)	15 dropped-out after randomisation (excluded due to ineligibility or received non-protocol treatment) By 2-year FU: 12 patients died, 2 withdrew consent, 86 not analysable due to questionnaire non-compliance

Abbreviations: ADT: androgen deprivation therapy; CTCAE: Common Terminology Criteria for Adverse Events; HIFU: high-intensity focused ultrasound; IMRT/VMAT: intensity modulated radiation therapy/volumetric arc therapy; NCCN: National Comprehensive Cancer Network, NCI: National Cancer Institute; FU: follow-up; RTOG: Radiation Therapy Oncology Group; UHT: ultra-hypofractionated therapy

4.3.2 Results

Studies reported GI and GU toxicities at various time points. The results are categorised according to follow-up lengths: from the end of radiation therapy up to 30 days, from 30 days up to three months, toxicity at one, two and five years. Three studies [34, 46, 47] covered the period from the end of treatment up to 30 days post-treatment for GI toxicity, while four studies [34, 38, 46, 47] did the same for GU toxicity. Two observational studies [46, 47] provided data for the period from 30 days up to three months follow-up. One RCT reported one-year follow-up data for GI toxicity and two RCTs [34, 38] for GU toxicity. Two RCTs [37, 38] reported two-year follow-up, and one RCT [38] reported five-year follow-up. Two RCTs reported results based on the per protocol population only [36-38]. The detailed toxicity results from RCTs are presented in Table 4.3-3 and from the prospective observational studies in Table 4.3-4.

GI/GU Toxizität: verschiedene Zeitpunkte (akut: bis 30 Tage, 30 Tage bis 3 Monate; spät: ab 30 Tage, 1 Jahr, 2 und 5 Jahre)

Toxicity at end of treatment to <30 days

GI toxicity at end of treatment was assessed in one RCT (n=64) [34] and two observational studies [46, 47]. The RCT highlighted a statistically significant difference in cumulative grade ≥1 results, indicating a substantial rate of early post-treatment GI issues particularly among the control group. While only 12% of a control group experienced no toxicity, the corresponding figure for the treatment group was 64%. Similarly, higher toxicity grades were more common in the control group, with 66% experiencing grade 1 and 21% grade 2, compared to 29% and 6% respectively in the intervention group. The single-arm observational studies also showed that 60% of patients did not experience toxicity, and if any toxicity was experienced, it was low grade (grade 1 in 32% of patients and 6% grade 2).

GI-Akuttoxizität bis 30 Tage:
1 RCT:
s.s. Unterschied in kumulativem Grad ≥1
Grad 0: 64% vs. 12%
Grad 1: 29% vs. 66%
Grad 2: 6% vs. 21%
2 Beobachtungsstudien:
Grad 0: 60%, Grad 1: 32%, Grad 2: 6%

GU toxicity immediately post-treatment was assessed in two RCTs [34, 38] (n=1,264) and two prospective observational studies [46, 47] (n=460). One RCT [38] (n=1,200) reported a non-significant difference in grade ≥2 toxicity with 28% in the treatment group versus 23% in controls (p=0.057). The other RCT [34] (n=64) found a statistically significant difference for cumulative grade ≥1, in favour of the intervention group (87% of patients experiencing toxicity in the intervention group versus 100% in the control group, p=0.04). The latter RCT did not specify the timeframe beyond labelling it "acute" and used different classification systems from the first. The observational studies reported 17% grade 1, 50% grade 2 and only less than 1% grade 3 or higher toxicities.

GU-Akuttoxizität bis 30 Tage:
2 RCTs:
kein Unterschied in Grad ≥2 (28% vs. 23%, p=0,057);
s.s. Unterschied in kumulativem Grad ≥1 (87% vs. 100%, p=0,04);
2 Beobachtungsstudien:
Grad 1: 17%, Grad 2: 50%, Grad ≥3: <1%

Toxicity at >30 days to 3 months

GI toxicity beyond 30 days and up to three months was assessed in two prospective cohort studies (n=460) [46, 47]. These studies noted minimal toxicity, with 95% of patients showing no signs of GI distress (grade 0) and only minor incidences of grade 1 (4.5%) and grade 2 (0.5%) toxicity. However, the studies lacked specific p-value reporting.

GI-Akuttoxizität bis 3 Monate:
2 Beobachtungsstudien:
Grad 0: 95%, wenige Grade ≥1

GU toxicity from over 30 days to three months post-treatment was reported in the same two prospective cohort studies (n=460) [46, 47]. These studies showed that 74.6% of patients experienced no toxicity (grade 0), while 14.7% had grade 1, and 9.7% had grade 2. Grade 3 toxicity was minimal at 0.9%. However, the studies lacked specific p-value reporting.

GU-Akuttoxizität bis 3 Monate:
Grad 0: 74,6%
Grad 1: 14,7%
Grad 2: 9,7%, wenige Grad 3

Toxicity at 1 year

GI-Toxizität nach 1 Jahr:
1 RCT:
kumulative Grad ≥1: 64% vs. 84%, p<0.001
Grad 1: 51% vs. 66%

GI toxicity at one-year post-treatment was reported in one RCT [34] (n=64). The cumulative grade ≥1 toxicity was 64% in the treatment group versus 84% in the control group, the difference being statistically significant (p<0.001). Lower grades of toxicity were similarly higher among the control group participants, with 51% of patients experiencing grade 1 toxicity in the treatment group compared to 66% in controls.

GU-Toxizität nach 1 Jahr:
2 RCTs:
Grad ≥2: 6,8% vs. 3,7%; s.s. Unterschied in 1 RCT (n=1.200)
kumulative Grad ≥1: 93% vs. 100%; p=0,23

GU toxicity at one year was investigated in two RCTs [34, 38] (n=1,264). Both studies utilised different classification systems and noted that significant toxicity (grade ≥2) was 6.8% in the intervention group versus 3.7% in the control group, with one of the studies [38] (n=1,200) showing a statistically significant difference of 4% for this grade (p=0.0037). The cumulative grade ≥1 toxicity in the other study [34] (n=64) showed a lower proportion of toxicity in the intervention group at 93% versus 100% (p=0.23).

Toxicity at 2 years

GI-Toxizität nach 2 Jahren:
2 RCTs: kein Unterschied in kumulativen Grad ≥2
1. RCT: 6% vs. 5%
2. RCT: 7,8% vs. 8,1% (HR 0,98; 95% CI 0,60–1,58)

GI toxicity over a two-year period was reported in two RCTs [37, 38] (n=2,074). Both studies reported per protocol results. The results showed non-significant differences between the treatment and control groups, with cumulative grade ≥2 toxicities being nearly identical across the two studies, with 6% (95% CI, 5−9%) versus 5% (95% CI, 4−8%) (log-rank p=1.00) in one RCT [38] and 7.8% (95% CI, 5.6% to 10.9%) versus 8.1% (95% CI, 5.8% to 11.1%) (HR 0.98; 95% CI, 0.60 to 1.58; log-rank p=0.92) in the other RCT [37].

GU-Toxizität nach 2 Jahren:
1. RCT: s.s. erhöhtes Risiko mit SBRT in kumulativen Grad ≥2: 18,3% vs. 10,6% (HR 1,80; p=0,0015)
2. RCT: kein Unterschied in kumulative Grad ≥2

GU toxicity after two years was examined in two RCTs [37, 38] (n=2,074). Both studies reported per protocol results. One RCT [37] noted a cumulative grade ≥2 toxicity of 18.3% versus 10.6%, showing a statistically significant increase in risk with SBRT (HR 1.80, p=0.0015). The other RCT [38] reported a cumulative grade ≥2 toxicity of 13% versus 9%, with no significant difference (p=0.63).

Toxicity at 5 years

GI-Toxizität 5 Jahren:
1 RCT: kein Unterschied in kumulativen Grad ≥2: 10% in beiden Gruppen

GI toxicity at the five-year mark was reported in one RCT [38] (n=1,200). The study found no significant differences in grade 2 or higher toxicities between treatment and control groups. Both groups had a cumulative grade ≥2 toxicity rate of 10%.

GU-Toxizität 5 Jahren:
1 RCT: kein Unterschied in kumulativen Grad ≥2: 18% vs. 17%; p=0,63

GU toxicity at five years was assessed in a single RCT [38] (n=1,200), noting a cumulative grade ≥2 of 18% versus 17%, with no statistically significant difference (p=0.63).

Table 4.3-3: Safety results (RCTs) with SBRT

Endpoint: Toxicity			
Author, year, reference	**Tree 2022 [37], Ratnakumaran 2023 [36]** **PACE-B**	**Widmark 2019 [38]** **HYPO-RT-PC**	**Poon 2021 [34]**
Complications (CTCAE-classification) *RTOG-criteria, At end of treatment to <30-days FU, I vs. C	NR	*Acute toxicity (at the end of radiotherapy)* **GI*** NR **GU*** Grade ≥2: 158/569 (28%) vs. 132/578 (23%), p=0.057	*Acute toxicity*[21] **GI** Grade 0: 20/31 (64%) vs. 4/33 (12%) Grade 1: 9/31 (29%) vs. 22/33 (66%) Grade 2: 2/31 (6%) vs. 7/33 (21%) Grade ≥3: 0% vs. 0% Cumulative grade ≥1: 11/31 (35%) vs. 29/33 (87%), **p<0.0001** **GU** Grade 0: 3/31 (9%) vs. 0% Grade 1: 26/31 (83%) vs. 25/33 (75%) Grade 2: 1/31 (3%) vs. 8/33 (24%) Grade ≥3: 0% vs. 0% Cumulative grade ≥1: 27/31 (87%) vs. 33/33 (100%), **p=0.04**
Complications (CTCAE-classification) *RTOG-criteria, ≥1-year FU, I vs. C	*Late toxicity (2-year FU)* **GI*** Grade 0: 323/414 (84%) vs. 320/430 (84%) Grade 1: 55/414 (14%) vs. 51/430 (13%) Grade 2: 6/414 (2%) vs. 8/430 (2%) Grade 3: 0% vs. 3/430 (1%) Grade 4: 0% vs. 0% Grade 5: 0% vs. 0% Grade ≥2: 6/384 (2%) vs. 11/382 (3%), absolute difference -1.3% (95% CI, -3.9% to 1.1%); p=0.32 Cumulative grade ≥2: 32/414 (7.8%; 95% CI, 5.6% to 10.9%) vs. 34/430 (8.1%; 95% CI 5.8% to 11.1%); HR 0.98 (95% CI, 0.60 to 1.58); log-rank p=0.92 **GI** Grade 0: 288/414 (75%) vs. 283/430 (74%) Grade 1: 85/414 (22%) vs. 84/430 (22%) Grade 2: 13/414 (3%) vs. 15/430 (4%) Grade 3: 0% vs. 1/430 (<1%) Grade 4: 0% vs. 0% Grade 5: 0% vs. 0% Grade ≥2 absolute difference: -0.8% (–3.8% to 2.2%); p=0.70	*Late toxicity (>1-year FU)* **GI*** Cumulative Grade ≥2: At 2-year FU: 6% (95% CI, 5–9%) vs. 5% (95% CI, 4–8%); log-rank p=1.00 At 5-year FU: 10% (95% CI, 7–13%) vs. 10% (95% CI, 7–13%); log-rank p=1.00 At 5-year FU bowel toxicity 3/244 (1%) vs. 9/249 (4%), p=0.14 **GU*** Grade ≥2: At 1-year FU: 32/528 (6%) vs. 13/529 (2%), **p=0.0037** At 5-year FU: 11/243 (5%) vs. 12/249 (5%), p=1.00 Cumulative Grade ≥2: At 2-year FU: 13% (95% CI, 11–16%) vs. 9% (95% CI, 7–12%); log-rank p=0.63 At 5-year FU: 18% (95% CI, 15–22%) vs. 17% (95% CI, 14–20%); log-rank p=0.63 Number of events/patients at 5-year FU: Grade ≥1: 307/587 (52%) vs. 304/591 (51%) Grade ≥2: 103/587 (18%) vs. 100/591 (17%) Grade ≥3: 28/587 (5%) vs. 27/591 (5%)	*Late toxicity (1-year FU)* **GI** Grade 0: 11/31 (35%) vs. 5/33 (15%) Grade 1: 16/31 (51%) vs. 22/33 (66%) Grade 2: 4/31 (12%) vs. 6/33 (18%) Grade ≥3: 0% vs. 0% Cumulative grade ≥1: 20/31 (64%) vs. 28/33 (84%), **p=0.033** **GU** Grade 0: 2/31 (6%) vs. 0 Grade 1: 23/31 (74%) vs. 25/33 (75%) Grade 2: 5/31 (16%) vs. 7/33 (21%) Grade ≥3: 1/31 (3%) vs. 1/33 (3%) [22] Cumulative grade ≥1: 29/31 (93%) vs. 33/33 (100%), p=0.23

[21] Specified as <1 year follow-up. According to the methods applied in our review, acute is considered <3 months. The publication by Poon et al. did not separate results <3 months, therefore we present the results as supposedly acute according to our definition.

[22] Non-infective cystitis vs. Urinary incontinence

Endpoint: Toxicity			
Author, year, reference	**Tree 2022 [37], Ratnakumaran 2023 [36]** **PACE-B**	**Widmark 2019 [38]** **HYPO-RT-PC**	**Poon 2021 [34]**
	Cumulative grade ≥2: 51/414 (12.5%; 95% CI, 9.6% to 16.1%) vs. 52/430 (12.3%; 95% CI, 9.5% to 15.8%); HR 1.02 (95% CI, 0.70 to 1.51); log-rank p=0.91 **GU*** Grade 0: 299/414 (78%) vs. 320/430 (84%) Grade 1: 72/414 (19%) vs. 53/430 (14%) Grade 2: 11/414 (3%) vs. 7/430 (2%) Grade 3: 2/414 (<1%) vs. 1/430 (<1%) Grade 4: 0% vs. 0% Grade 5: 0% vs. 0% Grade ≥2: 13/384 (3%) vs. 8/381 (2%), absolute difference 1.3% (95% CI, −1.3% to 4.0%); p=0.39 Cumulative grade ≥2: 75/414 (18.3%; 95% CI, 14.9% to 22.4%) vs. 45/430 (10.6%; 95% CI, 8.0% to 14.0%); HR 1.80 (95% CI, 1.25 to 2.61); log-rank **p=0.0015**) **GU** Grade 0: 176/414 (42.5%) vs. 211/430 (49%) Grade 1: 161/414 (39%) vs. 146/430 (34%) Grade 2: 46/414 (11%) vs. 23/430 (5%) Grade 3: 1/414 (<1%) vs. 2/430 (<1%) Grade 4: 0% vs. 0% Grade 5: 0% vs. 0% Grade ≥2 absolute difference: 5.7% (95% CI, 1.6% to 9.8%; **p=0.010**) Cumulative grade ≥2: 132/414 (32.3%; 95% CI, 28.0% to 37.0%) vs. 84/430 (19.8%; 95% CI, 16.3% to 23.9%); HR 1.73 (95% CI, 1.32 to 2.28; log-rank **p=0.0001**)		

Abbreviations: C: control group; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FU: follow-up; GI: genitourinary; GU: gastrointestinal; HR: hazard ratio; I: intervention group; NR: not reported; RTOG: Radiation Therapy Oncology Group.

Table 4.3-4: Safety results (prospective cohort studies) with SBRT

Endpoint: Toxicity		
Author, year, reference	**Jorgo 2021 [46]**	**Lukka 2018 [47]**
Complications (CTCAE-classification), ≤3 months FU	*At end of treatment:* **GI** Grade 0: 128/205 (62.4%) Grade 1: 65/205 (31.7%) Grade 2: 12/205 (5.9%) Grade 3: 0/205 (0%) Grade ≥4: 0/205 (0%) **GU** Grade 0: 35/205 (17.1%) Grade 1: 63/205 (30.7%) Grade 2: 104/205 (50.7%) Grade 3: 3/205 (1.5%) *At 3 months FU:* **GI** Grade 0: 195/205 (95%) Grade 1: 9/205 (4.5%) Grade 2: 1/205 (0.5%) Grade 3: 0/205 (0%) **GU** Grade 0: 153/205 (74.6%) Grade 1: 30/205 (14.7%) Grade 2: 20/205 (9.7%) Grade 3: 2/205 (1%)	*Acute toxicity (≤30 days)* **GI** Grade 3: 3/240 (1.2%) Grade 4: 0/240 (0%) Grade 5: 0/240 (0%) **GU** Grade 3: 1/240 (0.4%) Grade 4: 0/240 (0%) Grade 5: 0/240 (0%) *Late toxicity (> 30 days)* **GI** Grade 3: 2/240 (0.8%) Grade 4: 0/240 (0%) Grade 5: 0/240 (0%) **GU** Grade 3: 2/240 (0.8%) Grade 4: 0/240 (0%) Grade 5: 0/240 (0%)

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; FU: follow-up; GI: gastrointestinal; GU: genitourinary

4.3.3 Certainty of the evidence

Vertrauenswürdigkeit der Evidenz „niedrig" bis „moderat" für GI-Toxizität

The certainty of evidence for GI toxicity was rated as low for the time period end of treatment up to 30 days, from 30 days up to three months, and at one year. For two and five years, the certainty was considered moderate. This low certainty is attributed to two RCTs having a high risk of bias [34, 36, 37], while another RCT [38] presented concerns regarding safety outcomes. Furthermore, despite the moderate risk of bias inherently associated with their observational design, the prospective cohort studies' certainty was downgraded by one level. Additional factors contributing to the low certainty include a limited number of studies involving few patients and low event numbers, leading to potential imprecision in the effect estimates. In contrast, the two- and five-year follow-up results were assigned a moderate certainty due to the substantial number of patients, which mitigates concerns about precision.

Vertrauenswürdigkeit der Evidenz „sehr niedrig" bis „niedrig" für GU-Toxizität

For GU toxicity, the certainty of evidence from RCTs at the end of treatment up to 30 days was rated as low, while evidence from observational studies was deemed very low. From 30 days up to three months, the certainty remained low, but it improved to moderate for one-year, two-year, and five-year follow-ups. The reasons for the low and very low ratings for GU toxicity at the end of treatment up to 30 days were the same as those highlighted for GI outcomes, including high risk of bias in RCTs and issues inherent in observational study designs. Additionally, the low and very low ratings were influenced by inconsistency across studies. Detailed evidence profile for the toxicity results is displayed in Table 4.3-5.

Table 4.3-5: Evidence profile of SBRT: Safety

№ of studies/ patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates	Certainty
Outcome: GI toxicity at end of treatment to <30 days								
1/64 [34]	RCT	Serious[a]	Not serious	Not serious	Serious[e]	Stat.significant difference for the cumulative grade ≥1 results. The study did not report the timeframe, only reported "acute" toxicity.	Grade 0: 64% vs. 12% Grade 1: 29% vs. 66% Grade 2: 6% vs. 21% Grade ≥3: 0 vs. 0 Cumulative grade ≥1: 35% vs. 87%, **p<0.0001**	Low
2/460 [46, 47]	Prospective cohort study	Serious[c]			Serious[f]	One study [47] defined only the lower limit (>30 days) of reporting toxicity results (QoL outcomes were reported up to 2 years). P-values were not reported in the studies.	Grade 0: 62.4% Grade 1: 31.7% Grade 2: 5.9% Grade 3: 0.7% (range 0% to 1.2%) Grade ≥4: 0% (range 0% to 0%)	Low
Outcome: GI toxicity at >30 days to 3 months								
2/460 [46, 47]	Prospective cohort study	Serious[c]	Not serious	Not serious	Serious[d]	One study [47] defined only the lower limit (>30 days) of reporting toxicity results (QoL outcomes were reported up to 2 years). P-values were not reported in the studies.	Grade 0: 95% Grade 1: 4.5% Grade 2: 0.5% Grade 3: 0.4% (range 0% to 0.8%) Grade ≥4: 0%	Low
Outcome: GI toxicity at 1 year								
1/64 [34]	RCT	Serious[a]	Not serious	Not serious	Serious[e]	Stat. significant result for the cumulative grade ≥1 results.	Grade 0: 35% vs. 15% Grade 1: 51% vs. 66% Grade 2: 12% vs. 18% Grade ≥3: 0 vs. 0 Cumulative grade ≥1: 64% vs. 84%, **p=0.033**	Low
Outcome: GI toxicity at 2 years								
2/2074 [37, 38]	RCT	Serious[a]	Not serious	Not serious	Not serious	Non-significant differences in both RCTs.	1.RCT: Cumulative Grade ≥2: 6% (95% CI, 5–9%) vs. 5% (95% CI, 4–8%); log-rank p=1.00 2. RCT: Absolute difference in Grade ≥2 toxicities: -1.3 (95% CI, -3.9 to 1.1), p=0.32 Cumulative Grade ≥2[23]: 7.8% (95% CI, 5.6% to 10.9%) vs. 8.1% (95% CI, 5.8% to 11.1%); HR 0.98 (95% CI, 0.60 to 1.58); log-rank p=0.92	Moderate
Outcome: GI toxicity at 5 years								

[23] From the two studies reporting this outcome, Tree used only RTOG criteria, while Widmark used both CTCAE and RTOG. For data synthesis purposes we present here only the RTOG results from Widmark. CTCAE results are similar.

№ of studies/ patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates	Certainty
1/1200 [38]	RCT	Serious[a]	Not serious	Not serious	Not serious	Non-significant difference for grade 2 toxicity, and no difference for cumulative grade ≥2.	Grade 2: 1% vs. 4%, p=0.14 Cumulative Grade ≥2: 10% (95% CI, 7–13%) vs. 10% (95% CI, 7–13%); log-rank p=1.00	Moderate
Outcome: GU toxicity at end of treatment to <30 days								
2/1264 [34, 38]	RCT	Serious[a]	Serious[b]	Not serious	Not serious	1.RCT: non-significant difference. Study reports per protocol results. 2.RCT: stat. significant difference for the cumulative grade ≥1. The RCTs used different classification systems. The 2.RCT did not specify the timeframe, only reported "acute".	1.RCT: Grade ≥2: 28% vs. 23%, p=0.057 2. RCT: Grade 0: 9% vs. 0% Grade 1: 83% vs. 75% Grade 2: 3% vs. 24% Grade ≥3: 0% vs. 0% Cumulative grade ≥1: 87% vs 100%, **p=0.04**	Low
2/460 [46, 47]	Prospective cohort study	Serious[c]			Serious[d]	P-values were not reported in the studies.	Grade 0: 17.1% Grade 1: 30.7% Grade 2: 50.7% Grade 3: 0.9% (range 0.4% to 1.5%) Grade ≥4: 0%	Very low
Outcome: GU toxicity at >30 days to 3 months								
2/460 [46, 47]	Prospective cohort study	Serious[c]	Not serious	Not serious	Serious[d]	One study defined only the lower limit (>30 days) of reporting toxicity results (QoL outcomes were reported up to 2 years). P-values were not reported in the studies.	Grade 0: 74.6% Grade 1: 14.7% Grade 2: 9.7% Grade 3: 0.9% (range 0.8% to 1%) Grade ≥4: 0%	Low
Outcome: GU toxicity at 1 year								
2/1264 [34, 38]	RCT	Serious[a]	Not serious	Not serious	Not serious	The RCTs used different classification systems. Only grade ≥2 toxicities were reported in both studies with a stat. significant result in 1 RCT.	Grade 0: 6% vs. 0 Grade 1: 74% vs. 75% Grade ≥2: 6.8% vs. 3.7% (1.RCT: 6% vs. 2%, **p=0.0037**; 2.RCT: 19% vs. 24%, p-value NR) Cumulative grade ≥1: 93% vs. 100%, p=0.23	Moderate
Outcome: GU toxicity at 2 years								
2/2074 [37, 38]	RCT	Serious[a]	Not serious	Not serious	Not serious	Both studies report per protocol results. Non-significant absolute difference of grade ≥2 and statistically significant difference in risk of cumulative grade ≥2 in one RCT and non-significant difference in the other RCT.	1.RCT: Grade 0: 78% vs. 84% Grade 1: 19% vs. 14% Grade 2: 3% vs. 2% Grade 3: <1% vs. <1% Grade ≥4: 0 vs. 0 Grade ≥2: 3% vs. 2%, absolute difference 1.3% (95% CI, –1.3 to 4.0); p=0.39	Moderate

№ of studies/ patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates	Certainty
							Cumulative grade ≥2[24]: 18.3% (95% CI, 14.9% to 22.4%) vs. 10.6% (95% CI, 8.0% to 14.0%); HR 1.80 (95% CI, 1.25 to 2.61); log-rank **p=0.0015** 2.RCT: Cumulative grade ≥2: 13% (95% CI, 11–16%) vs. 9% (95% CI, 7–12%), log-rank p=0.63	
Outcome: GU toxicity at 5 years								
1/1200 [38]	RCT	Serious[a]	Not serious	Not serious	Not serious	Study reports per protocol results. Non-significant difference.	Cumulative grade ≥2: 18% (95% CI, 15–22%) vs. 17% (95% CI, 14–20%), log-rank p=0.63	Moderate

[a]: *The studies were rated to have high overall risk of bias and some concerns regarding overall risk of bias.*

[b]: *Between the RCTs and between the cohort studies there is inconsistency of the results.*

[c]: *The studies were observational studies with moderate risk of bias unclear if patients were recruited consecutively and estimates for random variability not reported in one of the two studies).*

[d]: *Only grade 3 toxicities were reported in both studies, for the rest of the toxicities, results come from only one study with few patients.*

[e]: *Only one study with very few patients.*

[f]: *Only grade 3 and 4 were reported in both studies, for the rest of the toxicities, results come from only one study with few patients.*

[24] From the two studies reporting this outcome, Tree used only RTOG criteria, while Widmark used both CTCAE and RTOG. For data synthesis purposes we present here only the RTOG results from Widmark. CTCAE results are similar.

4.4 Proton therapy (PT)

8 Studien: 6 Beobachtungsstudien, 2 RCTs, die 2 Formen der PT verglichen, daher als einarmige Studien analysiert

We identified six prospective cohort studies [48-53], of which two studies [49, 51] used the same study cohort but analysed a different subset of the cohort, and two RCTs [54, 55], which compared two forms of PT therapy (standard or moderate fractionation versus extreme hypofractionation), therefore we considered them relevant for safety analysis only and we report the study results as two single cohorts. Detailed study and patient characteristics are presented in Table 4.4-1, Table 4.4-2 and Table 4.4-3.

4.4.1 Included studies

Study characteristics

Studien aus den USA, Japan, und Korea

From the two studies [54, 55], which were conducted as RCT but were considered single-arm in the present analysis, one study was conducted in the U.S. [55], while another was carried out in Korea [54]. From the six prospective observational studies [48-53], three were prospective registries [49-51]. Of the observational studies, two were conducted in Japan [48, 53], and four [49-52] in the U.S. Five studies [49-52, 54] reported funding received from various grants with one study [54] reporting no conflicts of interest of the authors, while the other four reported that authors received fees from various radiation companies. One study did not report any funding details [48] and two studies reported no funding and no conflict of interest [53, 55]. Five studies [48, 50, 52-54] were conducted as single-centre, while three studies were multi-institutional [49, 51, 55].

Interessenskonflikte der Autoren in 4 Studien

5 Einzelzentrum-Studien, 3 multizentrische Studien

Nachbeobachtung: 16,5 Monate bis 7,5 Jahre

insg. 5.514 Patienten

All studies featured extended follow-up periods; the median follow-up duration ranged from 16.5 months to 7.5 years. The number of included patients ranged from 75 to 2,772, the eight studies included in total 5,514 patients. All but one study [52] used the CTCAE classification criteria, while one study [54] used both CTCAE and RTOG criteria for reporting toxicity outcomes.

heterogenes Tumorstadium: 2 Studien niedriges bis mittleres Risiko, 1 Studie hohes Risiko, 3 Studien keine Angaben, 2 Studien alle Risikoklassen

ADT-Nutzung heterogen in den Studien

In terms of the inclusion criteria in the included studies, all studies included patients with a histologically confirmed diagnosis of PCa, with several studies specifying that participants should not have undergone previous radical treatments such as prostatectomy or significant radiation therapy. The stage of cancer allowed varied across studies: two studies [51, 55] limited inclusion to lower-risk [55] and low- to intermediate risk [51] (early-stage PCa, T1-T2). Other studies [53, 54] included broader stages (from T1 to T3). Specifically high-risk was an inclusion criterion in one study [49]. Three studies [48, 50, 52] did not detail the requirement for risk stage. Differences were also evident in criteria regarding prior cancer treatments and surgeries. Five studies [48-50, 52, 53] specified that previous radiation therapy, or prostatectomy or both were exclusion criteria. Criteria around the use of ADT varied, with some studies requiring participants to be naive to or sufficient time passing since last ADT treatment [48, 51, 52, 54], while others incorporated it as part of the treatment regimen [50, 52, 53].

The studies varied not only in the radiation doses and schedules but also in the technological sophistication of the delivery methods (treatment planning, use of fiducial markers, use of hydrogel spacers, dose conformality) considerably. Standard fractionation (SFRT) was used in one study [50], delivering smaller radiation doses over a longer period. Conventional fractionation, which may involve slightly higher doses per fraction, was applied in another study [52]. Hypofractionation was a focus in several studies: moderate (3-4.7 CGE/day) to extreme (7 CGE/day) hypofractionation schedules were explored [54], with extreme schedules also applied in another study [55]. Both normo-fractionated and moderately hypo-fractionated regimens were investigated in another study [53]. Various total doses across a range of fraction numbers, suggesting potential traditional to slight hypofractionation approaches, were noted in another analysis [48]. Details on fractionation or doses were notably absent in studies by two authors [49, 51].

heterogene Fraktionierungen: Standard, konventionelle, oder Hypofraktionierung (moderat bis extrem und normo- und moderat Regime)

verschiedene Gesamtdosen und Fraktionszahlen

Patient characteristics

The typical age range for participants across the studies was mid-60s to early 70s. One study [53] reported a broader age range of 47 to 86 years for patients undergoing normo-fractionated and moderately hypo-fractionated treatments. Androgen deprivation therapy (ADT) was variably used, with high usage reported in some studies [52, 53], while others did not allow ADT [48, 49, 51]. A significant number of patients presented with T1 and T2 across studies, six studies included patients in over 90% with T1 and T2 [48-52, 54], one study approximately 80% [53] and one study did not provide this information [55]. Six studies [48-50, 52-54] also included patients classified into higher T stages (T3 and T4), albeit in a smaller proportion, ranging from 4% to 20%. Gleason scores predominantly ranged from 6 to 10 across all studies except for one, which did not report such information [55]. One study [51] included Gleason scores 6 and 7 only. Risk stratification varied widely within and across studies as well. Risk categories were established based on NCCN or D'Amico classification criteria. Four studies enrolled patients from all risk categories [50, 52-54], one study only intermediate and high-risk [48] and three studies [49, 51, 55] did not report this information. Patients classified as low risk were included in four studies, with proportions ranging from 5.3% to 34% [50, 52-54]. Five studies [48, 50, 52-54] included patients at intermediate risk, with percentages varying between 30.7% and 54.2%, and high-risk patients, with their presence ranging from 11.4% to 41.4%. Very high risk was noted only in one study [52], with 4.2% of patients falling into this category.

Alter: ähnlich in den Studien, nur 1 Studie mit breiterer Range

heterogene ADT-Nutzung

Tumorstadien: überwiegend T1-T2

Gleason Scores: überwiegend 6-10

Risikostratifikation variiert stark

Risk of bias assessment

The risk of bias assessment is presented in the appendix (Table 8.2-2). The overall risk of bias was assessed as moderate for all studies except one, which was considered to have a low risk of bias [50]. The primary reasons for the moderate risk rating included the non-blinding of outcome assessors and unclear documentation concerning the consecutive recruitment of participants.

Bias-Risiko: moderat in 7 Studien und niedrig in 1 Studie

Table 4.4-1: Study characteristics (prospective cohort studies) with PT (part I)

#	Vargas 2018 [55] (NCT01230866)	Ha 2019 [54] (NCT01709253)
Country	U.S.	Republic of Korea
Comparison	Standard fractionation (SFRT) vs. extreme hypofractionated radiation (EHF)	Moderate fractionation (MFR) vs. EHF
Funding / conflicts of interest (CoI)	Funding: none CoI: none	Funding: National Cancer Center Grant (NCC-1010480, NCC-1310080, NCC-1610590, and NCC-1710060). CoI: none
Setting, time period	Multi-centre, phase 3 RCT, from July 2011 to August 2014	Single-institution, phase 2 RCT
Details of the intervention (number of fractions, total dose, equipment)	SFRT: 38 Gy relative biologic effectiveness (RBE) in 5 fractions EHFRT: 79.2 Gy RBE in 44 fractions	Treatment planning with Eclipse proton beam system (Varian Medical Systems). Hypofractionated schedule and equivalent dose 2 Gy (EQD2) delivered in 5 arms: MFR (arm 1: 3 CGE/day, 20 fractions over 5 weeks; arm 2: 3.6 CGE/day, 15 fractions over 5 weeks, 3 fractions/week; arm 3: 4.7 CGE/day, 10 fractions over 5 weeks, 2 fractions/week) and EHF (arm 4: 7 CGE/day, 5 fractions over 2.5 weeks, 2 fractions/week; arm 5: 7 CGE/day, 5 fractions over 4 weeks, 1 fraction/week). MFR was defined as <5 Gy and EHF as >5 Gy per fraction.
Follow-up period	Median 36 months (max. 48 months)	Median 7.5 years (1.3–9.6 years)
Toxicity classification	CTCAE v4.0	CTCAE v3.0, RTOG (primary outcome)
Inclusion criteria	Histologically confirmed low-risk PCa (T1a-T2a N0 M0, Gleason score >6, PSA <10 ng/mL), no pelvic lymph nodes, age ≥18 years, ECOG performance status 0-1, IPSS score ≤16, AUASI score ≤17	Patients with biopsy-proven ADT-naive PCa, stage T1-3 N0 M0, ECOG performance status 0–2
Number of patients	75	82
Patient characteristics (age – average and range, ADT in %)	Age: NR ADT: NR	Age: 68 (44–85) ADT: 0
Tumour classification (T1-T3) (% of patients)	NR	T1: 35 T2: 54 T3: 11
Gleason Score (% of patients)	NR	≤6: 63 7: 29 8–10: 7
Risk status of patients (D'Amico or NCCN) (% of patients)	NR	*NCCN* Low: 34 Intermediate: 45 High: 21
Loss to follow-up	At 48 months: 70% of patients lost to FU	3 patients died[25]

Abbreviations: ADT: androgen deprivation therapy; AUASI: American Urological Association Symptom Index; CGE: Cobalt Gray Equivalent; CoI: conflict of interest; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EHF: extreme hypofractionated radiation; EQD2: equivalent dose in 2Gy fractions; FU: follow-up; Gy: Gray, MFR: moderate fractionation therapy; NCCN: National Comprehensive Cancer Network; NR: not reported; PCa: prostate cancer; PSA: prostate specific antigen; RBE: relative biologic effectiveness; SFRT: standard fractionation therapy

[25] It was not clearly reported how many patients were lost to follow-up for the toxicity outcomes. However, it was reported that at the 7-year follow-up, data was available for 43 patients (48% lost to FU) for biochemical failure free survival.

Table 4.4-2: Study characteristics (prospective cohort studies) with PT (part II)

Author, Year, Reference	Arimura 2018 [48]	Lee 2018 [50] (NCT01255748)	Mishra 2019 [51] and Hasan 2023 [49] PCG 001-09 trial (NCT01255748)	
Country	Japan	U.S.	U.S.	
Funding / conflicts of interest (CoI)	Funding: NR CoI: none	Funding: Institute of Translational Health Science grant support (UL1 TR002319 from NCATS/NIH). CoI: one author received grants from the NIH/NCI, one author was in a scientific advisory position with Varian Medical Corporation	Funding: American Society of Radiation Oncology (ASTRO) Comparative Effectiveness Grant CoI: one author reported grants from ASTRO Comparative Effectiveness Research and personal fees from Varian.	Funding: Proton Collaborative Group CoI: none
Study type	Prospective observational cohort	Prospective registry	Multi-institutional prospective registry	
Setting, time period	1 centre, from January 2011 to July 2014	1 centre, from 2013 to 2016	10 participating proton centers, from 2009 to 2017	9 centres, from 2009 to 2019
Details of the intervention (number of fractions, total dose, equipment)	70 GyE/28 fr: 30% 74 GyE/37 fr: 42% 78 GyE/39 fr: 28% of patients All patients were treated with 210 MeV horizontal proton beams, produced by a beam-wobbling system (Mitsubishi Electric Corporation).	<79.2 Gy (RBE): 14% ≥79.2 Gy (RBE): 86% All patients received treatment with standard fractionation (1.8–2.0 CGE fractions).	Pencil beam scanning (PBS) and passive scattering/uniform scanning (PS/US)	
Follow-up period	Median 52 months (range 24–76)	2 years	PBS: 16.5 months PS/US: 27.2 months	2 years
Toxicity classification	CTCAE v4.0	CTCAE v4.0.	CTCAE v4.0	
Inclusion criteria	Pathologically confirmed PCa, no metastasis within 3 months before treatment, no prior malignancy within 5 years, no history of surgery and radiotherapy in pelvis; life expectancy of >5 years, rectal endoscopy within 3 months and endoscopic mucosal resection for polyps that were detected on the abdominal wall of the rectum at least 2 weeks before treatment. Patients who declined ADT were enrolled.	Patients treated consecutively with proton beam therapy (PBT) for localized PCa. Patients were excluded for prior radical prostatectomy, prior radiotherapy, treatment with mixed photon and proton radiation, or follow-up <1-year.	Men enrolled on PCG 01-009 with low- to intermediate-risk PCa treated with PBT to the prostate ± seminal vesicles with CFRT to a dose of >75 Gy using passive scatter or PBS techniques. Patients on ADT were excluded, as were patients with a history of prior pelvic radiation.	Men enrolled on PCG 01-009, from which patients were excluded for not meeting localized "high risk" criteria, defined as non-nodal, nonmetastatic adenocarcinoma of the prostate with either Gleason 8 or higher, PSA 20 or higher, or cT3a or higher. Patients were excluded for insufficient for a lack of proton treatment data, for having prior prostate surgery, for receiving SBRT or an EQD2 dose less than 74 Gy.
Number of patients	218	192	1343 (PBS: 283, PS/US: 1105) from the 4278 consecutive prostate patients of the PCG 001-009 trial	605 from the 4278 consecutive prostate patients of the PCG 001-09 trial
Patient characteristics (age in years– average and range, ADT in %)	Age: 65 (39–86) ADT was not allowed.	Age: 68 (50–85) ADT: 37	Age: PBS: 66.6 (SD 6.4), PS/US: 65.2 (SD 7.6), p<0.001 ADT was not allowed.	Age: 71 ADT was not allowed.

Author, Year, Reference	Arimura 2018 [48]	Lee 2018 [50] (NCT01255748)	Mishra 2019 [51] and Hasan 2023 [49] PCG 001-09 trial (NCT01255748)	
Tumour classification (T1-T3) (% of patients)	T1c: 43 T2a: 34 T2b: 5 T2c: 9 T3a: 7 T3b: 1	T1: 54.2 T2a: 25.5 T2b: 13.0 T2c: 2.1 T3-T4: 5.2	cT1: 71.7 cT2a: 17.7 cT2b: 2.9 cT2c: 3	T1c: 46.1 T2a: 18.5 T2b: 11.7 T2c: 11.1 T3a: 7.6 T3b: 5
Gleason Score (% of patients)	6: 9 7: 61 8: 20 ≥9: 10	6: 21.9 3 + 4: 41.7 4 + 3: 18.8 8: 7.3 9–10: 10.4	6: 49.2 7: 50.8	3 + 3: 4.6 3 + 4: 8.6 4 + 3: 6 4 + 4: 49.3 4 + 5 or 5 + 5: 31.6
Risk status of patients (D'Amico or NCCN) (% of patients)	*D'Amico classification* Intermediate: 55 High: 45	*D'Amico classification* Low: 19.8 Intermediate: 54.2 High: 26.0	NR	
Loss to follow-up, n (%)	14 (5)	0	181 (13.4)	At 1-year: 142 At 2-year: 374

Abbreviations: ADT: androgen deprivation therapy; ASTRO: American Society of Radiation Oncology; CFRT: conventional fractionation radiation therapy; CGE: Cobalt Gray Equivalent; CoI: conflict of interest; CTCAE: Common Terminology Criteria for Adverse Events; EQD2: equivalent dose in 2Gy fractions; GyE: Gray equvivalent; NCATS: National Center for Advancing Translational Sciences; NCCN: National Comprehensive Cancer Network; NCI: National Cancer Institute; NIH: National Institute of Health; NR: not reported; PBS: pencil beam scanning; PBT: proton beam therapy; PCA: prostate cancer; PS/US: passive scattering/uniform scanning; PSA: prostate specific antigen; RBE: relative biologic effectiveness; SFRT: standard fractionation therapy

Table 4.4-3: Study characteristics (prospective cohort studies) with PT (part III)

Author, Year, Reference	Sosa 2023 [52]	Takaoka 2023 [53]
Country	U.S.	Japan
Funding / conflicts of interest (CoI)	Funding: Cancer Center Support (Core) Grant CA016672 from NCI CoI: one author received personal fees from RefleXion, another author from Eli Lilly and Elekta; grants and personal fees from C4 Imaging and Hitachi; personal fees from Varian, Boston Scientific, and the National Comprehensive Cancer Network (NCCN); and other support from Breakthrough Chronic Care	Funding: none CoI: none
Study type	Prospective registry	Prospective observational study comparing normo-fractionated proton therapy (NFPT) and moderately hypo-fractionated proton therapy (MHPT)
Setting, time period	Single centre, from May 2006 to January 2020	Single centre, from September 2018 to September 2021
Details of the intervention (number of fractions, total dose, equipment)	PT was delivered by either passive scatter or spot scanning technique. SpaceOAR hydrogel spacers were placed in 56 patients at the treating physician's discretion. All patients were treated to a total dose of 72–79.2 Gy(RBE) at 1.8–2.4 Gy(RBE) per fraction, with most receiving 76 Gy(RBE) (29% of patients) or 78 Gy(RBE) (63% of patients). Androgen deprivation therapy (ADT) was prescribed at the treating physician's discretion.	Plans were generated with PBS of Proteus® One (Ion Beam Applications S.A.). For plan calculation, the RayStation treatment planning system (RaySearch Medical Laboratories) was used with a pencil beam algorithm. Two gold fiducial markers (Gold Anchor; GA Japan Company) were implanted in the prostate and daily patient alignments were achieved by matching the fiducial markers. Hydrogel spacers (SpaceOAR system; Boston Scientific) were implanted. It took 20–30 s to irradiate 3 Gy RBE to the whole clinical target volume (6–9 Gy RBE/min). Neoadjuvant ADT was used for 6 months in intermediate- and high-risk patients, and adjuvant ADT for 2 years in high-risk patients.
Follow-up period	Median 7 years	Median 36 (12-48) and 18 (6-36) months
Toxicity classification	RTOG	CTCAE v4.0
Inclusion criteria	Histologically confirmed PCa; no involved lymph nodes or distant metastases at the time of disease staging; documentation of clinical T category, Gleason score, and pretreatment PSA level to stratify patients; PT consisting of conventionally fractionated or moderately hypofractionated PT only; no prior pelvic RT or local therapy including partial prostatectomy, large volume enucleation, cryotherapy, HIFU, or hyperthermia; no long-term management (>6 months) with ADT alone; no postoperative radiation or combined modality with brachytherapy boost.	Histologically confirmed localised Pca with no metastatic lesion (cT1-T3 NO MO), ECOG performance status of 0-1, no previous irradiation of the pelvic area, organs at risk were not exceeding dose constraints.
Number of patients	2772	227
Patient characteristics (age in years– average and range, ADT in %)	Age: 66 ADT: 59	NFPT and MHPT Age: 73 (47–86) and 71 (49–84) ADT: 95
Tumour classification (T1-T3) (% of patients)	Tx: 0.1 T1a: 0 T1b: 0.3 T1c: 62.4 T2a: 22.2 T2b: 8.4 T2c: 2.8 T3a: 2.4 T3b: 1.0 T3c: 0 T4: 0.3	T1: 8.8 T2: 71.8 T3: 19.4
Gleason Score (% of patients)	6: 25.7 3 + 4: 41.3 4 + 3: 20.2 8: 7.7 9-10: 5.0	6: 14 3+4: 37.4 4+3: 27.3 8-10: 21.1

Author, Year, Reference	Sosa 2023 [52]	Takaoka 2023 [53]
Risk status of patients (D'Amico or NCCN) (% of patients)	*NCCN* Low risk: 23.1 Favourable intermediate risk: 30.7 Unfavourable intermediate risk: 30.7 High risk: 11.4 Very high risk: 4.2	*NCCN* Low risk: 5.3 Intermediate risk: 53.3 High risk: 41.4
Loss to follow-up	0	3 patients discontinued treatment due to acute grade 2 haematuria and miction grade.

Abbreviations: ADT: androgen deprivation therapy; CoI: conflict of interest; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; Gy: Gray; HIFU: high-intensity focused ultrasound; NCCN: National Comprehensive Cancer Network; NCI: National Cancer Institute; NFPT: normo-fractionated proton therapy ; NR: not reported; MHPT: moderately hypo-fractionated proton therapy; PBS: pencil beam scanning; PT: proton therapy; PCa: prostate cancer; PSA: prostate specific antigen; RBE: relative biologic effectiveness; RT: radiation therapy.

4.4.2 Results

Acute GI and GU toxicity (that is less than three months follow-up) was reported in five [49-52, 54] and six studies [49-54], respectively. GI and GU toxicity with longer than three months follow-up was reported in seven studies [48-54]. One study [54] did not specify the follow-up duration but mentioned that acute GI and GU toxicity was measured; hence, it has been included in the analysis for toxicities assessed within three months, aligning with our definition of acute. The same study lacked a clear definition of the length of follow-up for late GI and GU toxicity, hence it has been included in the analysis for toxicities over a three-month follow-up period. Three studies reported toxicities other than GI and GU: skin and tissue [51], erectile dysfunction [49, 50] and hip fractures [50] were reported in these studies. One study [52] utilised the RTOG classification system, while the others used the CTCAE.

Akute GI/GU-Toxizität (<3 Monate): in 5 bzw. 6 Studien

GI/GU-Spättoxizität (>3 Monate): in 7 Studien

unklare Follow-up-Dauer: 1 Studie

Toxicity at < 3 months

GI toxicity assessed within a three-month follow-up period was evaluated in five prospective cohort studies [49-52, 54] (n=4,994). Not all studies provided data for every toxicity grade, with variations reported between one and five studies. The observed toxicity levels were as follows: grade 0 in 85% of cases, grade 1 varied from 10.3% to 19.6% (unweighted mean: 13.3%), grade 2 ranged from 0% to 21.8% (unweighted mean: 5.2%), and grade 3 ranged from 0% to 0.5% (unweighted mean: 0.02%). Both grades 4 and 5 showed no occurrences (0%).

5 Studien, 4.994 Patienten

Grad 0: 85%
Grad 1: 10,3% bis 19,6%
Grad 2: 0% bis 21,8%
Grad 3: 0% bis 0,5%
Grad 4 und 5: 0%

GU toxicity was assessed within a follow-up period of up to three months in six prospective cohort studies [49-54] (n=5,221). Not all studies reported data for each toxicity grade, with variations reported between one and six studies. In terms of toxicity levels, 26% of patients experienced no toxicity (grade 0). Grade 1 toxicity varied from 32.3% to 70.2% (unweighted mean: 44.8%), grade 2 ranged from 5% to 44.8% (unweighted mean: 27.9%), grade 3 fluctuated from 0% to 0.5% (unweighted mean: 0.2%), and grade 4 was extremely rare at 0% to 0.03% (unweighted mean: 0.03%).

6 Studien, 5.221 Patienten
Grad 0: 26%
Grad 1: 32,3% bis 70,2%
Grad 2: 5% bis 44,8%
Grad 3: 0% bis 0,5%
Grad 4: 0% bis 0,03%

Hip fracture and pain toxicity were extremely rare, with only 1% of patients experiencing grade 2 toxicity in one study [50] (n=192). **Skin and tissue** toxicities were observed as grade 1 in 13% of patients and grade 2 in 4% of patients in one study [51] (n=1,343).

Hüftfraktur und Schmerzen: sehr selten
Haut- und Gewebetoxizität:
Grad 1: 13%.
Grad 2: 4%

Toxicity at > 3 months

7 Studien, 5.287 Patienten

Grad 0: 31%
Grad 1: 18,6% bis 52%
Grad 2: 3,9% bis 15%
Grad 3: 0% bis 2%
Grad 4: 0% bis 0,25%
Grad 5: 0%
Kumulative Ergebnisse:
1. Studie: Grad 2 stieg über 48 Monate
2. Studie: Grad ≥2 nach 24 Monaten: 21,3%
3. Studie: Grad 2 von 6 bis 24 Monate: 3,9%

GI toxicity was assessed over various follow-up periods up to 48 months in seven prospective cohort studies [48-52, 54, 55] (n=5,287). Not all studies reported on each toxicity grade, with reports varying between one and five studies; additionally, two studies [48, 55] provided only cumulative results. Regarding toxicity levels, 31% of patients experienced no toxicity (grade 0). Grade 1 toxicity varied from 18.6% to 52% (unweighted mean: 25%), grade 2 ranged from 3.9% to 15% (unweighted mean: 6.6%), grade 3 fluctuated from 0% to 2% (unweighted mean: 0.6%), and grade 4 was very rare at 0% to 0.25% (unweighted mean: 0.2%). No occurrences of grade 5 toxicity were reported (0%). In one study [55], cumulative toxicity for grade 2 was reported at various time points until 48 months and showed an increase over time: 8% at 6 months, 9% at 12 months, 13% at 18 months, 17% at 24 months, 18.7% at both 36 and 48 months. In another study [50] cumulative grade ≥2 at 24 months was 21.3% (95% CI, 13.9% to 28%). In a third study [48] reporting cumulative results, 3.9% was the cumulative grade 2 toxicity from six months until the 24-month follow-up.

7 Studien, 5.287 Patienten

Grad 0: 62%
Grad 1: 17,1% bis 40,3%
Grad 2: 5,8% bis 16%
Grad 3: 0,8% bis 1,7%
Grad 4: 0% bis 0,07%
Kumulative Ergebnisse:
1. Studie: Grad 2 stieg über 48 Monate
2. Studie: Grad 2 von 7 bis 46 Monate: 3,4%
3. Studie: Grad ≥2 über 24 Monate: 26,4%

GU toxicity over varied follow-up periods up to 48 months was evaluated in seven prospective cohort studies [48-52, 54, 55] (n=5,287). Reports on each toxicity grade varied between one and four studies; two studies [48, 55] provided only cumulative results, and two studies [48, 49] reported per protocol results only. Concerning toxicity levels, 62% of patients experienced no toxicity (grade 0). Grade 1 toxicity varied from 17.1% to 40.3% (unweighted mean: 24.8%), grade 2 ranged from 5.8% to 16% (unweighted mean: 13.5%), Grade 3 fluctuated from 0.8% to 1.7% (unweighted mean: 0.9%), and grade 4 was extremely rare at 0% to 0.07% (unweighted mean: 0.06%). In one study [55], cumulative toxicity for grade 2 was reported at various time points and showed an increase over time: 12% at six months, 20% at 12 months, 22.7% at 18 months, 28% at both 24 and 36 months, and 32% at 48 months. Another study [48] reported the cumulative grade 2 events from 7 to 46 months at a rate of 3.4%. In the third study [50] reporting cumulative events, the grade ≥2 toxicity at 24 months was reported as 26.4% (95% CI, 13.8% to 31.3%).

Hüftfrakturen und Schmerzen: sehr selten

Hip fractures and pain remained extremely rare in the longer-term, with 1.5% of patients experiencing grade 2 and grade 3 toxicities in one study [50] (n=192).

Haut- und Gewebetoxizität: Grad 1 und 2: 21%, Grad 3 < 1%

Skin and tissue toxicity were reported at 21% for both grade 1 and grade 2, with grade 3 occurrences being very rare, just below 1% [51] (n=1,343).

Erektile Dysfunktion: Grad ≥2 in >50%; und kumulative Grad 2 in >23%

Two studies (n=423) indicate that **erectile dysfunction** was more common with grade 2 and higher toxicity being present in over 50% of patients and in one study [51] and cumulative grade 2 and higher toxicity being present in 23% of patients (95% CI, 14-31) in the other study [50].

Table 4.4-4: Safety results with PT (prospective cohort studies) (part I)

Safety endpoints: toxicity						
Author, year, reference	**Ha 2019 [54]**	**Lee 2018 [50]**	**Mishra 2019 [51]**	**Hasan 2023 [49]**	**Sosa 2023 [52]**	**Takaoka 2023 [53]**
Complications (CTCAE-classification) *RTOG classification < 3 months follow-up	*Acute toxicity (<1 month))* **GI** Grade 0: 70/82 (85%) Grade 1: 12/82 (15%) Grade 2: 0% **GU** Grade 0: 21/82 (26%) Grade 1: 57/82 (70%) Grade 2: 4/82 (5%)	*Acute toxicity (<3 months)* **GI** Grade 2: 5/192 (2.6%) Grade 3: 1/192 (0.5%) Grade 4: 0% Grade 5: 0% **GU** Grade 2: 86/192 (44.8%) Grade 3: 1/192 (0.5%) **Hip fracture or pain** Grade 2: 2/192 (1%)	*Acute toxicity (<3 months)* **GI** Grade 1: 263/1343 (19.6%) Grade 2: 31/1343 (2.3%) Grade 3: 0/1343 (0%) **GU** Grade 1: 943/1343 (70.2%) Grade 2: 216/1343 (16%) Grade 3: 3/1343 (0.2%) **Skin and tissue** Grade 1: 172/1343 (12.8%) Grade 2: 56/1343 (4.2%) Grade 3: 0%	*Acute toxicity (<3 months)* **GI** Grade 2: 132/605 (21.8%) Grade 4: 0/605 (0%) Grade 5: 0/605 (0%) **GU** NR	*Acute toxicity (<3 months)* **GI*** Grade 1: 285/2772 (10.3%) Grade 2: 90/2772 (3.2%) Grade 3: 0/2772 (0%) Grade 4: 0/2772 (0%) **GU*** Grade 1: 896/2772 (32.3%) Grade 2: 905/2772 (32.6%) Grade 3: 5/2772 (0.2%) Grade 4: 1/2772 (0.03%)	*Acute toxicity (<3 months)* **GI** NR **GU** Grade 1: 85/227 (37.4%), **p=0.02** Grade 2: 78/227 (34.4%), **p=0.02** Grade ≥3: 0%
Complications (CTCAE-classification) *RTOG classification > 3 months follow-up	*Late toxicity (timeframe not defined)* **GI** Grade 0: 25/82 (31%) Grade 1: 43/82 (52%) Grade 2: 12/82 (15%) Grade 3: 2/82 (2%) **GU** Grade 0: 51/82 (62%) Grade 1: 23/82 (28%) Grade 2: 8/82 (10%)	*Late toxicity (>3 months)* **GI** Cumulative grade ≥2 at 2-years: 34 (21.3%; 95% CI, 13.9 to 28.0%) Grade 3: 2/192 (1%) Grade 4: 0% Grade 5: 0% **GU** Cumulative grade ≥2 at 2-years: 51 (26.4%; 95% CI, 19.4 to 32.9%) Grade 3: 2/192 (1%) Grade 4: 0% Grade 5: 0% **Erectile dysfunction** Cumulative grade ≥2 at 2-years: 23.0% (95% CI, 13.8 to 31.3%) Grade 3: 2/192 (1%) **Hip fracture or pain** Grade 2: 3/192 (1.5%) Grade 3: 3/192 (1.5%)	*Late toxicity (>3 months)* **GI** Grade 1: 250/1343 (18.6%) Grade 2: 81/1343 (6%) Grade 3: 1/1343 (<0.1%) **GU** Grade 1: 542/1343 (40.3%) Grade 2: 144/1343 (10.7%) **Skin and tissue** Grade 1: 290/1343 (21.6%) Grade 2: 291/1343 (21.7%) Grade 3: 9/1343 (0.6%)	*Late toxicity (>3 months)* **GI** Grade 2: 23/463 (5%) **GU** Grade 2: 27/463 (5.8%) Grade 3: 8/463 (1.7%) **Erectile dysfunction** (at 2-year FU, n=231) Grade 2: 111/231 (48%) Grade 3: 19/231 (8%)	*Late toxicity (>3 months)* **GI*** Grade 1: 760/2772 (27.4) Grade 2: 199/2772 (7.2) Grade 3: 21/2772 (0.75) Grade 4: 7/2772 (0.25) **GU*** Grade 1: 475/2772 (17.1) Grade 2: 449/2772 (16.2) Grade 3: 22/2772 (0.8) Grade 4: 2/2772 (0.07)	NR

Table 4.4-5: Safety results with PT (prospective cohort studies) (part II)

Safety endpoints: toxicity		
Author, year, reference	**Vargas 2018 [55]**	**Arimura 2018 [48]**
Complications (CTCAE-classification) ***RTOG classification,** **> 3 months follow-up**	**GI** *Cumulative* grade 2 At 6 months: 6/75 (8%) At 12 months: 7/75 (9%) At 18 months: 10/75 (13%) At 24 months: 13/75 (17%) At 36 months: 14/75 (18.7%) At 48 months: 14/75 (18.7%) Grade 3: 0% **GU** *Cumulative* grade 2 At 6 months: 9/75 (12%) At 12 months: 15/75 (20%) At 18 months: 17/75 (22.7%) At 24 months: 21/75 (28%) At 36 months: 21/75 (28%) At 48 months: 24/75 (32%) Grade 3: 0%	**GI** Cumulative grade ≥2: At <6-month FU: 0% At >6 and <24-month FU: 8/204 (3.9%)[26] Grade ≥3: 0% **GU** Cumulative grade ≥2: At <7-month FU: 48/204 (23.5%)[27] At >7 month and <46-month FU: 7/204 (3.4%)[28] Grade ≥3: 0%

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; GI: gastrointestinal; GU: genitourinary; RTOG: Radiation Therapy Oncology Group

[26] The percentage was reported in the publication and the number of events. The number of patients was calculated by the review authors, and it corresponds to the per protocol, population.

[27] The percentage was reported in the publication and the number of events. The number of patients was calculated by the review authors, and it corresponds to the per protocol, population.

[28] The percentage was reported in the publication and the number of events. The number of patients was calculated by the review authors, and it corresponds to the per protocol, population.

4.4.3 Certainty of the evidence

Vertrauenswürdigkeit der Evidenz „niedrig" für alle Endpunkte

The overall certainty of the evidence for all outcomes (GI and GU toxicities at all timepoints) was assessed to be low due to the observational study design, and the wide variations in the reporting of toxicities, especially grade 1 and 2. Additionally, one study [55] failed to report on clear baseline patient characteristics. Detailed evidence profile for the toxicity results is displayed in Table 4.4-6.

Table 4.4-6: Evidence profile of PT: Safety

№ of studies/ patients	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect	Certainty
Outcome: GI toxicity (<3 months)								
5/4994 [49-52, 54]	Prospective cohort	Serious[a]	Serious[b]	Not serious	Not serious	Not all studies reported on all grades (reporting varied between 1 and 5 studies). One study [52] used a different classification system.	Grade 0: 85% Grade 1: 13.3% (range 10.3% to 19.6%) Grade 2: 5.2% (range 0% to 21.8%) Grade 3: 0.02% (range 0% to 0.5%) Grade 4: 0% (range 0% to 0%) Grade 5: 0% (range 0% to 0%)	Low
Outcome: GU toxicity (<3 months)								
6/5221 [49-54]	Prospective cohort	Serious[a]	Serious[b]	Not serious	Not serious	Not all studies reported on all grades (reporting varied between 1 and 6 studies). One study [52] used different classification system.	Grade 0: 26% Grade 1: 44.8% (range 32.3% to 70.2%) Grade 2: 27.9% (range 5% to 44.8%) Grade 3: 0.2% (range 0 to 0.5%) Grade 4: 0.03% (range 0 to 0.03%)	Low
Outcome: GI toxicity (>3 months)								
7/5287 [48-52, 54, 55]	Prospective cohort	Serious[a]	Serious[b]	Not serious	Not serious	Patient baseline characteristics are not described in one study [55]. Definition of "late" was not available in some studies. Not all studies reported on all grades (reporting varied between 1 and 5 studies) and some studies reported only cumulative results. One study [52] used a different classification system.	Grade 0: 31% Grade 1: 25% (range 18.6% to 52%) Grade 2:6.6% (range 3.9% to 15%) Grade 3: 0.6% (range 0% to 2%) Grade 4: 0.2% (range 0% to 0.25%) Grade 5: 0% (range 0% to 0%) Cumulative grade 2: At 6 months: 8% At 12 months: 9% At 18 months: 13% At 24 m: 17% At 36 m: 18.7% At 48 m: 18.7% From 6 to 24 m: 3.9% Cumulative grade ≥2 at 2 years: 21.3% (95% CI, 13.9% to 28%)	Low
Outcome: GU toxicity (>3 months)								

7/5287 [48-54]	Prospective cohort	Serious[a]	Serious[b]	Not serious	Not serious	Patient baseline characteristics are not described in one study [55]. Definition of "late" was not available in some studies. Not all studies reported on all grades (reporting varied between 1 and 4 studies) and some studies reported only cumulative results. One study [52] used a different classification system.	Grade 0: 62% Grade 1: 24.8% (range 17.1% to 40.3%) Grade 2: 13.5 % (range 5.8% to 16%) Grade 3: 0.9 (range 0.8% to 1.7%) Grade 4: 0.06 (range 0% to 0.07%) Cumulative grade 2: At 6 months: 12% At 12 months: 20% At 18 months: 22.7% At 24 m: 28% At 36 m: 28% At 48 m: 32% From 7 to 46 m: 3.4% Cumulative grade ≥2 at 2 years: 26.4% (95% CI, 13.8% to 31.3%) and 28%	Low

[a] *Prospective observational study design with mainly moderate risk of bias.*

[b] *Very wide range of grade 1 and 2 toxicities.*

5 Discussion

This update report aimed to identify the latest evidence since the 2018 report on the effectiveness and safety of the three interventions potentially suitable for the primary treatment of localised, non-metastatic PCa (IRE, SBRT and PT) in comparison to a range of other treatment options for this indication (e.g., prostatectomy, hormone therapy, active surveillance).

untersucht wurden 3 Interventionen, die prinzipiell für die primäre Behandlung von lokalisiertem nicht-metastasierten PCa in Frage kommen

5.1 Summary of the evidence

Compared to the report from 2018, the current update continues to highlight the need for high-quality RCTs to provide definitive conclusions regarding the effectiveness and safety of IRE, SBRT, and PT. While some new evidence has emerged for SBRT, the findings remain inconclusive, and the need for rigorous, long-term studies persists across all three interventions.

2018 und Update-Report: Bedarf an qualitativ hochwertigen RCTs

For IRE, the evidence base remains unchanged with no RCTs identified in both the 2018 report and the current update. In lack of RCTs, no definitive conclusions on efficacy are feasible, and the certainty of the evidence regarding toxicity remains very low to low. Nonetheless, toxicity assessments indicate a general trend of decreasing toxicity over time.

IRE: weiterführend keine RCTs

For SBRT, the 2018 report found no RCTs and relying on observational studies found similar acute GU and GI toxicity rates to conventional photon therapy, a type of EBRT. The current update identified three RCTs providing moderate certainty evidence for survival outcomes, indicating no significant difference between SBRT and CFRT. Bowel symptoms showed mixed results across studies. Sexual and hormonal symptoms were generally better in the SBRT arms. For urinary symptoms, there was no difference in the short-term, but a significant worsening in urinary incontinence was observed with SBRT compared to CFRT in longer-term follow-ups, while no difference was found in urinary obstructive symptoms. Low certainty evidence from the RCTs suggest that acute GU toxicity is lower with SBRT compared to the control intervention, but long-term results show mixed trends with moderate certainty. In the single-arm studies, approximately half of the patients experienced no acute toxicity or only mild toxicity and this number even increased with time, however, the certainty of evidence is low. For acute GI toxicity the evidence was likewise of low certainty for shorter-term outcomes, while it was moderate for two- and five-year outcomes. There were significantly less cumulative grade ≥1 GI toxicities in the SBRT group compared to the control group at the end of treatment, with this difference persisting at one year. Beyond two years there was no difference. Single-arm studies showed no or primarily grade 1 acute toxicities.

SBRT: neue RCTs, moderate Evidenzqualität, keine Unterschiede in Überleben,

heterogene Ergebnisse in Lebensqualität

GU-Toxizität: akut niedriger bei SBRT, langfristig heterogene Trends

GI-Toxizität: akut niedriger bei SBRT, langfristig kein Unterschied

For PT, the 2018 report included RCTs that were methodologically flawed and did not compare PT directly with traditional therapies, showing no significant effect on overall survival and mixed results on biochemical relapse-free survival. Quality of evidence was low to moderate. In the current update no new RCTs could be identified. Low certainty evidence indicates differing trends in GI and GU toxicities. Short-term follow-up shows higher GU toxicity compared to GI, but long-term follow-up reveals a decrease in GU toxicity and a persistent presence of mild GI symptoms. Cumulative GU toxicity increases over time, indicating a need for long-term monitoring. The findings of the update report are summarised briefly below in Table 5.1-1.

PT: keine neuen RCTs, geringe Evidenzqualität, heterogene GI- und GU-Toxizität-Ergebnisse

Table 5.1-1: Summary of the evidence of the update report

Result	IRE	SBRT	PT
Included studies	No RCTs, 5 observational studies	3 new RCTs, 2 new observational studies	No new RCTs, 8 new observational studies
Included total population	846	2,598	5,514
Effectiveness findings (survival, QoL, avoidance of prostatectomy)	NA	**Survival**: *Overall survival* at 2 years: 98.6% vs 99%, at 5 years: 93.7% vs. 96.4% (HR 1.11, 95% CI, 0.73 to 1.69) *Disease-specific survival* at 2 years: no difference, at 5 years 98.2% vs. 99.8% *Metastases-free survival* at 2 years: 99.5% vs. 99.7% and at 5 years 98.7% vs. 98.3% *Biochemical failure-free survival*: no difference **QoL**: *Bowel* symptoms: mixed results *Sexual* and *hormonal* symptoms: better in the SBRT arms *Urinary* symptoms: no difference on the short-term, significant worsening in urinary incontinence with SBRT vs. CFRT on longer-term follow-ups, no difference in urinary obstructive symptoms.	NA
Safety findings (acute and late toxicities)	**Acute** (organ class not reported): Grade 1: 0.5%-47.2%, Grade 2: 0.8%-12.3% **Late** (organ class not reported): Grade 2: 0.6% at 24 months; no toxicity at 48 months	**Acute**: *GI*: cumulative grade 1: 35% vs. 87% (p<0.0001), grade ≥2: < 6% *GU*: cumulative grade ≥1: 87% vs. 100% (p=0.04); approx. 50% no toxicity or grade 1 in the single-arm studies at end of treatment, approx. 90% no toxicity or grade 1 at 3 months **Late**: *GI*: 64% vs. 84%, p=0.033 at 1 year, no difference beyond 2 years *GU*: grade ≥2: 6% vs. 2% (p=0.0037) at 1 year; cumulative grade ≥2: 18.3% vs. 10.6% (HR 1.80; 95% CI, 1.25 to 2.61) at 2 years	**Acute**: *GI*: 85% no toxicity, grade 1: 13%, grade 2: 5%, grade 3: <1% *GU*: 26% no toxicity, grade 1: 45%, grade 2: 28%, grade 3: <1% **Late**: *GI*: 31% no toxicity, grade 1: 25%, grade 2: 6.6% *GU*: 62% no toxicity, cumulative grade 2: 12% at 6 months, 32% at 48 months
Conclusion	Inconclusive, low certainty evidence, long-term monitoring needed	Moderate certainty for non-inferiority of SBRT compared to CFRT in low and intermediate risk PCa, low certainty evidence on acute toxicity results favouring SBRT and moderate certainty evidence on mixed long-term toxicity results.	Low certainty evidence, long-term monitoring needed

Abbreviations: CFRT: conventionally fractionated radiation therapy; CI: confidence interval; GI: gastrointestinal; GU: genitourinary; HR: hazard ratio; IRE: irreversible electroporation; PT: proton therapy; SBRT: stereotactic body radiation therapy; QoL: quality of life

Interpretation of findings

The results of this review are in line with the current clinical practice guidelines and other recent SRs. For IRE, our review and other SRs [56-61] emphasise the need for high-quality comparative studies with long-term follow-up, considering it promising treatment option with minimal complications. Clinical practice guidelines also highlight that IRE is still experimental and should only be used in clinical trials due to the lack of robust evidence.

IRE. experimentell, Bedarf an hochwertigen RCTs

Leitlinien: nur in klinischen Studien empfohlen, Evidenz unzureichend

Concerning SBRT, our findings, along with other SRs [62-64], generally regard SBRT as a safe and effective treatment option for PCa. Our review found no significant difference between SBRT and CFRT in terms of survival outcomes, with a lower rate of acute toxicity observed with SBRT. However, long-term results remain uncertain. Other SRs also advise against SBRT becoming standard practice, especially in high-risk PCa, without more robust evidence and extensive follow-up. Guidelines align with these findings in terms of the extent of their recommendations: the AUA/ASTRO guidelines recommend SBRT for low and intermediate-risk PCa, the EAU guidelines recommend it only for intermediate-risk PCa, while the AWMF guidelines suggest its use only in clinical trials due to limited evidence.

SBRT: sicher und effektiv, geringere akute Toxizität als mit CFRT, aber Langzeitergebnisse sind unsicher,

nicht als Standardpraxis empfohlen

Leitlinien: uneinheitliche Empfehlungen

Regarding PT, our 2018 report found no significant effect on overall survival and mixed results on biochemical relapse-free survival. In this update, no new evidence was found that would enable us to draw conclusions on effectiveness. The toxicity results show a trend that GU toxicities decreased over time, but GI toxicities persisted. However, cumulative GU toxicity also increased. A recent SR [65] also concluded that PT, compared with photon therapy, may result in similar overall survival and progression-free survival but may result in fewer toxicity events. Though, the certainty of evidence was rated as low, preventing any definitive conclusions. Clinical guidelines recommend PT only in clinical trials, emphasising the insufficient evidence for its broader use.

PT: keine neuen RCTs, GU-Toxizität nahm im Laufe der Zeit ab, GI-Toxizitäten blieben

Leitlinien: nur in klinischen Studien empfohlen, Evidenz unzureichend

Limitations of the evidence

The standardisation of definitions presents a significant challenge in the field, particularly concerning the categorisation of fractionation (moderate or extreme) and the parameters for focal therapy. Similarly, in both SBRT and PT, debates concerning the optimal dosage and the number of fractions remain unresolved.

Standardisierung der Definitionen (Fraktionierungen, Parameter der fokalen Therapie, optimale Dosierungen)

Often, different fractionation of SBRT and PT are compared with each other, but there were no studies comparing any of the interventions of our interest with more conventional therapy such as radical prostatectomy or watchful waiting. The different fractionation in the PT studies showcase different treatment intensities aimed at increasing therapy convenience and enhancing efficiency.

keine Vergleiche mit Standardtherapien

The inclusion criteria in the analysed studies sometimes allowed previous cancer treatments, which might be potential confounding factors that we cannot rule out.

heterogene Einschlusskriterien

Toxicity assessments vary widely, not only in the timeframes considered but also in the classification systems employed, leading to occasional reports of unclear toxicity data. Additionally, there are instances where studies neglect to report on all toxicity grades, without clarifying whether certain grades were not measured or if there were no occurrences of those grades. Statistical hypotheses and p-values are seldom provided in toxicity assessments, which hampers the ability to draw statistically significant conclusions.

variierende Zeitrahmen und Klassifikationssysteme

minimaler klinisch relevanter Unterschied (MCID) und p-Werte oft nicht berichtet

In terms of QoL outcomes, the minimum clinically important difference (MCID) is often not reported, and the scarcity of reported p-values further complicates the drawing of definitive conclusions. This lack of detailed statistical reporting underscores the challenges in interpreting and comparing the efficacy and safety outcomes.

„Losses to Follow-up" bei Langzeitbeobachtungen, mögliche Unterschätzung der Nebenwirkungen

The studies exhibited varying degrees of reliance on per-protocol analyses and given the significant proportion of patients lost to follow-up—particularly noticeable in the assessments of long-term toxicity—the results presented may potentially underestimate the true incidence of adverse effects.

Limitations of the report

nur RCTs zur Bewertung der Wirksamkeit

Only studies of the highest evidence level (RCTs) were used to evaluate the endpoints for efficacy in this analysis.

kleine und retrospektive Beobachtungsstudien wurden ausgeschlossen

Smaller case studies (<50 patients for PT and IRE and <200 patients for SBRT) were excluded from the safety assessment, as well as retrospective studies, as they pose a high risk of bias.

heterogene Studien, keine Meta-Analyse möglich

The included studies exhibited considerable heterogeneity in terms of risk categories, precluding the possibility of conducting a meta-analysis.

Ongoing Studies

laufende Studien

Thirteen ongoing randomised clinical studies with SBRT, five studies with IRE (three RCTs and two larger prospective observational studies), and eight with PT (one RCT and seven larger observational studies) were identified (see Tables Table 8.3-1, Table 8.3-2, Table 8.3-3). The biggest evidence gaps are for IRE and PT, hence the RCTs which compare IRE with radical prostatectomy with an estimated completion date in 2025 and 2026 (one study in 2031), and the study comparing PT with IMRT with an estimated completion in 2027 are highly anticipated.

6 Conclusion

unzureichende Evidenz für IRE, SBRT, PT als Ersatz für radikale Verfahren

SBRT bei niedrigem bis mittlerem Risiko nicht unterlegen gegenüber konventioneller Fraktionierung

weitere Forschung zur Langzeitwirksamkeit und Sicherheit nötig

Due to a limited and inconclusive body of evidence on SBRT, as well as the lack of comparative studies on PT and IRE, it cannot be determined whether IRE, SBRT, and PT can replace or prevent radically invasive procedures such as prostatectomy, or whether these therapies provide a significant benefit to patients in terms of improved QoL or survival chances. The current evidence indicates only that SBRT is non-inferior to conventional fractionation in terms of survival outcomes for low-to intermediate-risk cancer patients. Further high-quality research is required to demonstrate the long-term efficacy and safety of these therapies in comparison with standard treatments. Currently, several studies are underway, including a few RCTs that involve comparisons with conventional technologies and thus should enable statements on efficacy and safety.

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8 Appendix

8.1 Search strategy

Search strategy Cochrane CENTRAL

Date of search: 21.02.2024	
ID	Search
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	(prostat* near (cancer* or neoplasm* or carcinoma* or tumo*r* or adenoma* or adeno*carcenoma* or adeno-carcenoma* or sarcoma* or malignan* or lump* or mass or masses)) (Word variations have been searched)
#3	#1 or #2
#4	(primary or locali?ed or "stage I" or "stage II" or "stage 1" or "stage 2" or stageI or stageII or stage1 or stage2 or "stage one" or "stage two") (Word variations have been searched)
#5	#3 AND #4
#6	MeSH descriptor: [Radiosurgery] explode all trees
#7	((stereotactic* or hypo*fractionat* or hypo-fractionat*) near (therap* or radio*therap* or radio-therap* or irradiat* or radio*surg* or radio-surg* or surg* or technique*)) (Word variations have been searched)
#8	MeSH descriptor: [Radiation Dose Hypofractionation] explode all trees
#9	MeSH descriptor: [Stereotaxic Techniques] explode all trees
#10	SBRT:ti,ab,kw (Word variations have been searched)
#11	SABR:ti,ab,kw (Word variations have been searched)
#12	SRS:ti,ab,kw (Word variations have been searched)
#13	(cyber*Kni?e*) (Word variations have been searched)
#14	(cyber-Kni?e*) (Word variations have been searched)
#15	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	MeSH descriptor: [Proton Therapy] explode all trees
#17	((proton* or particle*) near (therap* or radiotherap*)) (Word variations have been searched)
#18	(proton*therap*) (Word variations have been searched)
#19	(proton-therap*) (Word variations have been searched)
#20	MeSH descriptor: [Protons] explode all trees
#21	((proton* or particle*) near beam*) (Word variations have been searched)
#22	PBT:ti,ab,kw (Word variations have been searched)
#23	#16 or #17 or #18 or #20 or #21 or #22
#24	MeSH descriptor: [Electroporation] explode all trees
#25	MeSH descriptor: [Electric Stimulation] explode all trees
#26	MeSH descriptor: [Nanotechnology] explode all trees
#27	(nano*kni?e*) (Word variations have been searched)
#28	(nano-kni?e*) (Word variations have been searched)
#29	(irrevers* near (electro*por* or electro-por* or electro*permeab* or electro-permeab*)) (Word variations have been searched)
#30	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#31	IRE:ti,ab,kw (Word variations have been searched)
#32	(LEDC):ti,ab,kw (Word variations have been searched)
#33	MeSH descriptor: [Electrochemotherapy] explode all trees
#34	(electro*chemo*) (Word variations have been searched)
#35	(electro-chemo*)
#36	MeSH descriptor: [Ablation Techniques] explode all trees
#37	((tissue* OR tumo*r*) near ablat*) (Word variations have been searched)

#38	(bipolar near (puls* or electrod* or mode*)) (Word variations have been searched)
#39	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 OR #16 or #17 or #18 or #20 or #21 or #22 OR #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #36 or #37 or #38
#40	#5 AND #39
#41	#5 AND #39 with Publication Year from 2018 to 2024, in Trials
#42	#5 AND #39 with Cochrane Library publication date Between Feb 2018 and Feb 2024
#43	#41 OR #42
#44	English:la
#45	German:la
#46	#44 OR #45
#47	#43 AND #46
#48	(conference proceeding):pt
#49	(abstract):so
#50	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#51	#48 OR #49 OR #50
#52	#47 NOT #51
195 Hits	

Search strategy CRD (Centre for Reviews and Dissemination)

Total hits: 7

Date of search: 21.02.2024

Search step #	Search query,"Hits","Searched At"
#43	(((((bipolar) AND (puls* or electrod* or mode*)) OR ((tissue* or tumor* or tumour*) AND (ablat*)) OR ("Ablation Techniques"[mhe]) OR (electro-chemo*) OR (electrochemo*) OR ("Electrochemotherapy"[mhe]) OR (LEDC) OR (IRE) OR ((electric*) AND (field* or stimul* or pulse* or cell* or membrane* or pore*)) OR ((irrevers*) AND (electropor* or electro-por* or electropermeab* or electro-permeab*)) OR (NanoKnive*) OR (Nano-Knive*) OR (Nano-Knife*) OR (NanoKnife*) OR ("Nanotechnology"[mhe]) OR ("Electric Stimulation"[mhe]) OR ("Electroporation"[mhe]) OR (PBT) OR ("Protons"[mhe]) OR ((proton* OR particle*) AND (therap* or radiotherap* or radio-therap* OR beam*)) OR (proton-therap*) OR (protontherap*) OR ("Proton Therapy"[mhe]) OR (Cyber-Knive*) OR (CyberKnive*) OR (Cyber-Knife*) OR (CyberKnife*) OR (SRS) OR (SABR) OR (SBRT) OR ("Stereotaxic Techniques"[mhe]) OR ("Radiation Dose Hypofractionation"[mhe]) OR ((stereotactic* or stereotactic* or hypofractionat* or hypo-fractionat*) AND (therap* or radiotherap* or radiotherap* or irradiat* or radiosurg* or radio-surg* or surg* or technique*)) OR ("Radiosurgery"[mhe])) AND ((primary or localised or localized or stage I or stage II or stage 1 or stage 2 or stageI or stageII or stage1 or stage2 or stage one or stage two) AND (((prostat*) AND (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or adenoma* or adenocarcinoma* or adeno-carcinom* or sarcoma* or malignan* or lump* or mass or masses)) OR ("Prostatic Neoplasms"[mhe])))) AND (English OR German)[Language]) FROM 2018 TO 2024,"7","2024-02-22T11:42:17.000000Z"
#42	((((bipolar) AND (puls* or electrod* or mode*)) OR ((tissue* or tumor* or tumour*) AND (ablat*)) OR ("Ablation Techniques"[mhe]) OR (electro-chemo*) OR (electrochemo*) OR ("Electrochemotherapy"[mhe]) OR (LEDC) OR (IRE) OR ((electric*) AND (field* or stimul* or pulse* or cell* or membrane* or pore*)) OR ((irrevers*) AND (electropor* or electro-por*

	or electropermeab* or electro-permeab*)) OR (NanoKnive*) OR (Nano-Knive*) OR (Nano-Knife*) OR (NanoKnife*) OR ("Nanotechnology"[mhe]) OR ("Electric Stimulation"[mhe]) OR ("Electroporation"[mhe]) OR (PBT) OR ("Protons"[mhe]) OR ((proton* OR particle*) AND (therap* or radiotherap* or radio-therap* OR beam*)) OR (proton-therap*) OR (protontherap*) OR ("Proton Therapy"[mhe]) OR (Cyber-Knive*) OR (CyberKnive*) OR (Cyber-Knife*) OR (CyberKnife*) OR (SRS) OR (SABR) OR (SBRT) OR ("Stereotaxic Techniques"[mhe]) OR ("Radiation Dose Hypofractionation"[mhe]) OR ((stereotactic* or stereotactic* or hypofractionat* or hypo-fractionat*) AND (therap* or radiotherap* or radiotherap* or irradiat* or radiosurg* or radio-surg* or surg* or technique*)) OR ("Radiosurgery"[mhe])) AND ((primary or localised or localized or stage I or stage II or stage 1 or stage 2 or stageI or stageII or stage1 or stage2 or stage one or stage two) AND (((prostat*) AND (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or adenoma* or adenocarcinoma* or adeno-carcinom* or sarcoma* or malignan* or lump* or mass or masses)) OR ("Prostatic Neoplasms"[mhe]))))) AND (English OR German)[Language],"32","2024-02-22T11:41:50.000000Z"
#41	(((bipolar) AND (puls* or electrod* or mode*)) OR ((tissue* or tumor* or tumour*) AND (ablat*)) OR ("Ablation Techniques"[mhe]) OR (electro-chemo*) OR (electrochemo*) OR ("Electrochemotherapy"[mhe]) OR (LEDC) OR (IRE) OR ((electric*) AND (field* or stimul* or pulse* or cell* or membrane* or pore*)) OR ((irrevers*) AND (electropor* or electro-por* or electropermeab* or electro-permeab*)) OR (NanoKnive*) OR (Nano-Knive*) OR (Nano-Knife*) OR (NanoKnife*) OR ("Nanotechnology"[mhe]) OR ("Electric Stimulation"[mhe]) OR ("Electroporation"[mhe]) OR (PBT) OR ("Protons"[mhe]) OR ((proton* OR particle*) AND (therap* or radiotherap* or radio-therap* OR beam*)) OR (proton-therap*) OR (protontherap*) OR ("Proton Therapy"[mhe]) OR (Cyber-Knive*) OR (CyberKnive*) OR (Cyber-Knife*) OR (CyberKnife*) OR (SRS) OR (SABR) OR (SBRT) OR ("Stereotaxic Techniques"[mhe]) OR ("Radiation Dose Hypofractionation"[mhe]) OR ((stereotactic* or stereotactic* or hypofractionat* or hypo-fractionat*) AND (therap* or radiotherap* or radiotherap* or irradiat* or radiosurg* or radio-surg* or surg* or technique*)) OR ("Radiosurgery"[mhe])) AND ((primary or localised or localized or stage I or stage II or stage 1 or stage 2 or stageI or stageII or stage1 or stage2 or stage one or stage two) AND (((prostat*) AND (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or adenoma* or adenocarcinoma* or adeno-carcinom* or sarcoma* or malignan* or lump* or mass or masses)) OR ("Prostatic Neoplasms"[mhe]))),"40","2024-02-22T11:41:05.000000Z"
#40	((bipolar) AND (puls* or electrod* or mode*)) OR ((tissue* or tumor* or tumour*) AND (ablat*)) OR ("Ablation Techniques"[mhe]) OR (electro-chemo*) OR (electrochemo*) OR ("Electrochemotherapy"[mhe]) OR (LEDC) OR (IRE) OR ((electric*) AND (field* or stimul* or pulse* or cell* or membrane* or pore*)) OR ((irrevers*) AND (electropor* or electro-por* or electropermeab* or electro-permeab*)) OR (NanoKnive*) OR (Nano-Knive*) OR (Nano-Knife*) OR (NanoKnife*) OR ("Nanotechnology"[mhe]) OR ("Electric Stimulation"[mhe]) OR ("Electroporation"[mhe]) OR (PBT) OR ("Protons"[mhe]) OR ((proton* OR particle*) AND (therap* or radiotherap* or radio-therap* OR beam*)) OR (proton-therap*) OR (protontherap*) OR ("Proton Therapy"[mhe]) OR (Cyber-Knive*) OR (CyberKnive*) OR (Cyber-Knife*) OR (CyberKnife*) OR (SRS) OR (SABR) OR (SBRT) OR ("Stereotaxic Techniques"[mhe]) OR ("Radiation Dose Hypofractionation"[mhe]) OR ((stereotactic* or stereotactic* or hypofractionat* or hypo-fractionat*) AND (therap* or radiotherap* or radiotherap* or irradiat* or radiosurg* or radio-surg* or surg* or technique*)) OR ("Radiosurgery"[mhe]),"1137","2024-02-22T11:40:47.000000Z"
#39	(bipolar) AND (puls* or electrod* or mode*),"19","2024-02-22T11:40:09.000000Z"
#38	(tissue* or tumor* or tumour*) AND (ablat*),"120","2024-02-22T11:39:34.000000Z"
#37	"Ablation Techniques"[mhe],"466","2024-02-22T11:38:46.000000Z"
#36	electro-chemo*,"0","2024-02-22T11:38:15.000000Z"
#35	electrochemo*,"4","2024-02-22T11:38:00.000000Z"
#34	"Electrochemotherapy"[mhe],"3","2024-02-22T11:37:42.000000Z"
#33	LEDC,"0","2024-02-22T11:37:16.000000Z"

#32	IRE,"8","2024-02-22T11:37:00.000000Z"
#31	(electric*) AND (field* or stimul* or pulse* or cell* or membrane* or pore*),"163","2024-02-22T11:36:22.000000Z"
#30	(irrevers*) AND (electropor* or electro-por* or electropermeab* or electro-permeab*),"17","2024-02-22T11:35:22.000000Z"
#29	NanoKnive*,"0","2024-02-22T11:34:23.000000Z"
#28	Nano-Knive*,"0","2024-02-22T11:33:58.000000Z"
#27	Nano-Knife*,"0","2024-02-22T11:33:53.000000Z"
#26	NanoKnife*,"6","2024-02-22T11:33:47.000000Z"
#25	"Nanotechnology"[mhe],"6","2024-02-22T11:33:18.000000Z"
#24	"Electric Stimulation"[mhe],"316","2024-02-22T11:32:11.000000Z"
#23	"Electroporation"[mhe],"15","2024-02-22T11:30:41.000000Z"
#22	PBT,"12","2024-02-22T11:29:57.000000Z"
#21	"Protons"[mhe],"17","2024-02-22T11:29:29.000000Z"
#20	(proton* OR particle*) AND (therap* or radiotherap* or radio-therap* OR beam*),"72","2024-02-22T11:28:48.000000Z"
#19	proton-therap*,"0","2024-02-22T11:27:39.000000Z"
#18	protontherap*,"2","2024-02-22T11:27:34.000000Z"
#17	"Proton Therapy"[mhe],"13","2024-02-22T11:27:09.000000Z"
#16	Cyber-Knive*,"0","2024-02-22T11:26:28.000000Z"
#15	CyberKnive*,"0","2024-02-22T11:26:24.000000Z"
#14	Cyber-Knife*,"0","2024-02-22T11:26:16.000000Z"
#13	CyberKnife*,"16","2024-02-22T11:26:10.000000Z"
#12	SRS,"67","2024-02-22T11:25:49.000000Z"
#11	SABR,"6","2024-02-22T11:24:55.000000Z"
#10	SBRT,"17","2024-02-22T11:24:38.000000Z"
#9	"Stereotaxic Techniques"[mhe],"94","2024-02-22T11:24:22.000000Z"
#8	"Radiation Dose Hypofractionation"[mhe],"4","2024-02-22T11:23:43.000000Z"
#7	(stereotactic* or stereo-tactic* or hypofractionat* or hypo-fractionat*) AND (therap* or radiotherap* or radio-therap* or irradiat* or radiosurg* or radio-surg* or surg* or technique*),"89","2024-02-22T11:22:54.000000Z"
#6	"Radiosurgery"[mhe],"71","2024-02-22T11:20:03.000000Z"
#5	(primary or localised or localized or stage I or stage II or stage 1 or stage 2 or stageI or stageII or stage1 or stage2 or stage one or stage two) AND (((prostat*) AND (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or adenoma* or adenocarcinoma* or adeno-carcinom* or sarcoma* or malignan* or lump* or mass or masses)) OR ("Prostatic Neoplasms"[mhe])),"182","2024-02-22T11:19:01.000000Z"
#4	primary or localised or localized or stage I or stage II or stage 1 or stage 2 or stageI or stageII or stage1 or stage2 or stage one or stage two,"5864","2024-02-22T11:18:50.000000Z"
#3	((prostat*) AND (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or adenoma* or adenocarcinoma* or adeno-carcinom* or sarcoma* or malignan* or lump* or mass or masses)) OR ("Prostatic Neoplasms"[mhe]),"427","2024-02-22T11:16:04.000000Z"
#2	(prostat*) AND (cancer* or neoplasm* or carcinoma* or tumor* or tumour* or adenoma* or adenocarcinoma* or adeno-carcinom* or sarcoma* or malignan* or lump* or mass or masses),"411","2024-02-22T11:15:44.000000Z"
#1	"Prostatic Neoplasms"[mhe],"347","2024-02-22T11:13:54.000000Z"

Search strategy EMBASE

Search step #	Query	Results
#67	#65 NOT #66	804
#66	#65 AND 'Conference Abstract'/it	561
#65	#64 AND ([english]/lim OR [german]/lim)	1,369
#64	#63 AND [13-02-2018]/sd NOT [22-02-2024]/sd	1,369
#63	#51 OR #53 OR #55 OR #59 OR #60 OR #62	2,343
#62	#50 AND #61	449
#61	('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes* NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database* OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'data bases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10 (systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) AND 'human'/exp))	1,706,779
#60	#50 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	200
#59	#50 AND #58	808
#58	#56 OR #57	1,156,245
#57	(prospective NEAR/5 (study OR trial)):ti,ab,kw,lnk	728,789
#56	'prospective study'/exp	904,287
#55	#50 AND #54	1,734
#54	'adaptive clinical trial (topic)'/de OR 'adaptive clinical trial'/de OR 'clinical trial (topic)'/de OR 'clinical trial'/de OR 'controlled clinical trial (topic)'/de OR 'controlled clinical trial'/de OR 'double blind procedure'/de OR 'early termination of clinical trial'/de OR 'equivalence trial (topic)'/de OR 'equivalence trial'/de OR 'intention to treat analysis'/de OR 'multicenter study (topic)'/de OR 'multicenter study'/de OR 'non-inferiority trial'/de OR 'phase 1 clinical trial (topic)'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial (topic)'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial (topic)'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial (topic)'/de OR 'phase 4 clinical trial'/de OR 'pragmatic trial'/de OR 'randomized controlled trial (topic)'/de OR 'randomized controlled trial'/de OR 'superiority trial'/de OR 'multicenter study':ti,ab,kw OR 'phase i':ti,ab,kw OR 'phase ii':ti,ab,kw OR 'phase iii':ti,ab,kw OR 'phase iv':ti,ab,kw OR 'phase 1':ti,ab,kw OR 'phase 2':ti,ab,kw OR 'phase 3':ti,ab,kw OR 'phase 4':ti,ab,kw OR ((randomised OR randomized) NEAR/7 trial*) OR (controlled NEAR/3 trial*) OR (clinical NEAR/2 trial*) OR ((single:ti,ab,kw OR doubl*:ti,ab,kw OR tripl*:ti,ab,kw	3,081,312

	OR treb*:ti,ab,kw) AND (blind*:ti,ab,kw OR mask*:ti,ab,kw)) OR '4 arm':ti,ab,kw OR 'four arm':ti,ab,kw	
#53	#50 AND #52	879
#52	random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)	2,315,576
#51	#50 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	441
#50	#7 AND #37	4,673
#49	#47 NOT #48	468
#48	#47 AND 'Conference Abstract'/it	248
#47	#46 AND ([english]/lim OR [german]/lim)	716
#46	#45 AND [13-02-2018]/sd NOT [21-02-2024]/sd	718
#45	#39 OR #41 OR #42 OR #44	1,194
#44	#38 AND #43	449
#43	('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes* NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database* OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'data bases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10 (systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) AND 'human'/exp))	1,706,779
#42	#38 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	200
#41	#38 AND #40	879
#40	random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)	2,315,761
#39	#38 AND [randomized controlled trial]/lim	371
#38	#7 AND #37	4,673
#37	#8 OR #9 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36	236,331
#36	'nano-kni*e*'	38
#35	nano$kni?e*	381
#34	ire:ti,ab	4,170
#33	'electro$permeab*' OR 'electro-permeab*'	780
#32	electro$por* OR 'electro-por*'	29,707
#31	'irreversible electroporation device'/exp	403
#30	'irreversible electroporation'/exp	1,539
#29	pbt:ti,ab	3,309
#28	#27 AND ('drug therapy'/lnk OR 'radiotherapy'/lnk OR 'therapy'/lnk)	4,170
#27	#25 OR #26	60,924
#26	(proton* OR particle*) NEAR/1 beam*	9,528
#25	'proton'/exp	54,086

#24	(proton* OR particle*) NEAR/2 (therap* OR radio$therap* OR 'radio-therap*')	22,502
#23	'particle therapy'/exp	19,752
#22	'proton therapy'/exp	13,327
#21	cyber$kni?e*	5,892
#20	'cyber-kni*e*'	275
#19	'cyberknife'/exp	4,142
#18	srs:ti,ab	21,803
#17	imrt:ti,ab	26,228
#16	'intensity-modulat*' NEAR/1 radi*	41,137
#15	'intensity modulated radiation therapy'/exp	40,795
#14	sabr:ti,ab	3,089
#13	sbrt:ti,ab	15,360
#12	'stereotactic body radiation therapy'/exp	21,771
#11	#10 AND ('radiotherapy'/lnk OR 'surgery'/lnk OR 'therapy'/lnk)	33,028
#10	'stereotactic procedure'/exp	64,634
#9	(stereotactic* OR hypo$fractionat* OR 'hypo-fractionat*') NEAR/3 (therap* OR radio$therap* OR 'radio-therap*' OR irradiat* OR radio$surg* OR 'radio surg*' OR surg*)	56,124
#8	'radiosurgery'/exp	88,266
#7	#1 OR #6	64,895
#6	#4 AND #5	64,895
#5	primary OR locali?ed OR 'stage i' OR 'stage ii' OR 'stage 1' OR 'stage 2' OR stagei OR stageii OR stage1 OR stage2 OR 'stage one' OR 'stage two'	3,519,904
#4	#2 OR #3	337,953
#3	prostat* NEAR/1 (cancer* OR neoplasm* OR carcinoma* OR tumo$r* OR adenoma* OR adeno$carcinoma* OR 'adeno-carcinom*' OR sarcoma* OR malignan* OR lump* OR mass OR masses)	337,734
#2	'prostate tumor'/exp	309,282
#1	'localized prostate cancer'/exp	50

Search strategy Medline via OVID

Database: Ovid MEDLINE(R) ALL <1946 to February 20, 2024>, Date of search: 21.02.2024

#	Query	Results
1	exp Prostatic Neoplasms/	151957
2	(prostat* adj2 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenoma* or adeno?carcinoma* or adeno-carcinom* or sarcoma* or malignan* or lump* or mass or masses)).mp.	2433746
3	1 or 2	199620
4	(primary or locali#ed or stage I or stage II or stage 1 or stage 2 or stageI or stageII or stage1 or stage2 or stage one or stage two).mp.	2433746
5	3 and 4	35390
6	exp Radiosurgery/	20549
7	((stereotactic* or hypo?fractionat* or hypo-fractionat*) adj5 (therap* or radio?therap* or radio-therap* or irradiat* or radio?surg* or radio-surg* or surg* or technique*)).mp.	27066
8	exp Radiation Dose Hypofractionation/	1149
9	exp Stereotaxic Techniques/	38344
10	surgery.fs.	2299240
11	9 and 10	20498

12	SBRT.ti,ab.	6180
13	SABR.ti,ab.	1234
14	SRS.ti,ab.	13773
15	Cyber?Kni#e*.mp.	1957
16	Cyber-Kni#e*.mp.	61
17	exp Proton Therapy/	5475
18	proton?therap*.mp.	170
19	proton-therap*.mp.	7466
20	((proton* or particle*) adj3 (therap* or radio?therap* or radio-therap*)).mp.	12583
21	exp Protons/	33412
22	((proton* or particle*) adj2 beam*).mp.	6880
23	21 or 22	38791
24	"therapeutic use".fs.	2552786
25	therapy.fs.	2165375
26	24 or 25	4316969
27	23 and 26	1265
28	PBT.ti,ab.	2335
29	Electroporation/	8919
30	Electric Stimulation/	117079
31	exp Nanotechnology/	50987
32	nano?kni#e*.mp.	59
33	nano-kni#e*.mp.	13
34	34 (irrevers* adj4 (electro?por* or electro-por* or electro?permeab* or electro-permeab*)).mp.	1428
35	(electric* adj4 (field* or stimul* or pulse* or cell? or membrane* or pore?)).mp.	235983
36	Electric Stimulation Therapy/	22187
37	IRE.tw.	2621
38	LEDC.tw.	21
39	Electrochemotherapy/	825
40	electro?chemo*.mp.	1454
41	electro-chemo*.mp.	98
42	Ablation Techniques/	3505
43	((tissue* or tumo?r*) adj4 ablat*).mp.	12827
44	(bipolar adj4 (puls* or electrod* or mode?)).mp.	5077
45	6 or 7 or 8 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	379000
46	5 and 45	1443
47	limit 46 to (controlled clinical trial or randomized controlled trial)	85
48	((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.)	5168785
49	("adaptive clinical trial" or "clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv" or "controlled clinical trial" or "equivalence trial" or "multicenter study" or "pragmatic clinical trial" or "randomized controlled trial").pt. or double-blind method/ or "adaptive clinical trials as topic"/ or "clinical trials as topic"/ or "clinical trials, phase i as topic"/ or "clinical trials, phase ii as topic"/ or "clinical trials, phase iii as topic"/ or "clinical trials, phase iv as topic"/ or "controlled clinical trials as topic"/ or "equivalence trials as topic"/ or "intention to treat analysis"/ or "non-randomized controlled trials as topic"/ or "pragmatic clinical trials as topic"/ or "randomized controlled trials as topic"/ or "multicenter studies as topic"/ or (phase adj1 ("I" or "II" or "III" or "IV" or "1" or "2" or "3" or "4")).ti,ab,kf. or ((randomi?ed adj7	2088209

	trial*) or (controlled adj3 trial*) or ((clinical or pragmatic) adj2 trial*) or (research adj (studies or study)) or ((single or doubl* or tripl* or treb*) adj4 (blind* or mask*))).ti,ab,kf. or (("4" or four) adj arm).ti,ab,kf.	
50	exp Prospective Studies/	680871
51	(prospective adj5 (study or trial)).mp.	479534
52	48 or 49 or 50 or 51	6197467
53	46 and 52	790
54	limit 46 to (meta analysis or "systematic review")	51
55	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.	752319
56	46 and 55	129
57	47 or 53 or 54 or 56	846
58	limit 57 to ed=20180213-20240221	452
59	limit 57 to dt=20180213-20240221	519
60	58 or 59	565
61	limit 60 to (english or german)	553
62	remove duplicates from 61	551

8.2 Risk of bias of observational studies

Table 8.2-1: Risk of bias assessment of prospective cohort studies with SBRT

Study reference/ID	Jorgo 2021	Lukka 2018
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes
Study design		
2. Was the study conducted prospectively?	Yes	Yes
3. Were the cases collected in more than one centre?	No	Yes
4. Were patients recruited consecutively?	Unclear	Unclear
Study population		
5. Were the characteristics of the patients included in the study described?	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	Yes
Intervention and co-intervention		
8. Was the intervention of interest clearly described?	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes
Outcome measures		
10. Were relevant outcome measures established a priori?	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes
Statistical Analysis		
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
Results and Conclusions		
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No	Yes
18. Were the adverse events reported?	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes
Competing interests and sources of suppor		
20. Were both competing interests and sources of support for the study reported?	Partly (funding not reported)	Yes
Overall Risk of bias	Moderate	Moderate

Table 8.2-2: Risk of bias assessment of prospective cohort studies with PT

Study reference/ID	Arimura 2018	Hasan 2023 and Mishra 2019	Lee 2018	Sosa 2023	Takaoka 2023	Ha 2019	Vargas 2018
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design							
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	Yes	No	No	No	No	Yes
4. Were patients recruited consecutively?	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes
Study population							
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes	Yes	Partial
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intervention and co-intervention							
8. Was the intervention of interest clearly described?	Yes	No	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	No	Yes	Yes	Yes	Yes	Yes
Outcome measures							
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	Yes	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis							
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions							
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes	Yes	Yes	No	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Partial	Yes	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support							
20. Were both competing interests and sources of support for the study reported?	Partly (funding was not reported, no CoI)	Yes	Yes	Yes	Yes	Yes	Yes
Overall Risk of bias	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Moderate

Table 8.2-3: Risk of bias assessment of prospective cohort studies with IRE

Study reference/ID	Blazevski 2020	De la Rosette 2022	Scheltema 2018	Wang 2022	Zhang 2024
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes
Study design					
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	Yes	Yes	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Yes	Unclear	Unclear	Unclear
Study population					
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	Yes	Yes	Yes	Yes
Intervention and co-intervention					
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	No	No	No
Outcome measures					
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No (although patients were blinded to ensure unbiased QoL scores)	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes
Statistical Analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes
Results and Conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	No	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support					
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes	Yes	Yes
Overall Risk of bias	Moderate	Low	Moderate	Moderate	Moderate

8.3 Ongoing clinical studies

Table 8.3-1: Ongoing clinical studies (IRE)

Nr.	Registry number	Title (Sponsor)	Design	Intervention(s)	Patient population	Primary endpoints	Study completion date
1	NCT05513443	Prostate cancer IRE study (PRIS) (Karolinska University Hospital)	RCT	IRE Radical prostatectomy (RP)	n=184 ■ Adult male >40 yrs old ■ Gleason score 3 + 4 or 4 + 3 ■ PSA level ≤ 20 ng/ml ■ ≤ T2c	■ Urinary continence ■ Irritative urinary symptoms ■ Erectile dysfunction ■ Voiding function ■ Bowel function ■ Adverse events ■ Quality of life ■ Treatment failure	September 2025
2	NCT04278261	Comparison H-FIRE and laparoscopic RP in treating men with localised prostate cancer (Shanghai East Hospital)	RCT	Focal therapy (H-FIRE) Laparoscopic RP	n=216 ■ Male <80 yrs old ■ PSA<20ng/ml ■ ≤T2c ■ Gleason score ≤4+4 ■ No evidence of metastasis	■ Urinary function (ICIQ, EPIC, IPSS) ■ Sexual function (EPIC, IIEF-5) ■ Number of patients with disease progression ■ Bowel function ■ Quality of life (EORTC QLQ-C30, EPIC urinary, sexual and bowel domains bother scores) ■ Rates of primary treatment failure ■ Rates of adjuvant therapy ■ Perioperative data (operative time, haemoglobin loss, blood transfusion, length of hospital stay) ■ Pain ■ Adverse effects	September 2026
3	NCT02255890	Registry of irreversible electroporation for the ablation of prostate cancer with use of Nanoknife device (Clinical Research Office of the Endourological Society)	Observational prospective registry study	IRE with Nanoknife®	n=361 ■ Child, adult ■ histologically confirmed prostate cancer ■ scheduled for IRE Nanoknife®	■ Adverse events	April 2025
4	NCT06223295	Effectiveness of focal therapy in men with prostate cancer (Radboud University Medical Center)	RCT	Focal therapy (IRE, HIFU or TULSA) Usual care (RP or radiotherapy)	n=356 ■ Adult male >45 yrs old ■ Gleason score: 7 (3 + 4 or 4 + 3; ISUP grade 2/3) ■ PSA level ≤20 ng/ml ■ ≤ T2b	■ Oncological effectiveness (non-inferiority) defined as treatment failure ■ Quality of life (superiority) ■ Metastasis-free survival ■ HrQoL (EORTC QoL, ICI)	February 2031

Nr.	Registry number	Title (Sponsor)	Design	Intervention(s)	Patient population	Primary endpoints	Study completion date
					■ Life expectancy ≥10 yrs	■ Urinary function (IPSS) ■ Sexual function (IIEF-5) ■ Disease progression ■ Disease specific mortality, all-cause mortality ■ Operating time, hospital stay ■ Adverse events ■ Cost-effectiveness	
5	NCT04972097	Pivotal study of the NanoKnife system for the ablation of prostate tissue (PRESERVE) (Angiodynamics, Inc.)	Single-arm prospective cohort	IRE with Nanoknife®	n=121 ■ > 50 yrs old ■ > 10-year life expectancy ■ ≤ T2c ■ PSA ≤ 15 ng/mL or PSA density < 0.2 ng/mL2 if PSA is > 15 ng/mL ■ Gleason score 3+4 or 4+3	■ Adverse events (CTCAE) ■ Negative in-field biopsy	July 2024

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EPIC: Expanded Prostate Cancer Index Composite; H-FIRE: high-frequency irreversible electroporation; HIFU: high-intensity focused ultrasound; HrQoL: health-related quality of life; ICI: International Consultation on Incontinence; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; IRE: irreversible electroporation; ISUP: International Society of Urological Pathology; n: number; PSA: prostate specific antigen; RCT: randomised controlled trial; RP: radical prostatectomy; TULSA: transurethral ultrasound ablation, yrs: years

Table 8.3-2: Ongoing clinical studies (SBRT)

Nr.	Registry number	Title (Sponsor)	Design	Intervention	Patient population	Endpoints	Estimated study completion date
1	NCT06052683	A trial evaluating toxicity of SBRT and LDRB in localized prostate cancer (CHU de Quebec-Universite Laval)	RCT	SBRT vs. LDRB	n=208 ■ Age ≥ 18 years ■ ECOG performance status 0-1 ■ Low-risk: T1-T2a and Gleason 6 and PSA ≤ 10 ng/mL ■ Favourable intermediate risk defined by a single NCCN intermediate risk factor: T2b, PSA > 10 but ≤ 20 ng/mL, Gleason 7 (3+4)	■ Adverse events ■ QoL ■ Urinary function ■ Biochemical disease-free survival	September 2026
2	NCT02339701	Stereotactic body radiotherapy vs intensity-modulated radiotherapy in prostate cancer (Chinese University of Hong Kong)	RCT	SBRT vs. IMRT	n=68 ■ Age ≥ 18 ■ Low or intermediate risk prostate cancer (i.e. T1-T2c and PSA 20 and Gleason score < 8) with the risk of pelvic node metastasis 15% as calculated by Roach's formula ■ ECOG performance score 0-1	■ HrQoL ■ Acute and late GI and GU toxicity ■ Biochemical failure-free survival ■ Overall survival ■ Disease-specific survival	December 2026
3	NCT04861415	SBRT vs. conventional fractionation with HDR boost for prostate cancer (Dr. Gerard Morton)	RCT	SBRT vs. CFRT	n=55 ■ Age ≥ 18 ■ ECOG Performance Status 0-2 ■ No prior history of pelvic radiotherapy, brachytherapy, cryosurgery, HIFU, TURP or radical prostatectomy	■ Treatment feasibility ■ QoL ■ Toxicity ■ Overall survival ■ Cumulative biochemical failure ■ Cancer-free survival ■ Metastasis-free survival ■ Freedom from local failure ■ ADT-free survival	December 2027
4	NCT05946213	Testing shorter duration radiation therapy versus the usual radiation therapy in patients with high-risk prostate cancer (NRG Oncology)	RCT	SBRT vs. conventional EBRT	n=1209 ■ High-risk defined as having at least one or more of the following: cT3a-T3b, PSA > 20 ng/mL prior to starting ADT, Gleason Score of 8-10 or M1a, M1b or M1c ■ Age ≥ 18 ■ ECOG Performance Status of 0-2 ■ No prior radiotherapy to the prostate or RP ■ Patients enrolled in NRG-GU009 must be enrolled in NRG-GU013 prior to radiation therapy treatment planning and start of radiation therapy	■ Metastasis-free survival ■ Overall survival ■ Failure free survival ■ Toxicity ■ Urinary symptoms ■ Bowel symptoms ■ Fatigue ■ Costs	March 2041

Nr.	Registry number	Title (Sponsor)	Design	Intervention	Patient population	Endpoints	Estimated study completion date
5	NCT03938649	SRAM study prostate cancer (Chinese University of Hong Kong)	RCT	SBRT vs. conventional IMRT	n=120 ■ Age ≥ 18 ■ High risk prostate cancer (i.e. T3 to T4 disease and/or PSA > 20 and/or Gleason score ≥ 8) ■ ECOG performance score 0-1	■ Acute toxicity and late toxicity ■ Overall survival at 5 yrs ■ Progression-free survival at 5 yrs ■ Biochemical failure-free survival at 5 yrs ■ HrQoL	December 2025
6	NCT01584258	Prostate advances in comparative evidence (Royal Marsden NHS Foundation Trust)	RCT	PACE-A: RP vs. SBRT PACE-B and PACE-C: CFRT vs. SBRT	n=2205 ■ Age ≥ 18 ■ WHO performance status 0 - 2 ■ Patients considered candidates for surgery are eligible for PACE-A; patients not considered for surgery and patients who decline surgery or prefer to avoid surgery are eligible for PACE-B and PACE-C.	■ Freedom from biochemical or clinical failure ■ Acute and late toxicity ■ Acute and late bowel, bladder and erectile dysfunction symptoms ■ Disease-specific survival ■ Overall survival ■ Progression-free survival	December 2027
7	NCT02895854	LDR Brachytherapy Versus SBRT for Low and Intermediate Risk Prostate Cancer Patients (Kuopio University Hospital)	RCT	LDR brachytherapy vs. hypofractionated RT 5 x 7,25 Gy	n=41 ■ Gleason score ≤ 3+4 ■ TNM T1c-2c, N0-X, M0-X, PSA ≤ 20ng/ml and WHO 0-2 ■ Low or intermediate risk prostate cancer according to NCCN	■ Acute adverse events ■ Biological progression-free survival	December 2021 (no information if study is still ongoing, no results posted)
8	NCT02594072	Androgen Suppression With Stereotactic Body or External Beam Radiation Therapy (ASSERT) (University of British Columbia)	RCT	SABR with androgen suppression vs. EBRT with androgen suppression	n=80 ■ High risk is defined by any of: ≥T3a, PSA > 20, or Gleason Score≥ 8 ■ Intermediate risk is defined by: T1/T2 and/or Gleason ≤ 7 and/or PSA ≤20 and not low risk ■ Life expectancy ≥5 yrs ■ ECOG performance status 0 - 2 ■ No contraindication for 6 months and 18 months of ADT respectively for intermediate and high-risk disease.	■ Acute and late toxicities ■ Biochemical relapse-free survival at 5 yrs ■ HrQoL (EPIC)	December 2024

Nr.	Registry number	Title (Sponsor)	Design	Intervention	Patient population	Endpoints	Estimated study completion date
9	NCT03367702	Stereotactic Body Radiation Therapy or Intensity-Modulated Radiation Therapy in Treating Patients With Stage IIA-B Prostate Cancer (NRG Oncology)	RCT	SBRT vs. IMRT	n=698 ■ Previously untreated (no local therapy such as surgery, radiation cryotherapy, HIFU, etc.) localised prostate cancer ■ T1c or T2a/b ■ Stages T1a-T1b are eligible if patient underwent transurethral prostatic resection (TURP), ■ The patient must meet one of the following 3 criteria: Gleason score 7(3+4) with a PSA < 20 ng/mL, or Gleason 6(3+3) with a PSA > 10 ng/mL and < 20 ng/mL which is considered intermediate risk or Group Grade 1 with a PSA > 10 ng/mL and < 20 ng/mL or 2 with a PSA < 20 ng/mL.	■ Gastrointestinal and genitourinary toxicity ■ Disease-free survival ■ Biochemical failure ■ Distant metastasis ■ Local failure ■ Overall survival ■ HrQoL ■ Prostate cancer specific survival ■ Regional failure ■ Adverse events	December 2030
10	NCT04870567	HDR Brachytherapy vs SABR in Early-intermediate Prostate Cancer (N.N. Petrov National Medical Research Center of Oncology)	RCT	SBRT vs. HDR-brachytherapy	n=350 ■ WHO performance status of 0-2 ■ Gleason score 6-7 (4+3) ■ T1c-T2c, N0, M0 ■ PSA < 20 ng/ml ■ IPSS < 16	■ Adverse events ■ Erectile dysfunction ■ Biochemical relapse free survival	April 2025
11	NCT05705921	Standard Moderately Hypofractionated RT vs. Ultra-hypofractionated Focal Lesion Ablative Microboost in Prostate Cancer (The Netherlands Cancer Institute)	RCT	SBRT vs. moderately hypofractionated radiotherapy 62 Gy in 20 fractions of 3.1 Gy	n=484 ■ Age ≥ 18 ■ N0M0 ■ Intermediate- or high-risk PCa, defined as at least one of the following risk criteria: cT2c-T3a, Gleason score ≥ 4+3, (ISUP Grade groups 3,4 or 5), PSA ≥ 20 ng/mL, WHO performance score ≤ 2, IPSS score < 15, PSA ≤ 30 ng/mL	■ Biochemical disease-free survival ■ Acute and late toxicity ■ Overall survival ■ Disease-free survival ■ Distant metastases-free survival ■ Prostate cancer-specific survival ■ HrQoL (EORTC) ■ Urinary function (EPIC, IPSS) ■ Bowel function (EPIC) ■ Sexual function (EPIC)	January 2032
12	NCT02361515	Hypofractionated Radiotherapy Versus Stereotactic Irradiation With Hyaluronic Acid (Hospices Civils de Lyon)	RCT	SBRT vs. moderately hypofractionated radiotherapy	n=96 ■ Age ≥ 18 and < 80 yrs ■ Low- to intermediate-risk prostate cancer, according to D'Amico classification ■ WHO performance grade 0-2. ■ Indication of EBRT ■ IPSS < 15/35 (without alpha-blocker)	■ Survival rates without biological relapse ■ Acute urinary and rectal toxicities ■ Sexual function ■ Late rectal toxicities	January 2020 (study status unknown, no results posted)

Nr.	Registry number	Title (Sponsor)	Design	Intervention	Patient population	Endpoints	Estimated study completion date
13	ACTRN12618001806257	The NINJA Clinical Trial: Novel Integration of New prostate radiation schedules with adjuvant Androgen deprivation for patients with intermediate or low-high risk prostate cancer (Trans Tasman Radiation Oncology Group)	RCT	SBRT vs. virtual HDRB boost	n=472 ■ Unfavourable intermediate or low-high risk prostate cancer ■ ISUP 2 and either PSA 10-20, OR T2b/c AND ≥ 50% biopsy cores positive ■ ISUP 3 AND PSA ≤ 20 OR ■ ISUP 4-5 OR T3a AND PSA ≤ 20 ■ N0M0 ■ ECOG performance status of 0-1 ■ Life expectancy >5 yrs	■ Biochemical clinical control ■ Rate of replanning following knowledge-based planning feedback to trial centres ■ Rate of trial centre conversion to prostate MRI only planning	January 2030

Abbreviations: ADT: androgen deprivation therapy; CFRT: conventionally fractionated radiation therapy; EBRT: external beam radiotherapy; EORTC: European Organisation for Research and Treatment of Cancer; ECOG: Eastern Cooperative Oncology Group; EPIC: Expanded Prostate Cancer Index Composite; Gy: Gray; HDRB: high dose rate brachytherapy; HIFU: high-intensity focused ultrasound; HrQoL: health-related quality of life; IIEF: International Index of Erectile Function; IMRT: intensity modulated radiotherapy; IPSS: International Prostate Symptom Score; ISUP: International Society of Urological Pathology; LDRB: low dose rate brachytherapy; n: number; NCCN: National Comprehensive Cancer Network; MRI: magnetic resonance imaging; PSA: prostate specific antigen; QoL: quality of life; RCT: randomised controlled trial; RP: radical prostatectomy, RT: radiation therapy; SBRT: stereotactic body radiation therapy; TURP: transurethral resection of the prostate; WHO: World Health Organization; yrs: years

Table 8.3-3: Ongoing clinical studies (PT)

Nr.	Registry number	Title (Sponsor)	Design	Intervention	Patient population	Endpoints	Estimated study completion date
1	NCT01617161	Proton therapy vs. IMRT for ow or intermediate risk prostate cancer (Massachusetts General Hospital)	RCT	PT vs. IMRT	n=454 ■ Age ≥ 18 yrs ■ T1c to T2c ■ PSA <20 ■ Gleason score ≤6, 3 + 4 = 7, or 4 + 3 = 7 ■ ECOG performance of 0-1	■ Disease specific QoL ■ Cost effectiveness ■ Bowel, urinary and erectile function ■ Long-term survival	July 2027
2	NCT02040610	Hypofractionated image guided proton therapy for low and intermediate risk prostate cancer (Provision Center for Proton Therapy)	Single-arm observational cohort	Hypofractionated PT	n=235 ■ Age ≥ 18 yrs ■ T1-T2c ■ PSA < 20 ng/mL ■ Gleason Score < 7 ■ ECOG performance of 0-1 ■ M0 ■ No prior radiotherapy to the pelvic area, no prior prostate cancer therapy (prostatectomy, cryotherapy, chemotherapy or hyperthermia)	■ Toxicity	December 2025
3	NCT01368055	Hypofractionated proton radiation therapy for low and intermediate risk prostate cancer (PR07) (University of Florida)	Non-randomised parallel group (low vs. intermediate risk)	70 Gy/CGE PT vs. 72.5 Gy/CGE PT	n=361 ■ Age ≥ 18 yrs ■ Gleason score 2-6 or 7 ■ PSA ≤ 20 ng/ml	■ Cumulative incidence of treatment-related grade ≥ 2 rectal bleeding ■ Overall survival	September 2036
4	NCT04083937	Prostate cancer patients treated with alternative radiation oncology strategies (PAROS) (University Hospital Heidelberg)	RCT (the proton arm should be considered)	Hypofractionated PT (total dose 57.0 Gy RBE in 19 fractions)	n=897 (total, NA for the relevant arm) ■ Indication for prostate irradiation (adjuvant/ salvage) after prostatectomy ■ Karnofsky-Index ≥ 70% ■ Age ≥ 18 yrs	■ Toxicity ■ Overall survival	January 2029
5	JPRN-UMIN000046163	Hypofractionated proton beam therapy of 51.6Gy (RBE) in 12 fractions (3 weeks) with real-time-image gated spot-scanning system for non-metastatic prostate cancer (T1c-T4N0M0) (Kyoto Prefectural University of Medicine Department of Radiology)	Single-arm observational cohort	Hypofractionated PT with 51.6Gy (RBE) in 12 fractions (3 weeks)	n=180 ■ Age >20 yrs and <84 yrs ■ ECOG performance of 0-2 ■ T1c-T4 N0M0	■ Genitourinary early adverse events (up to 13 weeks from the start of treatment) ■ Genitourinary late adverse events (up to 5 years) ■ Gastrointestinal early adverse events ■ Gastrointestinal late adverse events	December 2030

Nr.	Registry number	Title (Sponsor)	Design	Intervention	Patient population	Endpoints	Estimated study completion date
6	JPRN-UMIN000038279	Phase I/II clinical trial of hypofractionated image-guided proton therapy for prostate cancer (Nagoya City University West Medical Center)	Single-arm observational cohort	Image guided proton therapy	n=300 ■ >20 yrs ■ T1-T3b N0M0 ■ ECOG 0-2	■ Grade ≥ 2 acute and late genitourinary toxicity	December 2026
7	NCT03561220	A prospective comparative study of outcomes with proton and photon radiation in prostate cancer	Non-randomised parallel group (the proton arms should be considered)	Standard PT with 78.0 Gy (RBE) in 39 fractions, Hypofractionated PT with 60.0 Gy (RBE) in 20 fractions	n=3000 (total, NA for the relevant arm) ■ Age 30-85 yrs ■ Localised prostate cancer ■ Very low-risk, low-risk, intermediate-risk, or high-risk ■ ECOG/Zubrod performance of 0-2 ■ Candidate for definitive prostate RT (either IMRT or PT)	■ Grade ≥ 2 acute and late toxicity	April 2026

Abbreviations: CGE: cobalt gray equivalent; ECOG: Eastern Cooperative Oncology, Gy: Gray, QoL: quality of life, IMRT: intensity modulated radiation therapy, NA: not applicable; PSA: prostate specific antigen; PT: proton therapy, RBE: relative biological effectiveness; RCT: randomised controlled trial; RT: radiotherapy; yrs: years

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