Radiofrequency-Induced Intravesical Chemohyperthermia for Non-Muscle-Invasive Bladder Cancer

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

AE.....Adverse Event
AJCC .....American Joint Committee on Cancer
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
BCG.....Bacillus Calmette-Guérin
CE.....Conformité Européenne (European Conformity)
CG .....Control Group
CHT .....Chemohyperthermia
CI.....Confidence Interval
CIS.....Carcinoma in situ
CMID.....Clinically Minimum Important Difference
CR .....Complete Response
CRD .....Centre for Reviews and Dissemination
DFS .....Disease-free Survival
DSS .....Disease-specific Survival

EAU.....European Association of Urologists
EMDA.....Electromotive Drug Administration
EQ-5D .....EuroQual-5D (questionnaire for quality of life)
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
HG.....High-Grade
HPV.....Human Papilloma Virus
HR.....Hazard Ratio
HRQoL .....Health-related Quality of Life
HT .....Hyperthermia
IG.....Intervention Group
IHE.....Institute for Health Economies
LBI-HTA .....Ludwig Boltzmann Institute for Health Technology Assessment
LG .....Low-Grade
MHz .....Mega Hertz
MMC.....Mitomycin-C
NICE.....National Institute for Health and Care Excellence
NMIBC .....Non-Muscle Invasive Bladder Cancer
NR.....Not reported
NRCT.....Non-Randomised Controlled Trial
OR .....Overall Survival
PCS.....Physical Component Summary
PFS.....Progression-free Survival
POP .....Planned and Ongoing Projects database
QoL .....Quality of Life
RCT.....Randomised Controlled Trial
RF.....Radiofrequency
RF-CHT.....Radiofrequency-induced intravesical chemohyperthermia
RITE .....Radiofrequency-induced Thermo-Chemotherapy Effect
RoB.....Risk of Bias
SAE.....Serious Adverse Event
TNM.....Tumour, Node, Metastasis
TURBT .....Transurethral Resection of the Bladder Tumour
UK.....United Kingdom
WHO.....World Health Organisation

Executive Summary

Introduction

Health Problem

Bladder cancer is the 6th most common malignancy (estimated number of prevalent cases) worldwide and the 4th most common malignancy in Europe. The condition can be subdivided into non-muscle-invasive (superficial), muscle-invasive and metastatic disease, depending on the growth of the tumor and the dissemination and proliferation of the respective cancer cells. Non-muscle-invasive bladder urothelial carcinomas (NMIBC) is the condition of interest. NMIBC comprises a heterogeneous group of tumours: Ta, T1 and carcinoma in situ (CIS). It is estimated that 70% of all superficial bladder cancer are Ta tumours, approx. 7% are T1 (grade 3) and that between 5-10% of the patients have a CIS. Environmental exposures account for most cases of bladder cancer. For the individual, the associated clinical manifestations including irritative voiding symptoms, pain as a result of locally advanced or metastatic tumours and other constitutional symptoms (e.g. fatigue, weight loss, anorexia or failure to thrive, insomnia). Although not immediately life-threatening in the majority of cases, recurrence and progression remain significant issues with up to 55% of the patients relapsing within 5 years of diagnosis

NMIBC refers to a heterogeneous group of bladder tumours (Ta, T1 and CIS); whereby 70% belong to the Ta category

majority of patients experience the recurrence or progression of tumours hence lifelong checks are required

Description of Technology

The investigated technology combines intravesical chemotherapy with regional hyperthermia (HT) and is also referred to as thermochemotherapy or chemohyperthermia (CHT). The most commonly used application is the Synergo® system, in which local HT is administered via direct radiofrequency-induced irradiation of the urothelium. To distinguish it from other heat-generating techniques, which are not part of the present assessment, the intervention is referred to as radiofrequency-induced intravesical chemohyperthermia (RF-CHT) throughout the report. Generally RF-CHT is performed in an outpatient setting using a local anaesthetic urethra gel. The treatment typically consists of two 20-30 minutes sessions and aims to achieve a temperature above 41°C during at least 20 min per session. There are prophylactic protocols and ablative protocols, both consisting of a series of treatments.

Technology: Synergo® System, which induces intravesical hyperthermia via radiofrequency

Methods

Domain effectiveness

The following outcomes were defined as *crucial* to derive a recommendation:

- Overall survival (OS)
- Disease-specific survival (DSS)
- Quality of life (QoL)

critical endpoints for assessing effectiveness: survival, disease-specific survival, quality of life

OS measures the time from randomization until death from any cause in the intent-to-treat population and was reported by three controlled studies. DSS was reported by one controlled study. Quality of life was reported by 4 controlled studies, although only 1 used a standardised measure.

controlled studies included

The following outcomes were defined as *important* to derive a recommendation:

- Disease-free survival (DFS)
- Progression-free survival (PFS)/time to progression
- Recurrence-free survival (RFS)/time to recurrence

DFS was reported by 2 controlled studies, PFS by 3 controlled studies and RFS by 4 controlled studies.

The following outcomes were defined as *surrogates* to derive a recommendation:

- Complete response (CR), which was reported by 4 controlled studies
- Radical cystectomy (RC)/bladder preservation rate, which was reported by 1 controlled study

Domain safety

critical outcomes for the assessment of safety: serious adverse events

The following outcomes were defined as *crucial* to derive a recommendation:

- Serious adverse events (including reported deaths).

Additional *important* outcomes considered were

- Adverse events.

case series with 10 patients or more were additionally included for the safety analysis

The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. In addition to the RCTs and NRCTs used for the efficacy analysis, prospective studies without a control group were considered for the assessment of safety if they contained a minimum of 10 patients.

Results

Available evidence

4 RCTs and 1 NRCT were included

total patient population of 503 PatientInnen, of which 243 received the intervention

For evaluating the effect of RF-CHT on the treatment of non-muscle invasive bladder cancer, four RCTs and one NRCT were included. Of the controlled trials, there were 2 single-centre studies. All trials took place in Europe and Israel. Patients were included in the studies if they had been diagnosed with intermediate- or high-risk NMIBC (or the trials had been included in the NICE review upon which this update is based). The patient population (n=503, of whom 243 received the intervention) varied considerably in terms of stage of NMIBC, primary tumours versus recurrent lesions and/or a previous treatments. The mean age ranged from 64.3 to 77 years.6.6% to 35.7 % of the participants were female. Three studies used either intravesical instillations with MMC (2 study) or BCG (1 study) as comparators. The NRCT patients could choose between instillations with MMC or MMC provided via EMDA as comparators.

for the assessment of safety, an additional 11 case series studies were included

11 single-arm studies were included from the systematic literature search of the original NICE-Review on which this update was based. No new studies were identified in the updated systematic literature search. The single-arm studies included 480 patients with superficial transitional cell carcinomas of the bladder, of which 6.6% to 35.7% were female. The mean age ranged from 57.3 years to 73 years (median). Single-arm trials were conducted in Europe and Israel.

Regarding the 4 RCTs included, the overall RoB was graded with 'some concerns', mainly due to no available information in terms of the randomisation process, the blinding process and potential missing data. The NRCT was assessed with a moderate RoB and the 11 single-arm studies were assessed with a medium to high RoB.

RCTs: some quality concerns, NRCT: moderate RoB case series: medium to high RoB

Clinical effectiveness

Differences in overall survival were non-significant in 3/3 studies, classed as having a moderate strength of evidence. There were statistically significant differences found regarding DSS (in favour of the control group) and DFS (in favour of the intervention in 1 study); these outcomes were given a low strength of evidence rating. 2/3 studies reported no significant difference in RFS after 24 months (low strength of evidence), similarly 2/3 studies showed non-significant differences for PFS (low strength of evidence). 1 study reporting CR found a statistically significant difference in favour of the IG, but for the CIS subgroup non-significant differences were reported in the 2 studies (overall low strength of evidence). There was no information provided on statistical significance testing regarding differences in subjective symptom score and absolute differences in before/after scores appeared minimal (low strength of evidence). No statistically significant differences between scores were reported by the study that used the EQ-5D to measure QoL (low strength of evidence). 1 study looked at radical cystectomy rates and reported non-significant differences between groups (low strength of evidence).

no significant difference in overall survival (3 studies) and 2/3 studies reported no significant difference in RFS or PFS

some significant differences in DSS, DFS and CR (although latter not for CIS subgroup)

no statistically significant differences in QoL or radical cystectomy reported

Safety

11 SAEs in the IG and 14 SAEs in the CG were reported from the controlled trials, but no statistical testing was performed. The case series studies reported a total of 45 SAEs among patients treated with the intervention. The quality of the evidence relating to safety was given a very low rating.

24 SAEs reported in the controlled studies (IG 17, CG 7); 25 SAEs reported in case series studies

Upcoming evidence

Currently, there are no ongoing randomised controlled trials investigating the efficacy of the Synergo® system. However, the search in the clinical trial registries revealed two ongoing single-arm studies: NCT03335059 (with an estimated study completion dates in March 2025) and EUCTR2016-000049-30-ES (no estimated completion date provided).

2 single-arm studies underway

Reimbursement

The product is commercially available in the Netherlands, Austria, Germany, Norway, Italy, Czech-Republic, United Kingdom and Switzerland. Outside of Europe it is available in Israel, Turkey, Brazil and China (latter from mid-2020).

It has been CE-approved since 2001 and available since then in some public and university hospitals. The device is not yet approved by the FDA.

commercially available in Europe with CE (not FDA) approval

Discussion

1st systematic review of prospective evidence for RF-CHT

The aim of the present assessment was to summarize the available evidence using the NICE interventional procedure overview as a starting point and including any additional studies meeting the inclusion criteria from an updated systematic literature search. To our knowledge, this is the first systematic review of RF-CHT for patients with non-muscle invasive bladder cancer that is based on prospective evidence only.

pts population of 503 in controlled trials: 243 with RF-CHT

Overall, four RCTs and one NRCT were included in the analysis of clinical efficacy. In total, 243 patients were treated with RF-CHT, while 260 patients were part of the control groups either undergoing intravesical chemo- or immunotherapy, a sham procedure or treated with an alternative intravesical chemohyperthermia method (EMDA).

no likely impact on OS: moderate certainty of evidence

low levels of certainty for other survival outcomes and QoL

With a moderate level certainty of evidence we can conclude that RF-CHT has no impact on overall survival although there is only low certainty of evidence regarding all other survival-related outcomes as results were either contradictory or inconclusive. Similarly, evidence on QoL was generally poor with an absence of statistical significance testing, so no conclusions can be drawn. Where a standardised instrument and statistical testing were applied, no advantage for RF-CHT could be observed. The number of SAEs were relatively similar in the controlled studies and again without statistical significance testing, no firm conclusions can be drawn regarding the safety profile.

heterogeneity in reporting AE and lack of statistcal significance testing

24 SAEs were reported in total in the controlled studies (IG 17; CG 7). In addition, 25 SAEs occurred in the single-arm studies. There was considerable heterogeneity in the reporting of adverse events which prevents an analysis of the comparative safety of RF-CHT.

Conclusion

body of evidence does not support recommendations for use

technology is experimental and should only be used within a clinical trial setting

Due to the heterogeneity of the included study populations and indications and the variety of treatment regimens and comparators, a comprehensive understanding of the comparative risks and benefits of radiofrequency-induced intravesical chemohyperthermia compared to alternative treatment options or sham procedures is not possible based on the currently available evidence. This holds true even if you assess evidence separately for indications and comparators because the follow-up is too short and there is a lack of good quality evidence from randomised controlled trials. As current evidence is limited, the technology must be considered experimental. As such it is not recommended for inclusion in the catalogue of benefits but could be used within a clinical trials setting to add to the body of scientific knowledge.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

NMIBC bezieht sich auf eine heterogene Gruppe von Blasentumoren (Ta, T1 und CIS);

wobei 70 % zur Kategorie Ta gehören

Blasenkrebs (Urothelkarzinom) gehört weltweit (sechst-häufigste Tumorerkrankung) und in Europa (viert-häufigste Tumorerkrankung) zu den häufigsten Krebserkrankungen. Rund drei Viertel der PatientInnen weisen bei der Erstuntersuchung einen oberflächlichen, nicht-muskelinvasiven Tumor auf, bei dem restlichen Viertel ist der Tumor bereits in die Muskulatur eingewachsen oder hat auf andere Organe übergegriffen (invasive Tumore). Die Einteilung von Blasenkrebs basiert – ebenso wie bei anderen Tumoren – auf der Größe desTumors und der Dissemination und Proliferation der Tumorzellen in umliegendes Gewebe. Die in dieser Übersichtsarbeit relevante Indikation ist jene der nicht-muskelinvasiven Tumore (NMIBC), die eine heterogene Gruppe aus den Stadien Ta (ca 70 % der NMIBC sind nicht invasive papilläre Karzinome), T1 (bei ca 7 % durchdringt der Tumor die Schleimhaut, aber greift den Muskel nicht an) und CIS (5-10 % Carcinoma in Situ) ist.

Risiken:
Umwelt- und berufsbedingte Faktoren

individuelle Faktoren:
Rauchen

Risken für die Entstehung von Blasenkarzinomen sind zum einen Umwelt- und berufsbedingte Faktoren (Karzinogene, die mit dem Harn ausgeschieden werden) und zum anderen individuelle Faktoren wie Rauchen oder chronische Entzündungen der Harnblase (durch Harnblasensteine oder Dauerkatheter). Für den Einzelnen sind damit klinische Erscheinungsformen wie irritative Entleerungssymptome, Schmerzen infolge lokal fortgeschrittener oder metastasierender Tumore und andere Symptome (z. B. Müdigkeit, Gewichtsverlust, Gedeihstörungen, Schlaflosigkeit) verbunden.

Rezidive sin häufig und machen lebenslange Kontrollen erforderlich

Obwohl in der Mehrzahl der Fälle nicht unmittelbar lebensbedrohlich, sind Rezidive und progrediente Erkrankung häufig, die bei bis zu 55 % der PatientInnen innerhalb von 5 Jahren nach der Diagnose zu einem Rückfall führen und lebenslange Kontrolluntersuchungen erforderlich machen.

Beschreibung der Technologie

intravesikale Chemotherapie mit regionaler Hyperthermie (RF-CHT)

Synergo®:
Radiofrequenz induzierte Bestrahlung

ambulant
mehrere Behandlungen
20 Minuten pro Sitzung

Die untersuchte Technologie kombiniert die intravesikale Chemotherapie mit regionaler Hyperthermie (HT) und wird auch als Thermochemotherapie oder Chemohyperthermie (CHT) bezeichnet. Die am häufigsten verwendete Anwendung ist das Synergo®-System, bei dem die HT durch direkte Radiofrequenz-induzierte Bestrahlung des Urothels verabreicht wird. Zur Unterscheidung von anderen wärmeerzeugenden Techniken, die nicht Teil der vorliegenden Bewertung sind, wird die Intervention im gesamten Bericht als Radiofrequenz-induzierte intravesikale Chemohyperthermie (RF-CHT) bezeichnet. Im Allgemeinen wird die RF-CHT ambulant durchgeführt. Die Behandlung besteht in der Regel aus zwei 20-30-minütigen Sitzungen und zielt darauf ab, während mindestens 20 Minuten pro Sitzung eine Temperatur von über 41°C zu erreichen. Es gibt prophylaktische und ablative Protokolle, die beide aus einer Reihe von Behandlungen bestehen.

Methoden

Forschungsfrage: Ist RF-CHT im Vergleich zu anderen Interventionen wirksamer und sicherer?

Das Ziel dieser systematischen Übersichtsarbeit war es, die Frage zu beantworten, ob RF-CHT wirksamer und sicherer oder ebenso wirksam, aber sicherer in Bezug auf die relevanten Endpunkte ist. Die Forschungsfrage wurde durch eine systematische Auswertung der rezentesten Literatur über RF-CHT untersucht. Dabei wurde das EUnetHTA-Core-Modell® herangezogen.

Suche in 4 Datenbanken: 139 Treffer nach Deduplizierung

Die systematische Suche wurde am 9. und am 20. Dezember 2019 in vier Datenbanken (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA]) durchgeführt und basierte auf der Suchstrategie, die NICE in einem gleichnamigen Assessment verwendete. Die Literatursuche beschränkte sich auf den Zeitraum ab April 2018 (Ende der NICE Suche) und auf englische und deutsche Artikel. Nach der Deduplikation wurden 139 Zitate identifiziert.

Suche in CTRs nach laufenden Studien

Drei klinische Studienregister (ClinicalTrials.gov; World Health Organisation International Clinical Trials Registry Portal [WHO-ICTRP]; EU Clinical Trials) wurden am 3. Februar 2020 nach laufenden oder unveröffentlichten Studien durchsucht.

Klinische Wirksamkeit

Endpunkte zur Ableitung einer Empfehlung hinsichtlich Wirksamkeit

Die folgenden Ergebnisse wurden als *entscheidend* für die Ableitung einer Empfehlung definiert: Gesamtüberleben (OS), Krankheitsspezifisches Überleben (DSS), Lebensqualität (QoL). OS wurde in drei kontrollierten Studien berichtet. Über DSS wurde in einer kontrollierten Studie berichtet. Die Lebensqualität wurde in 4 kontrollierten Studien berichtet, obwohl nur 1 Studie ein standardisiertes Messinstrument verwendete.

kritische Endpunkte zur Beurteilung: Überleben, krankheitsspezifisches Überleben, Lebensqualität

Die folgenden Ergebnisse wurden als *wichtig* für die Ausarbeitung einer Empfehlung definiert: Krankheitsfreies Überleben (DFS), Progressionsfreies Überleben (PFS), Rezidivfreies Überleben (RFS). Über die DFS wurde in 2 kontrollierten Studien berichtet, über die PFS in 3 kontrollierten Studien und über die RFS in 4 kontrollierten Studien.

4 RCTs
1 NRCT

Die folgenden Ergebnisse wurden als *Surrogate* definiert, um eine Empfehlung abzuleiten: Vollständige Reaktion (CR), die in 4 kontrollierten Studien berichtet wurde; Radikale Zystektomie (RC)/Blasenerhaltungsrate, die in 1 kontrollierten Studie berichtet wurde.

Sicherheit

kritischer Endpunkt für die Bewertung der Sicherheit

Die folgenden Ergebnisse wurden als *entscheidend* für die Ausarbeitung einer Empfehlung definiert: Schwere unerwünschte Ereignisse (einschließlich gemeldeter Todesfälle). Weitere *wichtige* Ergebnisse, die berücksichtigt wurden, waren Unerwünschte Ereignisse. Die Einschlusskriterien der Studie zur Beurteilung der Sicherheit unterschieden sich von den Kriterien zur Beurteilung der klinischen Wirksamkeit. Zusätzlich zu den für die Wirksamkeitsanalyse verwendeten RCTs und NRCTs wurden prospektive Studien ohne Kontrollgruppe für die Beurteilung der Sicherheit berücksichtigt, wenn sie mindestens 10 PatientInnen enthielten.

schwere unerwünschte Ereignisse auch Fallserien mit ≥ 10 PatientInnen

Ergebnisse

Verfügbare Evidenz

4 RCTs und 1 NRCT wurden eingeschlossen

Zur Bewertung der Wirksamkeit von RF-CHT in der Behandlung von nicht-muskelinvasivem Blasenkrebs wurden vier RCTs und ein NRCT eingeschlossen. Unter den kontrollierten Studien waren 2 Single-Center-Studien. Alle Studien fanden in Europa und Israel statt. PatientInnen wurden in die Studien eingeschlossen, wenn bei ihnen NMIBC mit mittlerem oder hohem Risiko diagnostiziert worden war (oder die Studien in dem NICE-Review inkludiert waren, auf dem dieses Update basiert). Die PatientInnenpopulation (n=503, von denen 243 die Intervention RF-CHT erhielten) variierte erheblich hinsichtlich des Stadiums der NMIBC, der Primärtumoren und/oder rezidivierenden Läsionen und/oder einer früheren Behandlung. Das mittlere Alter war 64,3 bis 77 Jahre. In drei Studien wurden entweder intravesikale Instillationen mit Mitomycin-C (MMC; 2 Studien) oder mit Bacille Calmette-Guérin Immuntherapie (BCG; (1 Studie) als Vergleich herangezogen. Die NRCT-PatientInnen konnten zwischen Instillationen mit MMC oder MMC, die über EMDA (Electromotive drug administration) bereitgestellt wurden, als Komparatoren wählen.

gesamte PatientInnenpopulation: 503 PatienInnen, davon 243 die RF-CHT erhielten

für die Bewertung der Sicherheit wurden zusätzlich 11 Fallserien eingeschlossen

Aus der systematischen Literaturrecherche des ursprünglichen NICE-Review, auf dem dieses Update basierte, wurden 11 einarmige Studien einbezogen. In der aktualisierten systematischen Literaturrecherche wurden keine neuen Studien identifiziert. Die einarmigen Studien schlossen 480 PatientInnen mit oberflächlichen Übergangszellkarzinomen der Blase ein. Das mittlere Alter lag zwischen 57,3 und 73 Jahren. Auch die ein-armigen Studien wurden in Europa und Israel durchgeführt

RCTs: einige Qualitätsmängel
NRCT: moderates RoB
Fallstudien: mittleres bis hohes RoB

Das Risk of Bias (RoB) der vier eingeschlossenen RCTs wurde mit „einigen Bedenken“ eingestuft, hauptsächlich aufgrund fehlender Informationen über den Randomisierungsprozess, den Verblindungsprozess und möglicherweise fehlender Daten. Die NRCT wurde mit einer moderaten RoB und die 11 einarmigen Studien mit einer mittleren bis hohen RoB bewertet.

Klinische Wirksamkeit

kein Unterschied im OS (3 Studien) und 2/3 Studien berichteten über keinen Unterschied in RFS oder PFS

Die Unterschiede in der Gesamtüberlebenszeit waren in drei von drei Studien (die darüber berichteten), die als mäßig aussagekräftig eingestuft wurden, nicht signifikant. Es wurden statistisch signifikante Unterschiede bezüglich DSS (zugunsten der Kontrollgruppe) und DFS (zugunsten der Intervention in 1 Studie) gefunden; diese Ergebnisse wurden mit einer niedrigen Evidenzstärke bewertet. Zwei von drei Studien berichteten keinen signifikanten Unterschied bei RFS nach 24 Monaten (geringe Evidenzstärke), ebenso zeigten zwei von drei Studien nicht-signifikante Unterschiede bei PFS (geringe Evidenzstärke). Eine Studie, die über CR berichtete, fand einen statistisch signifikanten Unterschied zugunsten der IG, aber für die CIS-Untergruppe wurden in den zwei Studien nicht-signifikante Unterschiede berichtet (insgesamt niedrige Evidenzstärke).

einige signifikante Unterschiede bei DSS, DFS und CR (letzteres nicht für die CIS-Untergruppe)

keine Unterschiede bei LQ oder bei radikaler Zystektomie berichtet

Es wurden keine Informationen über statistische Signifikanztests bezüglich der Unterschiede im subjektiven Symptom-Score gegeben, und die absoluten Unterschiede in den Vorher/Nachher-Scores erschienen minimal (geringe Evidenzstärke). In der Studie, die den EQ-5D zur Messung der Lebensqualität verwendete, wurden keine statistisch signifikanten Unterschiede zwischen den Scores berichtet (geringe Evidenzstärke). Eine Studie untersuchte radikale Zystektomie-Raten und berichtete über nicht-signifikante Unterschiede zwischen den Gruppen (geringe Evidenzstärke).

Sicherheit

24 SAEs in den kontrollierten Studien (IG 17, CG 7); 25 SAEs in Fallserien

In den kontrollierten Studien wurden 11 SAE in der Interventionsgruppe und 14 SAE in der Kontrollgruppe dokumentiert, aber es wurden keine statistischen Tests durchgeführt. Die Fallserien berichteten über insgesamt 45 SAEs unter den mit der Intervention behandelten PatientInnen. Die Qualität der Evidenz in Bezug auf die Sicherheit wurde als sehr niedrig bewertet.

Laufende Studien

2 laufende einarmige Studien

Derzeit gibt es keine laufenden randomisierten kontrollierten Studien, die die Wirksamkeit des Synergo®-Systems untersuchen. Die Suche in den Registern zu klinischen Studien ergab jedoch zwei laufende einarmige Studien: NCT-03335059 (mit einem geschätzten Abschluss der Studie im März 2025) und EUCTR2016-000049-30-ES (kein geschätztes Abschlussdatum angegeben).

Kostenerstattung

in Europa kommerziell verfügbar

CE- Mark (2001), aber nicht FDA- Zulassung

Das Produkt ist in den Niederlanden, Österreich, Deutschland, Norwegen, Italien, der Tschechischen Republik, Großbritannien und der Schweiz erhältlich. Außerhalb Europas ist es in Israel, der Türkei, Brasilien und China (ab Mitte 2020) erhältlich. Es hält seit 2001 eine CE-Zertifizierung und ist seitdem in einigen öffentlichen und Universitätskliniken verfügbar. Das Gerät ist derzeit nicht von der FDA zugelassen.

Diskussion

systematischer Review der prospektive Evidenz für RF-CHT präsentiert

Das Ziel der vorliegenden Bewertung war es, die verfügbare Evidenz zur RF-CHT zusammenzufassen, wobei ein NICE-Review (2018) als Ausgangspunkt genommen wurde und zusätzliche Studien, die die (strengeren) Einschlusskriterien in dieser systematischen Literaturrecherche erfüllten, eingeschlossen wurden. Es ist dies die erste systematische Übersicht über die RF-CHT für PatientInnen mit nicht-muskelinvasivem Blasenkrebs, die sich nur auf prospektive Evidenz stützt.

Gesamtpopulation von 503 PatientInnen in den kontrollierten Studien, davon 243 mit RF-CHT

Insgesamt wurden vier RCTs und ein NRCT in die Analyse der klinischen Wirksamkeit einbezogen, davon wurden 243 PatientInnen mit RF-CHT behandelt, während 260 PatientInnen zu den Kontrollgruppen gehörten, die sich entweder einer intravesikalen Chemo- oder Immuntherapie, einem Scheinverfahren oder einer alternativen intravesikalen Chemohyperthermie-Methode (EMDA) unterzogen.

wahrscheinlich keine Auswirkung auf das Gesamtüberleben

nur geringe Gewissheit für andere Ergebnisse und LQ

Mit einer moderaten Sicherheit kann der Schluss gezogen werden, dass die RF-CHT keinen Einfluss auf das Gesamtüberleben hat. Die Evidenz zu anderen Endpunkten war von geringer Qualität und widersprüchlich. Auch die Evidenz zur Lebensqualität war im Allgemeinen schlecht, da es keine statistischen Signifikanztests gab, so dass keine Schlussfolgerungen gezogen werden können. Wo ein standardisiertes Instrument und statistische Tests angewandt wurden, konnte kein Vorteil für die RF-CHT beobachtet werden. Die Anzahl der SAEs war in den kontrollierten Studien relativ ähnlich, und auch hier können ohne statistische Signifikanztests keine Schlussfolgerungen hinsichtlich des Sicherheitsprofils gezogen werden.

Heterogenität bei der Meldung unerwünschter Ereignisse und fehlende statistische Signifikanztests

In den kontrollierten Studien wurden insgesamt 24 schwerwiegende Nebenwirkungen (SAE) gemeldet (IG 17; CG 7). Darüber hinaus traten in den einarmigen Studien 25 SAE auf. Die Berichterstattung über unerwünschte Ereignisse war sehr heterogen, was eine Analyse der vergleichenden Sicherheit von RF-CHT verhindert.

Empfehlung

vorliegende Evidenz zu heterogen und gering

Technologie ist experimentell und sollte nur im Rahmen klinischer Studien eingesetzt werden

Aufgrund der Heterogenität der eingeschlossenen Studienpopulationen und Indikationen sowie der Vielfalt der Behandlungsschemata und Komparatoren ist ein umfassendes Verständnis der vergleichenden Risiken und Vorteile der Radiofrequenz-induzierten intravesikalen Chemohyperthermie (RF-CHT) im Vergleich zu alternativen Behandlungsoptionen oder Scheinverfahren auf der Grundlage der derzeit verfügbaren Evidenz nicht möglich. Dies gilt selbst dann, wenn man die Evidenz getrennt nach Indikationen und Komparatoren bewertet, weil die Nachbeobachtung zu kurz ist und es an qualitativ hochwertiger Evidenz aus randomisierten kontrollierten Studien fehlt. Da die derzeitige Evidenz begrenzt ist, muss die Technologie als experimentell betrachtet werden. Als solche wird sie nicht für die Aufnahme in den Leistungskatalog empfohlen, könnte aber im Rahmen klinischer Studien eingesetzt werden, um den wissenschaftlichen Kenntnisstand zu erweitern.

1 Scope

1.1 PICO question

PIKO-Frage

Is radiofrequency-induced intravesical chemohyperthermia (RF-CHT) more effective and safer in terms of overall survival, disease-specific survival time, quality of life and serious adverse events than other treatments in patients with intermediate or high-risk non-muscle invasive bladder cancer (NMIBC) who are Bacillus Calmette-Guérin (BCG) immunotherapy naïve (or who previously received but stopped BCG more than three years ago)?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion and exclusion criteria

Population	**Inclusion criteria** Patients with intermediate-/high-risk non-muscle-invasive bladder cancer (NMIBC) who have never been treated with BCG immunotherapy or who previously received but stopped BCG more than three years ago **Exclusion criteria** stage ≥ T2 tumors previous treatment with intravesical BCG therapy less than 3 years ago **Treatment regimen** Neoadjuvant (before transurethral resection) or adjuvant (after transurethral resection, also referred to as prophylactic treatment) **MeSH-terms** Urinary Bladder Neoplasms_MeSH Unique ID: D001749 Malignant neoplasm of bladder _ICD-10 code: C67
Intervention	radiofrequency-induced intravesical chemohyperthermia **Synonyms** microwave-induced bladder wall hyperthermia (HT)/intravesical chemotherapy and hyperthermia by radiation/radiofrequency-induced thermo-chemotherapy effect (RITE) **Device** Synergo® system in combination with chemotherapy or immunotherapy **Excluded hyperthermia devices** Hyperthermia systems based on conductive (Combat BRS® and Unithermia®) or loco-regional heating through external RF-induced waves (BSD-2000®) **MeSH-terms** Radiofrequency Ablation_MeSH Unique ID: D000078703 Induced Hyperthermia_MeSH Unique ID: D006979
Control	❁ Intravesical chemotherapy ❁ Intravesical immunotherapy (BCG) ❁ Radical cystectomy

Outcomes	
Efficacy	**Clinical and patient-relevant endpoints** • Overall survival (OS) • Disease-specific survival time (DSS) • Quality of life (including symptoms) (QoL) • Disease-free survival (DFS) • Progression-free survival (PFS)/time to progression • Recurrence-free survival (RFS)/time to recurrence **Surrogate endpoints** • Complete response (CR) • Radical cystectomy/Bladder preservation rate
Safety	• Serious adverse events (SAEs) • Adverse events (AEs)
Study design	
Efficacy	• Randomised controlled trials (RCT) • prospective non-randomised controlled trials (NRCT)
Safety	• Randomised controlled trials (RCT) • prospective non-randomised controlled trials (NRCT) • Prospective Case Series $\geq$ 10 patients

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is the radiofrequency-induced intravesical chemohyperthermia and the comparator(s)?
A0020	For which indications has radiofrequency-induced intravesical chemohyperthermia received marketing authorisation or CE marking?
B0002	What is the claimed benefit of radiofrequency-induced intravesical chemohyperthermia in relation to the comparators?
B0004	Who administers radiofrequency-induced intravesical chemohyperthermia and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use radiofrequency-induced intravesical chemohyperthermia and the comparator(s)?
B0009	What supplies are needed to use radiofrequency-induced intravesical chemohyperthermia and the comparator(s)?
A0021	What is the reimbursement status of radiofrequency-induced intravesical chemohyperthermia?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is radiofrequency-induced intravesical chemohyperthermia used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for non-muscle-invasive bladder cancer?
A0004	What is the natural course of non-muscle-invasive bladder cancer?
A0005	What is the burden of disease for the patients with non-muscle-invasive bladder cancer?
A0006	What are the consequences of non-muscle-invasive bladder cancer for the society?
A0024	How is non-muscle-invasive bladder cancer currently diagnosed according to published guidelines and in practice?
A0025	How is non-muscle-invasive bladder cancer currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is radiofrequency-induced intravesical chemohyperthermia utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of radiofrequency-induced intravesical chemohyperthermia on mortality?
D0003	What is the effect of radiofrequency-induced intravesical chemohyperthermia on the mortality due to causes other than the target disease?
D0005	How does radiofrequency-induced intravesical chemohyperthermia affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does radiofrequency-induced intravesical chemohyperthermia affect progression (or recurrence) of the disease or health condition?

Clinical Effectiveness	
Element ID	**Research question**
D0011	What is the effect of radiofrequency-induced intravesical chemohyperthermia on patients' body functions?
D0016	How does the use of radiofrequency-induced intravesical chemohyperthermia affect activities of daily living?
D0012	What is the effect of radiofrequency-induced intravesical chemohyperthermia on generic health-related quality of life?
D0013	What is the effect of radiofrequency-induced intravesical chemohyperthermia on disease-specific quality of life?
D0017	Was the use of radiofrequency-induced intravesical chemohyperthermia worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is radiofrequency-induced intravesical chemohyperthermia in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying radiofrequency-induced intravesical chemohyperthermia?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of radiofrequency-induced intravesical chemohyperthermia?
C0007	Are the radiofrequency-induced intravesical chemohyperthermia and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of radiofrequency-induced intravesical chemohyperthermia and the comparator?

2.2 Sources

Description of the technology

Quellen: systematische Suche, Handsuche sowie Informationen der Hersteller

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers

Health problem and Current Use

Quellen: Handsuche, Informationen der Hersteller und Einreicher

- Hand search for guidelines on the management of bladder cancer in the database of the Arbeitsgemeinschaft der Wissenschafltichen Medizinischen Fachgesellschaften e.V. (AWMF), in PubMed and in Google
- Documentation provided by the manufacturers
- Information provided by the submitting hospitals

Hand search in the UpToDate database, PubMed and in Google

Update der systematischen Literatursuche des NICE-Interventional Procedure Overviews

For the domains of clinical effectiveness and safety, a recently published NICE-Review [1] was used as the basis for this report and a systematic update literature search was conducted to capture relevant studies published since the NICE-Review. Both information retrieving processes are described in detail in the following chapter.

2.3 Systematic literature search

NICE: systematische Literatursuche in vier Datenbanken

During the scoping process we identified a recently published NICE review [1] providing an interventional procedure overview of RF-CHT for non-muscle-invasive bladder cancer. The corresponding literature search was conducted on April 30th 2018 in the following databases

- Medline via Ovid
- PreMedline via Ovid
- Embase via Ovid
- The Cochrane Library (CDSR, CENTRAL, HTA)

NICE: basierend auf drei Reviews, 2 RCTs und 1 Fallserie

The authors stated that trial registries and the internet were also searched. No language restriction was applied to the searches. The search strategy for Medline was published in the above mentioned review. The authors stated that a similar search strategy was used to identify relevant papers in the alternative databases. No information about the total number of hits was given. The NICE-Review was primarily based on one systematic review [2], an update thereof [3] and a further non-systematic review [4], two RCTs [5-7] (the latter publication was a long-term follow-up of the study described in 2003) and one case series [8].

LBI-HTA Bericht exkludiert retrospektive Studien und nicht publizierte Daten aus NICE-Reviews

Update-Suche ergibt 139 Treffer

We included the studies that had been included in the NICE review but excluded any retrospective studies and unpublished data that had been included in the NICE-Review and conducted a (systematic) update search on December 20th 2019 using the search strategy from the NICE review. The systematic search was restricted to articles published from April 2018 onwards (so as not to duplicate the search in the NICE-Review) and to articles published in English or German. After deduplication, 139 new citations were identified. The specific search strategies employed can be found in the Appendix.

Suche nach laufenden Studien ergibt 2 (jedoch einarmige) Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials (EudraCT)) was conducted on the 03.02.2020 resulting in 34 hits. Of those, only two single-arm trials were investigating radiofrequency-induced intravesical chemohyperthermia using the SYNERGO® device (see Appendix, Chapter “List of ongoing randomised controlled trials”). The other 32 ongoing trials were excluded because of other study designs (e.g. single-arm), other interventions or other populations.

Herstellerinformation ergibt keine neuen Studien

The manufacturers of the SYNERGO®-device were contacted on December 9th 2019. They submitted 49 publications. But no new citations were identified.

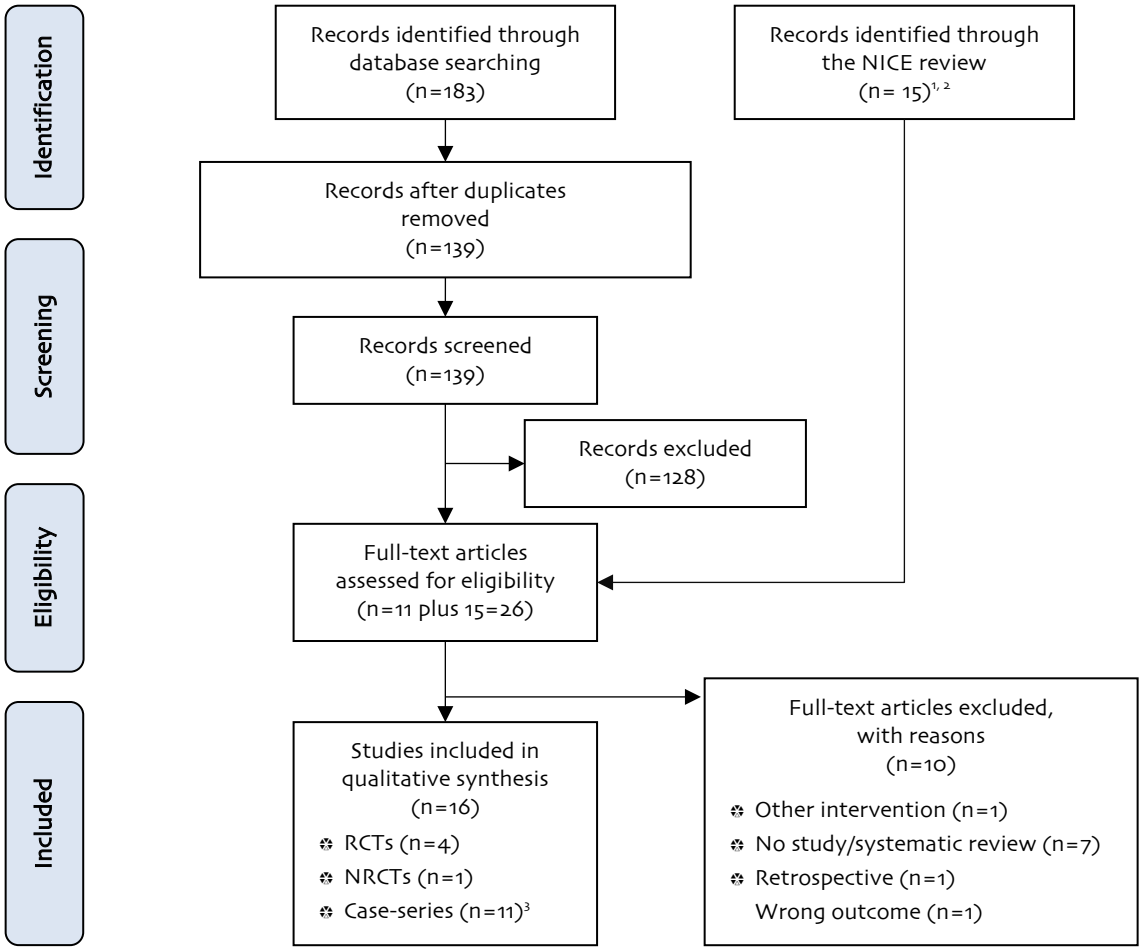
2.4 Flow chart of study selection

Literaturauswahl: 16 Studien eingeschlossen

Overall, we included 15 studies from the NICE-review.

The update of the systematic literature search revealed 139 hits. The references were screened by two independent researchers (EF, LS) with any disagreements being resolved through discussions. Excluded were reviews, editorials, preclinical studies and case reports with fewer than 10 patients. In contrast to the NICE review, we did not include conference abstracts or retrospective studies.

The selection process is displayed in Figure 2-1.



[1] *Colombo, 2003 [6] and Colombo, 2011 [7] are summarized as one study, since both publications refer to the same study population, but include different follow-up periods.*

[2] *Arends, 2014 [5] was considered a retrospective study and thus excluded from the analysis.*

[3] *Erturhan, 2015 [8] was initiated as RCT, but due to a global problem supplying BCG, finally conducted as a single-arm trial.*

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

2.5 Analysis

Daten der einzelnen Studien extrahiert und kontrolliert

The data retrieved from the selected studies (see Chapter 2.4) were systematically extracted into a data extraction table by one researcher (EF) (see Appendix Table A-1 to Table A-4). Another researcher (LS) checked the data for integrity and completeness. No further data processing (e.g., indirect comparison) was applied.

Bewertung des Bias-Risikos mittels Cochrane RoB 2.0 tool, ROBINS-I und IHE-Checklist

The quality of the studies were systematically assessed by both authors using the revised Cochrane Risk of Bias tool (RoB 2.0) [9] for randomised controlled studies, the Risk of Bias in non-randomised studies of intervention tool (ROBINS-I) [10] for non-randomised controlled trials and the Institute for Health Economics (IHE) Checklist for single-arm studies [11]. The quality assessments are presented in Table A-5 to Table A-7 in the Appendix).

2.6 Synthesis

Evidenzsynthese mittels GRADE

Based on the data extraction tables (see Appendix), data on each selected outcome category were analysed across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [12] by the first author (EF) and checked by the second author (LS) [12]. The research questions were answered in plain text format with reference to GRADE evidence tables that are included in the Appendix, the results of which were summarised in Table A-8.

3 Description and technical characteristics of technolgy

Features of the technology and comparators

B0001 – What is radiofrequency-induced intravesical chemohyperthermia?

The investigated technology combines intravesical chemotherapy with regional hyperthermia (HT) and is also referred to as thermochemotherapy or chemohyperthermia (CHT) [13].

Technologie: Chemohyperthermia

The most commonly used application is the Synergo® system, in which local HT is administered via direct radiofrequency-induced irradiation of the urothelium. **To distinguish it from other heat-generating techniques, which are not part of the present assessment, the intervention is referred to as radiofrequency-induced intravesical chemohyperthermia (RF-CHT) throughout the report.**

Gerät: Synergo® System, welches Hyperthermie intravesikal mittels Radiofrequenz induziert

Radiofrequency is produced by a 915 MHz intravescial applicator, which is located at the distal end of a three-way transurethral 20F catheter. Within the catheter, there is a lumen for the inflation of the balloon, a lumen for fluid introduction and another lumen for the outflow of the fluid [3].

The target intravesical temperature is set between 41°C and 44°C and is measured by five integrated thermocouples. Three of these are tangentially distended from catheter tip to measure the temperature at the bladder neck, the dorsal and lateral bladder walls; two more distantly placed thermocouples measure the temperature in proximal urethra [3]. Throughout the procedure, the temperature and the RF power are continuously monitored and regulated on an external computerised unit, to which the catheter is connected by means of a closed circuit. Additionally, the unit regulates the speed of the peristaltic pump and the cooling of the fluid being pumped into the bladder. The latter is important for urethral thermal protection [3].

intravesikale Temperatur während der Behandlung zwischen 41°C und 44°C

Chemotherapeutikum wird extern gekühlt und in einem geschlossenen Kreislauf wieder in Harnblase gepumpt

In general, RF-CHT is performed in an outpatient setting using a local anaesthetic urethra gel. Ultrasound guidance is sometimes used to assess the position of the device. The treatment typically consists of two 20-30 minutes sessions and aims to achieve a temperature above 41°C during at least 20 min per session [1, 3]. The chemotherapeutic agent is dissolved in 50-60 ml of saline or distilled water. The reasons for changing the solution are the continuous dilution by newly produced urine and serum exudation, potential disintegration of the solution and/or absorption [3].

Behandlung erfolgt in 2 aufeinanderfolgenden Einheiten von 20-30 min, wobei jeweils eine neu hergestellte Lösung verwendet wird

Most commonly, the prophylactic treatment schedule consists of an induction phase of six once-weekly sessions, while the induction phase of ablative protocols in general consists of eight once-weekly sessions. Both protocols are extended for 4 to 12 monthly or quarterly sessions [3, 4]).

prophylaktische und ablative Anwendung möglich

Patients should not be treated with RF-CHT if the bladder volume is less than 150 cm^3, a urinary bladder diverticulum with a cumulative diameter of larger than 1 cm is present (risk of perforation and intraperitoneal diffusion) or catheterisation problems are expected. Furthermore, alternative options should be considered in the presence of non-controlled bladder overactivity, urethral strictures and active urinary tract infections [3, 4].

Ausschlussgründe: geringes Blasenvolumen, Divertikel > 1 cm, akute Infektionen des Harntraktes etc.

Comparators

alternative Therapieoptionen

At present, there are three other device-assisted therapies for non-muscle-invasive bladder cancer available [13]:

Hyperthermie basierend auf konduktiver Hitzeerzeugung (z. B. Combat BRS®)

- Hyperthermia systems based on conductive heat generation (e.g. UniThermia or Combat BRS® system). These systems heat the chemotherapeutic solution externally and recirculate it into the urinary bladder at a stable pressure, constant temperature and flow rate[13].

Hyperthermie aufgrund externer Wärmeerzeugung (z. B. BSD-2000®)

- Hyperthermia systems based on loco-regional heating (e.g. BSD-2000®). The system uses an applicator, which consists of an external phased array of four twin dipole antenna mounted concentrically around the torso and coupled with a water bolus to deliver radiofrequency waves to produce a steerable focal region within the pelvis.

erhöhte Bewegung des Chemotherapeutikums durch elektrischen Strom

- Electromotive drug administration (EMDA), which uses electric currents (between an electrode placed in the bladder and electrodes fixed on the abdomen) to accelerate the movement of drugs.

A0020 – For which indications has radiofrequency-induced intravesical chemohyperthermia received marketing authorisation or CE marking?

Hersteller von Synergo® ist Medical Enterprises Ltd.; CE-Kennzeichnung seit 2001

The manufacturer of the Synergo® radiofrequency hyperthermia device is Medical Enterprises. The device consists of a 915-MHz microwave applicator for delivering chemotherapeutic agent under hyperthermal conditions and a catheter tubing line set (accessory to the RF device) as well as a closed drainage set (accessory to the RF device). The product is CE approved since 2001.

laufende Zulassungsstudie in USA (bis 2022)

Currently, it is not approved by the FDA. However, there is an ongoing trial in the USA (NCT03335059) with an estimated completion date on July 2022 to achieve FDA-clearance in the near future [14].

B0002 – What is the claimed benefit of radiofrequency-induced intravesical chemohyperthermia in relation to the comparators?

am häufigsten verwendetes Chemotherapeutikum: Mitomycin-C

Mitomycin-C (MMC) is the most common intravesical chemotherapy agent used in combination with CHT [2]. There have been several potential reasons described for the improved MMC efficacy when combined with heat. It increases the penetration of MMC into the urothelium due to increased cellular membrane permeability and/or modified blood perfusion. Furthermore, hyperthermia itself possesses a cytotoxic effect, which is known to alter the intracellular metabolism to damage DNA, to impair cellular proliferation and to increase tumour cell apoptosis. Finally, hyperthermia has been shown to increase the cytotoxicity of MMC via a synergistic effect (potentiation), thus making the drug itself more efficient [2, 3]. Besides MMC, Bacillus Calmette-Guérin (BCG), cisplatin, gemcitabine, doxorubincin and epirubicin could be used [13].

Hyperthermie verursacht eine erhöhte Penetration des Therapeutikums in das urotheliale Gewebe und verstärkt dessen zytotoxischen Effekt

RF-CHT ermöglicht ev. kontrolliertere und wirksamere Temperaturerhöhung

Although all comparators use the drug potentiation effect of hyperthermia, the reason for choosing RF-CHT over other applications is the assumption that a more controlled and effective heating can be achieved [3].

Administration, Investments, personnel and tools required to use radiofrequency-induced intravesical chemohyperthermia and the comparator(s)

B0004 – Who administers radiofrequency-induced intravesical chemohyperthermia and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use radiofrequency-induced intravesical chemohyperthermia?

B0009 – What supplies are needed to use radiofrequency-induced intravesical chemohyperthermia

According to the information received by the submitting hospital, the intervention is performed in specialised centres, however it is provided in an outpatient setting, thereby allowing the patient to return to his/her daily activities immediately afterwards. The supplies needed are the Synergo® device as well as additional disposable instruments/equipment and the chemotherapeutic agent of choice.

Intervention nur in spezialisierten Zentren möglich

ambulant/tagesklinisch

The intervention is performed by a well-trained urologist in association with an experienced nurse.

erfahrene/r Urologe/in sowie KrankenpflegerIn nötig

Regulatory & reimbursement status

A0021 – What is the reimbursement status of radiofrequency-induced intravesical chemohyperthermia?

The product is commercially available in the Netherlands, Austria, Germany, Norway, Italy, Czech-Republic, United Kingdom and Switzerland. Outside of Europe it is available in Israel, Turkey, Brazil and China (latter from mid-2020).

Produkt in mehreren europäischen Ländern sowie in Israel, der Türkei, Brasilien und China erhältlich

It has been CE-approved since 2001 and available since then in some public and university hospitals. The device is not yet approved by the FDA, although a clinical study is currently being performed in the USA to determine whether the Synergo® device in combination with MMC treatment is efficacious as second-line therapy for CIS NMIBC BCG-unresponsive patients (NCT03335059) [16]. The registered trial, a multicenter, single-arm study, aims to recruit 106 patients and has been open since 2017.

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is radiofrequency-induced intravesical chemohyperthermia used?

Bladder cancer is the 6th most common malignancy (estimated number of prevalent cases) worldwide and the 4th most common malignancy in Europe [17]. The predominant histologic type in the United States and in Europe is the urothelial (or transitional cell) carcinoma, which accounts for more than 90 percent of all bladder cancers. In all other global areas, non-urothelial carcinomas are more frequent [18]. According to the global cancer observatory, the age-standardized incidence in Austria is 6.2 per 100,000 persons (Europe: 11.3 per 100,000), the age-standardized mortality is 2.7 per 100,000 persons (Europe: 3.0 per 100,000) [17].

Blasenkrebs ist weltweit die 6.-häufigste, in Europa die 4.-häufigste maligne Erkrankung; häufigste Erscheinungsfrom (>90%) ist das Urothelialkarzinom

The condition can be subdivided into non-muscle-invasive (superficial), muscle-invasive and metastatic disease depending on the growth of the tumor and the dissemination and proliferation of the respective cancer cells.

Blasenkrebs unterteilt in nicht-muskel invasiv, muskel invasive und metastasierend

The most prominent symptom of bladder cancer is painless hematuria. However, predominantly in women, the diagnosis is often delayed due to the similarity of symptoms to those of benign disorders e.g. urinary tract infections [19]. Generally, the likelihood of existing bladder cancer increases when the hematuria is visible macroscopically rather than microscopically. Irritative voiding symptoms (e.g. in terms of frequency or urgency, dysuria or urge incontinence) are most common in patients with carcinoma in situ (CIS) and may result from a functional decrease in the bladder capacity, detrusor overactivity, invasion of the trigone or obstruction of the bladder neck or urethra [19]. Constitutional symptoms include fatigue, weight loss, anorexia etc., which are signs of advanced or metastatic disease and therefore are accompanied by a poor prognosis. Associated pain is usually the result of locally advanced or metastatic tumors.

häufigstes (oft auch transientes) Symptom: Hämaturia;
mit zunehmender Schwere der Erkrankung: Inkontinenz, Schmerzen, Müdigkeit

However, due to early diagnosis and treatment, many patients do not die due to their condition, but instead experience multiple recurrences of the disease [19].

frühe Diagnose und Behandlung führt zu längerem Überleben, gleichzeitig jedoch erhöhter Wahrscheinlichkeit eines Wiederauftretens

A0002 – What is the disease or health condition in the scope of this assessment?

According to the WHO system 2016, urothelial neoplasms are classified as either high-grade or low-grade based upon the degree of nuclear anaplasia and architectural abnormalities [19]. The most important element in staging is the extent of invasion into the deeper layers of the bladder itself and the surrounding tissues. In Table 4-1, the Tumour-Node-Metastasis (TNM)-classification schema of the American Joint Committee on Cancer (AJCC) is presented [20].

WHO-Klassifikation als hochgradig oder niedrig-gradig

Staging nach TNM-System

Table 4-1: TNM-classification schema of the American Joint Committee on Cancer (AJCC) [20]

T-primary tumour	
TX	Primary tumour cannot be assessed
To	No evidence of a primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N – regional lymph nodes	
NX	Regional lymph nodes cannot e assessed
No	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the pelvis (hypogastric, obturator, external iliac or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
N3	Metastasis in common iliac lymph node(s)
M – distant metastasis	
Mo	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastases

Abbreviations: ***T****– tumour,* ***N****– (lymph) node,* ***M****– metastatsis,* ***AJCC****– American Joint Commitee on Cancer*

nicht-muskel invasiver Blasenkrebs weiter unterteilt abhängig vom histologischen Befund (Grading)

Non-muscle-invasive bladder urothelial carcinomas (NMIBC) is the condition of interest. This type of bladder cancer can be further divided into subgroups depending on the corresponding histological findings. Table 4-2 shows the histological grading according to the World Health Organisation (WHO).

Table 4-2: Histological grading of non-muscle-invasive bladder cancer according to the WHO (WHO grading according to the European association of urology [21])

1973 WHO grading	
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated
2004 WHO grading system (papillary lesions)	
Papillary urothelial neoplasm of low malignant potential (PUNLMP)	
Low-grade (LG) papillary urothelial carcinoma	
High-grade (HG) papillary urothelial carcinoma	

Abbreviations: ***WHO****– World Health Organisation,* ***LG****– low-grade,* ***HG****– high-grade*

The term superficial bladder cancer comprises a heterogeneous group of tumours: Ta, T1 and carcinoma in situ (CIS). It is estimated that 70% of all superficial bladder cancer are Ta tumours, approx. 7% are T1 (grade 3) and that between 5-10% of the patients have a CIS [22].

NMIBC bezeichnet heterogene Gruppe von Tumoren (Ta, T1 and CIS); wobei 70% zur Kategorie Ta zählen

CIS is defined as a flat, high-grade, non-invasive urothelial carcinoma of the bladder, which can be misinterpreted as an inflammatory lesion during cystoscopy if it is not clarified by biopsy and subsequent histology. It is often multifocal and can occur in the bladder as well as in the upper urinary tract. This stage of disease is classified according to its clinical manifestation as either primary (isolated CIS with no previous or concurrent papillary tumour and no previous CIS), secondary (detected during a follow-up visit of patients with previous tumour not classified as CIS) or concurrent CIS (CIS in presence of any other urothelial tumour in the bladder [21].

CIS-Subgruppen: primär, sekundär oder in Gegenwart von anderen urothelialenTumoren

Although, cystoscopy represents the gold standard for the initial diagnosis and staging, any visible tumour or suspicious lesion should be either biopsied or resected transurethrally to determine its histology and depth of invasion into the submucosal and muscle layers of the bladder. In patients, who present with a positive urine cytology and whose initial cystoscopy showed no visible tumour or suspicious lesion, biopsies of apparently normal appearing urothelium as well as from the prostatic urethra should be performed. Furthermore, a selective catheterization of the ureters and the renal pelvis to collect urine specimens for subsequent cytological examinations is required. Yet, urine cytology has a relatively poor sensitivity, particularly for low-grade tumours [19].

Diagnose mittels Zystoskopie

Tumoren oder verdächtige Stellen können mittels Biopsie untersucht oder vollständig mittels TURBT entfernt werden

A0003 – What are the known risk factors for non-muscle-invasive bladder cancer?

Environmental exposures account for most cases of bladder cancer. It is hypothesised that the disease originates from potential carcinogens (or their activated precursors) that are excreted in the urine, which irritate the surface epithelium of the urinary tract [18].

Blasenkrebs durch Karzinogene, welche mit dem Harn ausgeschieden werden, verursacht

Cigarette smoke is the most important risk factor due to the presence of over 60 known carcinogens and reactive oxygen species. Smokers possess an increased relative risk of 3.89 (men) and 4.64 (women), respectively. Furthermore, the extent of smoking appears to be directly related to the aggressiveness of the cancer as heavy smokers ($\geq$ 30 pack per year) are more likely to suffer from a high-grade tumour and muscle-invasive disease compared to non-smokers [18].

Hauptrisiko: Rauchen

The relationship with occupational carcinogenic exposure was noted over a century ago and is responsible for approx. 10-20 percent of all bladder cancers. The risk in certain professional categories (e.g. leather, textile and electrical workers, miners, operators of plastics and those interacting with industrial chemicals) may be increased up to 200-fold, with the risk of death elevated even more than 30 years thereafter.

10-20 % aller Blasentumore durch beruflichen Umgang mit karzinogenen Stoffen

Further risk factors are chlorination of drinking water, miscellaneous factors like chronic cystitis, Human papilloma virus (HPV) infection, upper urinary tract cancer, bladder augmentation cystoplasty or iatrogenic reasons (e.g. previous radiation therapy, anti-tumour or immunosuppressive agents containing cyclophosphamides) [18].

weitere Risikofaktoren: u. a. Chlorung des Trinkwassers

A0004 What is the natural course of non-muscle-invasive bladder cancer?

häufige Rückkehr des Blasenkrebses als oberflächlicher Tumor

Bladder cancer is a multifocal disease that may pass through different stages (from atypia to dysplasia to tumour). The natural history of the disease is characterized by the disease's propensity to recur as superficial tumour. If a progression to muscle-invasive (stage T2 or higher) is observed, the associated risk of death is much higher.

mediane Überlebensrate ungefähr 10 Jahre

The median survival of patients with bladder cancer is approx. 10 years. Yet, the individual prognosis may differ from patient to patient, depending on existing clinical and pathological factors and potential effects of previously received intravesical treatments [22].

wichtigste Unterscheidung bei unbehandelten Tumoren: Ta/T1 zu CIS

In the case of untreated superficial bladder cancer, the most important distinction is made between patients with Ta/T1 tumours and patients with CIS. Based on a median follow-up of 5 years among non-treated patients, 47% of those with Ta/T1 tumours suffered from recurrences and 9% from progression to muscle-invasive diseases (the depth of invasion, the grade and presence of concomitant CIS have been identified as important prognostic factors for progression.)

hochgradige T1-Tumoren zeigen ähnliche Charakteristika wie muskel-invasive Typen

High-grade T1 tumours share many characteristics with muscle-invasive cancer, including varying degrees of aggressiveness and lethally potential. These tumours tend to recur in 40-70% of the cases and progress to muscle-invasion in 10-20% [23]. In comparison, up to 54% of CIS progress to muscle-invasive disease).

wichtigster prognostischer Faktor: Rückkehr des Tumors bei 1. FU-Untersuchung

Generally, recurrence at the first follow-up cystoscopy has been identified as one of the most important prognostic factors for both future recurrence and progression to muscle-invasive disease [22].

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with non-muscle-invasive bladder cancer?

klinische Symptome: Inkontinenz, Schmerzen

in Mehrheit der PatientInnen Wiederkehr bzw. Progression des Tumors, weshalb lebenslange Kontrolle nötig ist

For the individual, the associated clinical manifestations including irritative voiding symptoms, pain as a result of locally advanced or metastatic tumours and any other constitutional symptoms (e.g. fatigue, weight loss, anorexia or failure to thrive, insomnia) represent the major limitations. Although not immediately life-threatening in the majority of cases, recurrence and progression remain significant issues with up to 55% of the patients relapsing within 5 years of diagnosis [24]. Thus, NMIBC requires long-term surveillance with periodic cystoscopy and (in case of disease) intravesical therapy, which itself may negatively affect the health-related quality of life of the individual patients. Studies have revealed changes within the physical health of patients, which appeared worse than in healthy controls (decrements in physical component summary score, physical functioning and general health), whereas no significant changes regarding the mental health of participants were observed among cases with NMIBC compared to the controls [25]. Furthermore, cystoscopy itself significantly increases the burden of disease as it is an invasive procedure and causes pain and discomfort in one third of patients [24].

A0006 – What are the consequences of non-muscle-invasive bladder cancer for the society?

Blasenkrebs durch häufige Follow-up Untersuchungen teuerste behandelbare Krebserkrankung

Due to the high prevalence and frequency of recurrence, NMIBC patients will undergo many years of follow-up testing and procedures. Thus, bladder cancer represents the most costly cancer to treat on a per patient basis from diagnosis to death (due to costs associated with surveillance cystoscopy and urine cytology episodes) [26]. Approximately 75% of post-diagnosis costs relate to pre-operative and intra-operative management including post-surgical complications, triannual examinations and semi-annual diagnostic and laboratory testing in UK [27]. In contrast to NMIBC, expenditures for MIBC diseases are nearly three times those for patient with stage Tis/Ta and two times for those with stage T1 [27].

Current clinical management of the disease or health condition

A0024 – How is non-muscle-invasive bladder cancer currently diagnosed according to published guidelines and in practice?

Diagnose mittels Blasenspiegelung und Zytologie

The predominant symptom is the presence of an otherwise unexplained hematuria in individuals over 40 years. The evaluation should consist of cystoscopy, urinary cytology (microscopic and gross examination and dipstick chemical test) and evaluation of the upper tracts, since urothelial malignancy can be multifocal.

weiters werden Tastuntersuchung sowie bildgebende Verfahren eingesetzt

A physical examination, although unremarkable in most patients, might identify abnormal findings, which might appear as the following [19]:

- A solid pelvic mass may be felt in advanced cases
- Induration of the prostate gland, if the bladder cancer involves the bladder neck and invades the prostate
- Inguinal adenopathy can be present
- Nodularity in the periumbilical region in advanced lesions involving the dome of the bladder
- Abdominal examination may reveal the presence of substantially enlarged para-aortic lymph nodes or hepatic metastases.

Radiographic imaging of the upper tract either by computed tomography scan of the abdomen and/or the pelvis with urography or renal ultrasound to evaluate both the collecting systems and the renal cortex are recommended. MRI may be used in patients with known allergy to iodinated contrast agent.

TNM staging erfolgt nach transurethraler Resektion des Tumors (TURBT)

For staging, the TNM system (8th edition, 2017) is used [28]. It can be applied to urothelial carcinoma, squamous cell carcinoma, undifferentiated carcinoma and adenocarcinoma of the bladder and is determined by transurethral resection of the bladder tumour (TURBT) and bladder biopsies.

Unterteilung nach Risikogruppen entsprechend der Empfehlungen der EAU

Additionally, a risk stratification based on the European Association of Urologists (EAU) guidelines 2016 can be applied [29]:

- *Low risk* – solitary, low-grade Ta primary tumour, <3 cm in diameter, no CIS
- *Intermediate risk* – all tumours not meeting the criteria for low risk or high risk
- *High risk* – any of the following: CIS, high-grade disease, or a T1 lesion. In addition, tumours having all of the following are classified as high risk: multiple lesions, large (>3 cm), Ta low grade.

A0025 – How is non-muscle-invasive bladder cancer currently managed according to published guidelines and in practice?

Behandlung mittels TURBT, intermediäre- und hoch-risiko Tumoren zusätzlich mit intravesikaler Therapie

The initial treatment is a complete transurethral resection of the bladder tumour (TURBT). In low-risk cases, TURBT alone plus single dose of perioperative intravesical therapy (single postoperative instillation) is given. In patients with intermediate or high-risk tumours, an intravesical therapy is generally recommended. In patients with intermediate-risk tumours (with or without immediate instillation), 1-year full-dose BCG treatment (induction plus 3 weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy for a maximum of 1 year is recommended. For patients with a high-risk disease, immunotherapy such as BCG is the treatment of choice. An induction phase (weekly for six weeks) in patients with intermediate and high-risk disease is generally followed by a maintenance phase. The duration of the latter is generally based upon risk stratification.

bei allen PatientInnen sorgfältige Nachbeobachtung nötig

In all cases, careful surveillance for recurrent or secondary primary tumours in urinary tract is required. Usually, a program of cystoscopy and urine cytology begins three months after the initial treatment. Furthermore, patients with high-risk tumours should undergo a repeat cystoscopy and may require re-resection prior to the initiation of the intravesical therapy. Biopsies of normal-appearing mucosa adjacent and remote to the tumour should be done to determine whether a CIS is present.

in Österreich: intravesikale Therapie des NMIBC mit MMC, Doxorubicin oder Epirubicin

According to guidelines from the Austrian Society of Urology and Andrology, which follow EAU guidelines, NMIBC are treated with a single postoperative instillation, which is followed by 6 weekly instillations. As chemotherapeutic agents either MMC, doxorubicin or epirubicin are used. If an immunotherapy is considered, BCG-instillations or Hemocyan (Immucothel® von Biosyncorp) are applied [30].

Target population

A0007 – What is non-muscle-invasive bladder cancer in this assessment?

Mortalitätsrate in westeuropäischen Ländern zeigt rückläufigen Trend

In Europe, there were about 118,000 cases and 52,000 deaths in 2012. Although the mortality rates in several western European countries have exhibited a downward trends over the last decades, numbers are still increasing in some eastern European countries.

2-häufigste maligne Erkrankung bei älteren Männern und Männern mittleren Alters

Since many patients do not die from their disease, but experience multiple recurrences, a relatively large number of people are alive with history of bladder cancer. In middle-aged and older adult men, bladder cancer is the second most prevalent malignancy after prostate cancer [18].

A0023 – How many people belong to the target population?

mehr als 75 % der PatientInnen > 65 Jahre, deshalb Art der Behandlung von Komorbiditäten abhängig

Bladder cancer occurs primarily in older adults. More than 75% are patients are older than 65 years and survival rates decline with increasing age. Among the factors that may influence any treatment decision, existing comorbidity is often associated with the decision not to undergo cystectomy. Furthermore, the functional status and the clinical context should be considered [18].

in Österreich seit 20 Jahren konstante Rate an Neuerkrankungen

In Austria, there are approximately 1,600 new cases per year; this rate has been constant over the last 20 years [31]. In the same time period, the mortality decreased by 16-20%, amongst other things due to the use of neoadjuvant chemotherapy [30].

A0011 – How much radiofrequency-induced intravesical chemohyperthermia utilised?

Some hospitals in Austria are using this technology. Clinicians estimated that they would use the technique approximately 150 times per year which corresponds to a frequency of 7000 treatments per year across the country.

Schätzung:
ca 150 Anwendungen in 1 Klinik

5 Clinical effectiveness

5.1 Outcomes

kritische Endpunkte für die Bewertung der Wirksamkeit: Überleben, Krankheitsspezifisches Überleben, Lebensqualität

The following outcomes were defined as *crucial* to derive a recommendation:

- Overall survival (OS)
- Disease-specific survival (DSS)
- Quality of life (QoL)

Concerning crucial outcomes, the outcome **OS** is measuring the time from randomization until death from any cause in the intent-to-treat population and was reported by three studies. The demonstration of a statistically significant improvement in overall survival is clearly clinically significant [32]. The percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time is given by the **DSS.** It is either given as a time or rate. Patients who died from causes other than bladder cancer are not counted in this measurement [33, 34]. DSS was reported by one study.

Lebensqualität wurde mittels einem nicht validiertem *subjective symptom score* und dem EQ-5D Fragebogen ermittelt

The outcome **QoL**, that measures aspects of an individual's sense of well-being and ability to carry out activities of daily living, was assessed with either a non-validated questionnaire and given as 'subjective symptom score' or with the generic, standardized instrument EQ-5D. In the questionnaire used for assessing the 'subjective symptom score', the patients were asked about seven predefined disease-specific symptoms, three of which (daytime frequency, nocturia and dysuria) were assessed using a score from 1 to 4 (best to worse) and four of which (urgency, hematuria, urethrorrhagia and urethral pain) were assessed using a score from 1 to 3 (best to worse). The mean score of the individual treatment groups before, during and after treatment completion are reported by three studies [6, 35, 38]. One study applied the EQ-5D, which is a standardized instrument for measuring the generic health status. It is composed of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The respondents rate their level of severity on a 3-level scale. The overall scores is given along a continuum between 1 (best possible health) and 0 (dead) [36, 37].

PatientInnen-relevante Parameter für die Bewertung der Wirksamkeit: Krankheitsfreies Überleben, Progressionsfreies

The following outcomes were defined as *important* to derive a recommendation:

- Disease-free survival (DFS)
- Progression-free survival (PFS)/time to progression
- Recurrence-free survival (RFS)/time to recurrence

Concerning *important* outcomes, **DFS** refers to the time from randomization until disease recurrence or death from any cause [32]. Results regarding the DFS were reported by two studies. The outcome **PFS** (sometimes also referred to as time to progression) is defined as the time from randomization until objective tumour progression or death, whichever occurs first [33]. Three studies provided data concerning this outcome. In NMIBC, progression is defined by the presence or development of any of the following:

- Lamina propria invasion
- Muscle invasive disese (stage ≥ T2)

- Lymph node (N+) or distant metastasis (M1) disease (patient must have previously been diagnosed with N0 and/or M0 disease)
- Increase in grade from low to high (according to the WHO 2004 classification) (including CIS) [34].

Überleben, Überleben ohne Rückkehr des Tumors

Four studies reported the outcome **RFS**, which indicates whether the cancer has recurred, usually after a period of time during which the cancer could not be detected. In NMIBC, the outcome is further specified as reappearance of high-risk disease (high grade, T1 or CIS) after the start of therapy [33, 34].

Surrogate-Parameter für die Beurteilung der Wirksamkeit: komplettes Ansprechen, Radikale Zystektomie(-Rate)

The following outcomes were defined as *surrogates* to derive a recommendation:

- Complete response (CR)
- Radical cystectomy (RC)/bladder preservation rate

The outcome **CR**, which was reported by four studies, refers to patients, in which no detectable evidence of tumour was found. In NMIBC, it is defined as histologic disappearance of malignancy on bladder biopsy and normal cytology and cystectomy [34]. The outcome **RC** indicates the percentage of patients, in whom the bladder had to be removed surgically. Only one study provided results concerning this outcome.

5.2 Included studies

Study characteristics

4 RCTs und 1 NRCT wurden eingeschlossen

For evaluating the effect of radiofrequency-induced intravesical chemohyperthermia for the treatment of non-muscle invasive bladder cancer four RCTs [2, 5, 6, 38, 39] and one NRCT [35] were included. Four studies compared the intervention with intravesical chemotherapy using either BCG [5, 39] or MMC [6, 7, 38] as comparator. The NRCT was designed as a three-arm study, of which the two control groups were treated with MMC either as intravesical chemotherapy or with an EMDA procedure [35]. Two studies included patients with low stage, low grade cancer [35, 38] whilst the other studies included patients at intermediate and high-risk stages.

Studienpopulation insgesamt 503 PatientInnen, davon erhielten 243 die Intervention

There were two single-centre studies, both of which were conducted in Italy [35, 38], while patients from the multi-centre studies (three in total) were recruited from Italy, Israel, the Netherlands, Austria, France, Belgium [5-7] and the UK [39]. The studies were published between 1996 and 2018. The sample sizes of the controlled trials ranged from 52 to 190 patients. Overall, the total study population included 503 patients, of which 243 patients received the intervention.

Patient follow-up ranged from 24 months to 38 months (median). One study provided outcome data for a maximal observational period of (median) 90 months [7]. Most trials did not report on drop-outs.

1 Studie vom Hersteller finanziert, keine Information in 3 Studien

One trial was funded from the manufacturer [5]; one study was publicly funded [39]. The other three studies did not provide information regarding potential sponsorship.

Patients characteristics

PatientInnen mit intermediären- oder hochrisiko NMIBC eingeschlossen

Patients were included in the studies if they had been diagnosed with intermediate- or high-risk NMIBC (or the trials had been included in the NICE review upon which this update is based). In three studies, patients suffered from primary or recurrent tumours [5-7, 38], while two studies included patients with recurrent tumours only [35, 39]. Following the NICE-Review on which this update was based, we included 2 studies that included low-stage, low-grade patients, one of which included patients that had not been previously treated.

Further requirements were a WHO performance status ≥ 2 or 4 [5, 39], and the exclusion of upper tract disease during the last 12 months as well as normal haematological and biochemical blood tests [39]. One study included patients unwilling or unfit to have radical cystectomy [39], while another study explicitly included CIS patients with a positive cytology and/or biopsy [5].

generelle Ausschlussgründe: andere Tumorstadien, akute Infektionen, physiologische Hindernisse

alle PatientInnen (mit Ausnahme einer Studie) bereits mit Chemotherapeutikum behandelt

Generally, patients were not considered eligible due to tumours of different stages or grades, present infections or physiological therapy hindrances. Furthermore, patients with intravesical MMC treatments during the previous 12 months or any BCG therapy in the last 48 months [5] or known MMC or BCG allergy [5-7, 39] were excluded in some studies. One study did not allow any pre-treatment with either local or systemic chemotherapy [6, 7], while only patients receiving chemotherapy during the previous 6 months were excluded in another study [39]. Except for one study, which included previously untreated patients only [35], all study participants had received previous therapies: 6.3% to 41.1% of the patients had received MMC and 4.5% to 100% of the respective study populations had been treated with BCG. In one study, 55.2% to 56.5% of the participants had undergone previous chemotherapy cycles [38].

PatientInnen zwischen 64 und 77 Jahre alt, 15,8 %-29,2 % Frauen

The mean age of patients ranged from 64.3 to 77 years in three studies [5, 38, 39]. The percentage of female patients ranged between 15.8% and 29.2% [5-7, 38, 39]. One study provided no information regarding the age of the patients [6, 7], while another study did neither report the age nor the gender of its participants [35].

Detailed study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profiles in Table A-8.

5.3 Results

Mortality

D0001 – What is the expected beneficial effect of radiofrequency-induced intravesical chemohyperthermia on mortality?

Answering this research question was based on the outcomes “overall survival” and “disease-specific survival”.

keine signifikanten Unterschiede in der Überlebensrate, ...

Overall survival was reported by three studies [7, 38, 39], all of which found no statistically significant differences between the two treatment groups. At 24 months, the hazard ratio (HR) was 1.64 (95% CI: 0.79-3.39) [39]. No absolute numbers were reported by the other two studies [7, 38].

... jedoch statistisch signifikanter Unterschied im krankheitsspezifischen Überleben (1 Studie)

The outcome "disease-specific survival (time)" was reported by a single study [39] and showed a statistically significant difference at 24 months between the two treatment groups in favour of the intervention with a HR of 3.02 (95% CI: 1.04-8.76; p=0.04).

D0003 – What is the effect of radiofrequency-induced intravesical chemohyperthermia on the mortality due to causes other than non-muscle-invasive bladder cancer?

1 komparative Studie berichtet von insg. 15 Todesfällen (IG: 6; CG: 9)

Answering this research question was based on reported deaths during the follow-up period, which was reported by a single study [7]. During the median observational period of 90 months, a total of 15 deaths occurred (IG: 6; CG: 9) [7]. Of these, six deaths were due to unrelated tumours, one was due to a cerebral accident and one due to a heart attack. The aging process was accounted for in two cases, while the reason was unknown in the remaining fatalities.

Morbidity

D0005 – How does radiofrequency-induced intravesical chemohyperthermia affect symptoms and findings (severity, frequency) of non-muscle-invasive bladder cancer?

Answering this research question was based on the outcome QoL, measured with the subjective symptom score.

keine Information zur Signifikanz der Unterschiede im *Subjective Symptom Score*

In the three studies reporting the outcome QoL [6, 35, 38] the score of the intervention group ranged from 9.1 to 11.6 before therapy and from 12.6 to 12.7 after therapy. In the control group, the score ranged from 9.4 to 10.3 before therapy and from 10.7 to 12.2 after therapy. No information about the statistical significance of the differences between groups can be given as no statistical tests were reported.

D0006 – How does radiofrequency-induced intravesical chemohyperthermia affect progression (or recurrence) of non-muscle-invasive bladder cancer?

Answering this research question was based on the outcome "progression-free survival" and "recurrence-free survival" and "complete response".

2/3 Studien zeigen keinen signifikanten Unterschied im PFS

Three studies reported the outcome **PFS**. At 24 months, the percentage of patients without disease progression ranged from 83-100% in the IG and from 87-97.2% in the CG [6, 39]. One of these studies reported a corresponding HR of 1.64 (95% CI 0.82-3.27), which was not statistically significant (p=0.16) [39]. At 90 months, the outcome was reported by one study with 33 of 35 patients (94.3%) in the IG and 37 of 40 patients (92.5%) in the CG showing no sign of progression [7].

3/4 Studien berichten nicht signifikante Unterschiede im RFS

Four studies reported the outcome **RSF**. At 24 months, the percentage of patients without recurrence ranged from 23-84.6% in the IG and from 36.1-64.8% in the CG [5, 6, 39]. Two of these studies reported a non- statistically significant difference between the treatment groups, whereas one study observed a statistically significant difference (p<0.01) [6]. At 38 months, the percentage of patients without recurrence in the IG was 73% (21 of 29 patients), whereas in the CG the percentage was 61% (14 of 23 patients). The difference was not statistically significant (p> 0.30) [38]. At 90 month, 21 of 35 patients (60%) of the IG and 8 of 40 patients (20%) of the CG were recurrence free (no statistical testing reported) [7].

Four studies reported the outcome **CR**. One month after treatment, 60% of the patients receiving the intervention showed a complete response. In contrast, 27.7-40% of the patients receiving the alternative therapies showed a positive outcome. (No information about any statistical test result was given [35]). After a minimum of 36 months, 19 of 29 patients (66%) of the IG and 5 of 23 patients (22%) of the CG showed a complete response. This result was statistically significant ($p<0.01$) [38].

1/4 Studien: signifikanter Unterschied in der Anzahl der PatientInnen mit CR

Two studies reported the outcome for the **CIS-subgroup** [5, 39]. At three months, 88.9% of the patients in the IG vs. 85.7% of the patients of the CG [5] and 30% of the IG vs. 47% of the CG [39] showed a complete response. The differences were not statistically significant in either study.

2/2 Studien: kein signifikanter Unterschied bei CIS-PatientInnen

Function

D0011 – What is the effect of radiofrequency-induced intravesical chemohyperthermia on patients' body functions?

Answering this research question was based on the outcome "QoL" assessed with the subjective symptom score as it includes daytime frequency, nocturia and dysuria, which are considered relevant for answering the research question.

Subjective System Score lässt keine Rückschlüsse zu

Three studies reported an outcome corresponding to the patient's body functions [6, 35, 38], however results were only presented as mean scores without statistical testing, which prevented any further conclusion.

D0016 – How does the use of radiofrequency-induced intravesical chemohyperthermia affect activities of daily living?

Answering this research question was based on the outcome "QoL".

One study [39] applied the EQ-5D and reported no significant differences in scores between the treatment groups. (No absolute numbers or p-values were given).

1 Studie: kein signifikanter Unterschied in den Aktivitäten des tägl. Lebens

Health-related quality of life

D0012 – What is the effect of radiofrequency-induced intravesical chemohyperthermia on generic health-related quality of life?

Answering this research question was based on the outcome "QoL".

A single study [39] applied the EQ-5D and reported no differences in scores between the treatment groups. (No absolute numbers or p-values were given).

1 Studie: keine Unterschiede in der Lebensqualität

D0013 – What is the effect of radiofrequency-induced intravesical chemohyperthermia on disease-specific quality of life?

No evidence was found to answer the research question.

keine Evidenz zur (krankheitspezifischen) Lebensqualität

Patient satisfaction

D0017 – Was the use of radiofrequency-induced intravesical chemohyperthermia worthwhile?

No information was found to answer the research question.

keine Information zur Patientenzufriedenheit

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- Serious adverse events (including reported deaths).

kritischer Endpunkt zur Bewertung der Sicherheit: schwere unerwünschte Wirkungen

Additional *important* outcomes considered were

- Adverse events.

Both outcomes were summarized as 'complications' in the following chapter and in tables. The outcome 'complication' therefore includes direct intervention-related side effects as well as any other negative consequences observed during the follow-up period.

SAEs und AEs zusammengefasst unter "Komplikationen"

6.2 Included Studies

The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. In addition to the RCTs and NRCTs used for the efficacy analysis, prospective studies without a control group were considered for the assessment of safety if they contained a minimum of 10 patients. 11 single-arm studies were included from the systematic literature search of the NICE-Review [1]. No new studies were identified in the updated systematic literature search.

zur Bewertung der Sicherheit zusätzlich zu komparativen Studien 11 einarmige Studien (Fallserien) eingeschlossen

Study characteristics and results of the additionally included studies are displayed in Table A-3 and Table A-4 and in the evidence profile in Table A-8.

Study characteristics

Two studies were explicitly conducted as multicentre trials, where patients were recruited from Italy, Israel, Germany and the Netherlands [40] and from the Netherlands, Israel, Italy and Germany [41], respectively. The remaining nine studies were designed as single centres studies [8, 42-49] and conducted in Italy (n=5), Turkey (n=1), Switzerland (n=1), Israel (n=1) and the UK (n=1). The studies were carried out between 1991 and 2016 with a clinical follow-up ranging from 14 months to 38 months. One study followed its patients for 5.6 months to 9.6 months [46]. The loss-to follow-up was indicated with 4.8% in one study [45], while no drop-out were observed by two studies [8, 49]. No information was given by the remaining studies. None of the studies provided details about funding or potential conflicts of interest.

davon 2 multizentrische Studien

Studiendauer zwischen 14 und 38 Monaten

Four studies used two different concentrations of MMC [40, 44, 46, 49], thus either applying a prophylactic treatment (2x20 mg MMC) or an adjuvant/ curative regimen (2x40 mg MMC). In the remaining studies only single concentrations of MMC were used.

4 Studien verwendeten zwei unterschiedliche Konzentrationen des Chemotherapeutikums

Patients characteristics

Insgesamt 480 PatientInnen, davon 6,6 %-35,7 % Frauen

The single-arm studies included 480 patients with superficial transitional cell carcinomas of the bladder, of which 6.6% to 35.7% were female. The mean age ranged from 57.3 years to 73 years (median).

PatientInnen mit primären sowie wiederkehrenden Tumoren eingeschlossen

Patients with explicitly primary tumours were enrolled in one study [8], while three studies included exclusively patients with recurrent tumours [43, 44, 46]. Three studies included patients suffering from primary as well as recurrent tumours [41, 42, 47]. In four studies [40, 45, 48, 49] no information regarding tumour staging was provided. Patients were selected applying the EORTC scoring system for recurrence and progression and the WHO performance status in addition to several defined laboratory parameters in one study [45].

Ausschlussgründe: nieder-gradige Tumore, andere maligne Erkrankungen des Urogenitalsystems, geringes Blasenvolumen etc.

In terms of exclusion criteria, five studies explicitly excluded patients with stages other than intermediate- or high-risk carcinomas [44-47, 49], other cancers of the urinary system [8, 45, 49] or of variant histology [44, 46]. Further reasons for exclusion were a bladder capacity less than 150 cc [8, 45, 49], bladder diverticulum [8, 45, 46, 49], residual urine >100 ml [44, 47], urethral stricture [44, 45], active urinary tract infection [44, 47], voiding disturbances [45], patients after partial cystectomy [46] and situations impending a 20F catheterisation [46], previous pelvic radiation, neurogenic bladder, persistent hematuria [47], concomitant malignancy [49]. Furthermore, patients younger than 18 years and pregnant women were excluded in one study [44]. Three studies did not state their exclusion criteria [40, 42, 43].

frühere Chemotherapie bei 21,9 %-56,7 % der PatientInnen

Any previous treatment was reported in all but one [47] studies. The percentage of patients that had received chemotherapy ranged from 21.9% to 56.7%. 7.8% to 48% of the respective study population had been treated with MMC [41, 43, 44, 46]. 18.2% to 69.1% with BCG [40-46, 48, 49]. BCG in combination with other agents was applied to 3.33% to 21% [41, 43, 48]. Approx. 5% had been treated with epirubicin [41, 43] and 19% with farmorubicin [44].

6.3 Results

Patient safety

C0008 – How safe is radiofrequency-induced intravesical chemohyperthermia in comparison to the comparator(s)?

Answering the question was based on the outcome 'complications'.

Serious adverse events

in den kontrollierten Studien 24 SAEs (IG 17, CG 7)

Four comparative studies [5, 6, 35, 39] reported the outcome and observed in total 24 SAEs (IG 17; CG 7). In the IG, the complications were due to a contracted bladder (n=1), urethral bleeding (n=1), fever (n=3), tissue reaction (n=1), pain (n=3), dysuria (n=1), thermal reaction of the posterious wall (n=4), skin allergy (n=3), whereas in the CG they were due to retention (n=1), hematuria (n=1), urinary tract infection (n=1), fever (n=1), dysuria (n=1), grade ≥ 4 toxicities (n=2).

In the single-arm studies, 45 SAEs were described [43, 44, 48]. These were due to pain (n=11), severe bladder spasms (n=2), allergic reaction (n=2), iatrogenic urethral perforation (n=1), hematuria (n=3), urinary sepsis (n=3) and severe cystitis symptoms (n=3). In addition 43 cases of moderate to severe cystitis-type symptoms were reported in one study [48].

in den einarmigen Studien: 25 SAEs

A single study reported severe detrusor instabilities in 6/152 (3.9%) of the sessions [43].

Adverse events

In regard to adverse events, Arends and colleagues [5] reported in the IG 1,431 AEs per 1,540 treatments (92.2%) and in the CG 1,525 AEs per 1,923 treatments (79.9%). Of those episodes, significantly less events were observed in the IG group for the following: urinary frequency (OR 0.61; 95% CI 0.49-0.75), nocturia (OR 0.79; 95% CI 0.63-0.98), incontinence (OR 0.22; 95% CI 0.12-0.37), haematuria (OR 0.56; 95% CI 0.42-0.74), fever (OR 0.09; 95% CI 0.04-0.10); fatigue (OR 0.17; 95% CI 0.11-0.28) and arthralgia (OR 0.09; 95% CI 0.03-0.31). However, at the same time, patients receiving the intervention reported significantly more catheterisation difficulties (OR 16.7; 95% CI 5.1-54.0), urethral strictures (OR 2.3; 95% CI 1.3-4.1), bladder tissue reactions (OR 5.8; 95% CI 4.0-8.3), bladder spasms (OR 15.5; 95% CI 9.7-25.0), pain during sessions (OR 26.3; 95% CI 14.3-48.5), pain between sessions (OR 1.6; 95% CI 1.2-2.3) and allergies (OR 2.7; 95% CI 1.6-4.6).

Heterogenität in der Berichterstattung der AEs

In the study performed by Colombo (1996) [38], 29/29 of the patients (100%) in the IG suffered from cystistis syndrome; less cases were observed in the CG, yet the difference was not statistically significant (the exact number was not reported). In the study performed 2003 by the same group [6], 69 AE occurred in the IG and 30 AE in the CG. In both groups, tissue reactions and pain occurred most frequently.

One study described the prevalence of AE per treatment [39]. In the IG, dysuria (54%), increased frequency (52%), hematuria (48%), pain (45%) were reported most frequently, while the most prevalent AEs in CG were dysuria (59%), pain (56%), increased frequency (54%) and increased urgency (48%). In total, one or more adverse events occurred in 81% of the patients. No difference between the treatment modalities was observed [39].

In the single-arm studies, 425 AEs were reported, among which tissue reactions, lower urinary tract symptoms (dysuria, nocturia, urinary frequency), bladder spasms and pain were observed most frequently.

425 AEs in einarmigen Studien

C0002 – Are the harms related to dosage or frequency of applying radiofrequency-induced intravesical chemohyperthermia?

Due to the heterogeneity in reporting adverse events, no information was found to answer the research question.

keine Information zur Dosierung oder Häufigkeit sowie Änderungen über die Zeit

C0004 – How does the frequency or severity of harms change over time or in different settings?

No evidence was found to answer the research question.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of radiofrequency-induced intravesical chemohyperthermia?

keine Evidenz zu jener Patientengruppe, welche am meisten Schäden tragen, noch zu ev. weiteren Risiken

No evidence was found to answer the research question.

C0007 – Are radiofrequency-induced intravesical chemohyperthermia and comparator(s) associated with user-dependent harms?

No evidence was found to answer the research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of radiofrequency-induced intravesical chemohyperthermia and the comparator?

keine Information zu Monitoring

No information was found to answer the research question.

7 Quality of evidence

Biasrisiko der einzelen Studien mit RoB 2.0, ROBINS-I und IHE-Checklist bewertet

RoB for individual randomised controlled studies was assessed with the revised Cochrane risk of bias tool for randomised trials (RoB 2.0) [9]. Non-randomised controlled trials were evaluated using the risk of bias in non-randomised studies of interventions (ROBINS-I) [10]. The RoB for individual studies was assessed with the Institute of Health Economics (IHE) checklist for single-arm studies (CITE) [11]. The RoB assessments for the included studies are presented in Table A-5 to Table A-7 in the Appendix.

4 RCTs: einige Bedenken aufgrund fehlender Information

Regarding the 4 RCTs included, the overall RoB was graded with 'some concerns', mainly due to no available information in terms of the randomisation process, the blinding process and potential missing data.

1 NRCT: moderates Biasrisiko

The NRCT was assessed with a moderate RoB due to no information provided about potential confounding, possible bias due to deviations from intended interventions and bias due to non-blinding.

11 Fallserien: mittleres bis hohes Biasrisiko aufgrund fehlender Information und heterogener Studienpopulationen

The 11 single-arm studies were assessed with a medium to high RoB, with three studies being ranked as high [8, 40, 42] and eight studies as medium [41, 43-49]. The main reasons for downgrading were no information about exclusion criteria, blinding of the outcome assessors or no reports about any loss-to follow-up and patients entering the studies during different stages of the disease.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [12] for each endpoint individually. Each study was rated by two independent researchers (EF, LS). In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [12].

GRADE uses four categories to rank the strength of evidence:

hohe, mittlere, niedrige sowie sehr niedrige Stärke der Evidenz möglich

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-8.

Qualität der Evidenz zur klinischen Wirksamkeit: moderate bis niedrig

Overall the strength of evidence for the clinical effectiveness of RF-CHT in comparison to intravesical chemotherapy alone or institutional standard of care is moderate to very low. Reasons for downgrading were RoB due to a lack of information available, use of a non-validated questionnaire and due to two studies closing prematurely [6, 39].

Qualität der Evidenz zur Sicherheit: sehr niedrig

Regarding safety of the intervention, the quality of evidence was very low (for the outcome complications) due to a high RoB in the included studies, the observational design of more than two third of the trials and inconsistency in the reporting of the results.

Table 7-1: Summary of findings table of of radiofrequency-induced chemohyperthermia compared to alternative treatment for patients with NMIBC

Outcome	Absolute effects (explanation)	Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
Overall survival	IG: 85.0% vs. CG: 90% [39] differences **n.s.** in 3/3 studies	-	239 (3) [7, 38, 39]	⊕⊕⊕◯ MODERATE [a]	-
Disease-specific survival	IG: 89% vs. CG: 96%	HR 3.02 (95% CI 1.04-8.76), differences **stat.sig.** in 1/1 studies	104 (1) [39]	⊕⊕◯◯ LOW [b, c]	-
Disease-free survival	At 24 months IG: 35-60% vs. CG: 20-41%; differences **stat.sig.** in 1/2 studies 10-year estimate IG: 53% vs. CG: 15%, **stat.sig.**	-	187 (2) [6, 7, 39] 83 (1) [7]	⊕⊕◯◯ LOW [a, c]	-
Progression-free survival	At 24 months IG: 83-100% vs. CG:87-97.2% differences **n.s.** in 2/3 studies, p=NR in 1 study At 90 months IG: 33/35 (94.3%) vs. CG: 37/40 (92.5%), p=NR	-	371 (3) [5, 6, 39]	⊕⊕◯◯ LOW [a, c]	Time to progression was not reported by any study.
Recurrence-free survival	At 24 months IG: 23-84.6% vs. CG: 36.1-64.8% differences **stat.sig.** in 1/2 studies At 36-38 months IG: 21/29 (73%) vs. CG: 14/23 (61%) differences **n.s.** in 1/1 studies at 90 months IG: 21/35 (60%) vs. CG: 8/40 (20%), p=NR	-	423 (4) [5-7, 38, 39]	⊕⊕◯◯ LOW [c,d]	Time to recurrence was not reported by any study.
QoL (subjective symptom score)	Before therapy IG: 9.1-11.6 vs. CG: 9.4-10.3, p=NR After therapy IG: 12.6-12.7 vs. CG: 10.7-12.2, p=NR		215 (3) [6, 35, 38]	⊕⊕◯◯ LOW [c, e]	-
QoL (EQ-5D)	No difference between treatement groups was observed, p=NR	-	104 (1) [39]	⊕⊕◯◯ LOW [b, c]	-
Complete response	IG: 66% vs. CG: 22-40%, differences **stat.sig** in 1/2 studies (p=NR in 1/2 studies) CIS-subgroup IG: 30-88.9% vs. CG: 47-85.7%, differences **n.s.** in 2/2 studies	-	132 (CIS-Subgroup 288) (4) [5, 35, 38, 39]	⊕⊕◯◯ LOW [f, g]	Only two studies reported the outcome for the total study population, another two studies provided data for the CIS-subgroup only.

Outcome	Absolute effects (explanation)	Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
Radical cystectomy/bladder preservation rate	Radical cystectomy IG: 2/35 (5.7%) vs. CG: 3/40 (7.5%), differences **n.s.** in 1/1 studies Bladder preservation rate (10-year estimate) IG: 86.1% vs. CG: 78.9%, p=NR	-	83 (1) [7]	⊕⊕◯◯ LOW [b, f]	-
Complications	SAEs Controlled studies (RCT, NRCTs) IG: 11; CG: 14 Single-arm studies: 45		983 (16) [5-8, 35, 38-49]	⊕◯◯◯ VERY LOW [f, h, i]	-

Abbreviations: ***CG*** *– control group,* ***CI*** *– confidence interval,* ***CIS*** *– carcinoma in situ,* ***IG*** *– intervention group,* ***HR*** *– hazard ratio,* ***NR*** *– not reported,* ***n.s.*** *– statistically not significant,* ***QoL*** *– quality of life,* ***SAE*** *– severe adverse event,* ***stat.sig.*** *– statistically significant*

GRADE Working Group grades of evidence

High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect.*

Moderate certainty: *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*

Low certainty: *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect*

Very low certainty: *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.*

Reasons for downgrading:

[a] *2/3 trial terminated prematurely [6, 39]*

[b] *study closed prematurely due to higher than expected CIS recurrence in patients of the intervention group*

[c] *inconsistency due to heterogeneous results or no statistical testing reported so inconsistency could not be assessed*

[d] *imprecision due to wide range of sample estimates and short sample sizes for longer follow-up data points*

[e] *questionnaire used was non-validated*

[f] *high RoB in studies assessing the outcome*

[g] *due to small sample size of trials reporting the outcome for the total study population*

[h] *large degree of variation in reported adverse event rates across studies.*

[i] *11/16 studies were single-arm trials that were assessed with medium to high RoB*

8 Discussion

To our knowledge, this is the first systematic review of RF-CHT for patients with non-muscle invasive bladder cancer that is based on prospective evidence only. The three reviews described in the NICE interventional procedure overview, which was published in 2018, included both prospective as well as retrospective studies [2-4]. The authors of the above mentioned reviews conclude that since only a few properly designed RCTs are available, the intervention is promising, yet has to remain an experimental treatment modality. They do however conclude that the safety profile seem to be acceptable.

systematischer Review ausschließlich basierend auf best available evidence (nur prospektive Studien)

The aim of the present assessment was to summarize the available evidence using the NICE interventional procedure overview as a starting point and including any additional studies meeting the inclusion criteria from an updated systematic literature search.

aufbauend auf NICE-interventional procedure overview

Summary of evidence

Overall, four RCTs and one NRCT were included for the analysis of the clinical efficacy. In total, 243 patients were treated with RF-CHT, while 260 patients were part of the control groups either undergoing intravesical chemo- or immunotherapy, a sham procedure or treated with an alternative intravesical chemohyperthermia method (EMDA).

4 RCTs und 1 NRCTs zu Bewertung der klinischen Wirksamkeit herangezogen, insg. 260 PatientInnen mit der Intervention behandelt

Three studies [7, 38, 39] reported the outcome overall survival, but did not find any significant differences between the intervention and the control groups. One of these studies [39] presented non-significant differences in the outcome disease-specific survival, disease-free survival and quality of life (measured with EQ-5D). However, it has to be mentioned that the study was closed prematurely, thus failed to achieve the planned sample size. The study of Colombo presented statistically significant differences in favour of the intervention regarding the outcome disease-free survival; the trial was stopped early after an interim analysis showed superiority of the intervention [50].

keine signifikanten Unterschiede im generellen Überleben (3 Studien), im krankheitsspezifischen Überleben und in der Lebensqualität (je 1 Studie)

Four studies provided data for the outcome recurrence-free survival. At 24 months, only one study reported a statistically significant difference in favour of the intervention [6]. However, the authors failed to provide the results of any statistical tests after the long-term (90 months) follow-up [7].

nach 24 Monaten statistisch signifikanter Unterschied im RFS (1 Studie)

No statement regarding statistical or clinical significance can be made for the outcomes progression-free survival, quality of life (assessed with the subjective symptom score) or complete response.

For the analysis of safety, we additionally included 11 prospective single-arm studies with a total of 480 patients receiving the intervention. Overall, they were considered to have a moderate to high RoB. In the comparative analysis, 24 SAEs were reported in total (IG 17; CG 7). In addition, 25 SAEs occurred in the single-arm studies.

für die Beurteilung der Sicherheit zusätzlich 11 einarmige Studien herangezogen

Heterogeneity in reporting the outcome complications (without taken into account observed deaths) only allowed a descriptive listing of those most frequently observed. Thus, the comparative safety of RF-CHT cannot be analysed comprehensively.

heterogene Berichterstattung der unerwünschten Wirkungen

Internal and external validiy

moderate bis niedrige Qualität der Evidenz zur Wirksamkeit; sehr niedrige Qualität der Evidenz zur Sicherheit

Overall, the strength of evidence for clinical efficacy was considered moderate to low. Regarding safety, the quality of evidence was rated as very low.

All studies applied a similar protocol for the individual treatment sessions. However, the treatment regiments varied greatly. Throughout the individual studies, either 2x20 mg or 1x40 mg or 2x40 mg of MMC were used in the intervention groups and 4 to 12 induction sessions were applied. Those were followed by either none or various numbers of maintenance sessions for a maximum duration of two years.

Heterogenität in der Patientenpopulation und in der Vorbehandlung, kleine TeilnehmerInnenzahl

Additionally, the proportion of patients with each grade and stage of NMIBC differed between studies. According to the European Association of Urologists (EAU), the detection of (concurrent) CIS increases the risk of recurrence and progression, making further treatment (either intravesical BCG instillations or radical cystectomy) mandatory [29]. Furthermore, the patients had undergone different pre-treatments, which is a confounding factor that has not been accounted for properly. In terms of sample size, most of the studies were generally too small for proper subgroup analysis [51].

Verwendung nicht validierter Fragebögen zur Lebensqualität

In terms of adverse events, any comparisons are difficult as older studies used non-validated questionnaires, while more recent ones used the Common toxicity criteria for Adverse Effects (CTCAE). Furthermore, different denominator were used (numbers were given either per session, per treatment group or per patient). In addition, the use of pain medication (anticholnergic drugs) was not mentioned in most reports, which might lead to an underestimation of AEs [2].

generell auf den österreichischen Kontext übertragbar

In terms of external validity, the data is considered generalizable to the Austrian context as the countries of recruitment were exclusively European countries and Israel.

Evidence gaps and ongoing studies

kein Vergleich unterschiedlicher Chemotherapeutika, fehlende optimale Dosierungen oder Behandlungsschema

The studies did not compare different chemostatic agents or attempt to determine the optimal dosage or treatment regimens. In a meta-analysis including the individual patient data of nine RCTs, BCG has shown superiority in the prevention of tumour recurrences [52] however the beneficial effect has yet to be weighed against its known higher toxicity profile.

Current trials are investigating different therapy options for patients with NMIBC using alternative treatments such as cytokines, new intravesical chemotherapy combinations and PD(L)1 antagonists, which it is thought will change the landscape [51].

Limitations in the report

fehlende qualitative hochwertige Evidenz (RCTs)

For both outcomes, there was a distinct lack of prospective, comparative data. The studies identified had small sample sizes and lacked long-term follow-up, with follow-up times that were too short to detect important effects. Furthermore, patient-relevant outcomes like symptoms, effects on body functions or adverse events were reported heterogeneously, thereby limiting the ability to compare data across studies.

Ausschluss retrospektiver Studien

The exclusion of retrospective study designs limited the evidence base obtained in this review; however, this decision was justified given the validity concerns of retrospective designs.

Conclusion

abschliessende Bewertung nicht möglich

Due to the heterogeneity of the included study populations and indications and the variety of treatment regimens and comparators, a comprehensive understanding of the comparative risks and benefits of radiofrequency-induced intravesical chemohyperthermia compared to alternative treatment options or sham procedures is not possible based on the currently available evidence. This holds true even if you assess evidence separately for indications and comparators because the follow-up is too short and there is a lack of good quality evidence from randomised controlled trials.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	**The inclusion in the catalogue of benefits is *currently* not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended.**

The inclusion in the catalogue of benefits is currently not recommended.

Reasoning:

Current evidence is limited and the technology must be considered experimental, as such it is not recommended for inclusion in the catalogue of benefits but could be used within clinical trials to add to the body of scientific knowledge.

experimentelles Verfahren: nicht empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Radiofrequency-induced Intravesical Chemohyperthermia: Results from randomised controlled trials

Author, year	Arends, 2016 [5]	Colombo, 1996 [38]	Colombo, 2003 [6] and 2011 [7]	Tan, 2018 [39]
Country	Multicentre trial (Israel, Italy, the Netherlands, Austria, France, Belgium)	Italy	Multicentre trial (Italy, Israel)	Multicentre UK (14 centres)
Sponsor	Medical Enterprises Europe B.V. provided financial support and was involved in the design and conduct of the study and the collaction/management of the data	NR	NR	University College London, Cancer Research UK, Kyowa Kirin Pharmaceutical Development Ltd, Medical Enterprises Europe B.V.
Study design	RCT	RCT	RCT	RCT
Number of pts	(190 patients were randomised; 6 patients did not receive the intervention) 184 completed the treatment (IG: 95; CG: 89)	52 (IG: 29; CG: 23)	83 (IG: 42; CG: 41)[1]	104 (IG: 48; CG: 56)[2]
Intervention/ Product	Synergo system (SB-TS 101-1) with MMC weekly for 6 weeks, followed by six maintenance sessions (à 60 min) at 6-week intervals during the rest of year 1 using 2x 20mg MMC combined with local hyperthermia at 42±2°C.	Synergo system (SB-TS 101) in 6 to 8 session (à 60 min) with MMC once or twice a week for max. 6 weeks using 2x 40 mg MMC combined with local hyperthermia from 42.5-46.0°C.	Synergo system (SB-TS: 101-1) with an induction cycle of eight weekly session and a subsequent maintenance regimen (for patients disease-free at 3 months) of four monthly sessions using 2x 20 mg MMC combined with local hyperthermia from 42.0±2°C (min. 40 min)	Synergo system (SB-TS 101) with 6-weekly induction instillations using 2x20 mg MMC combined with local hyperthermia from 42.0±2°C (à 60 min), followed by one instillation every 6 weeks for one year and one instilllation every 8 weeks for the following year
Comparator	BCG (full dose) in six weekly induction sessions (à 120 min) and three weekly repeated maintenance sessions at months 3,6 and 12.	Intravesical chemotherapy (same treatment conditions except that microwave source not connected.)	Intravesical chemotherapy with 2x 20 mg MMC for 60 min, yet hyperthermia was not delivered applying one induction cycle of eight weekly session and a subsequent maintenance regimen of four monthly sessions	Six consecutive weekly BCG instillations followed by maintenance therapy (three consecutive weekly instillations at 3,6,12,18 and 24 months) or institutional standard of care
Inclusion criteria	Patients with intermediate- or high-risk NMIBC, i.e. any pT1 or grade 3 urothelial carcinoma (UC) and/or carcinoma in situ (CIS) or mulitfocal (six or more) pTa lesions and/or multiple (three or more) recurrences of pTa lesions in the last 24 months.	Superficial transitional cell carcinoma of the bladder (stages Ta to T1); (42 pts with recurrent disease)	Patients with intermediate and high-risk superficial TCC of the bladder (Ta-T1, G1-G2, multifocal, either primary or recurrent) and superficial high-risk bladder cancer (i.e. T1, G3 and CIS in association with papillary tumors); complete TURB confirmed by cystoscopy, biopsies and negative cytology	Patients with recurrence of intermediate- or high-risk NMIBC according to EAU guidelines following induction/maintenance BCG, completed TURB of papillary lesions, re-resection of pT1 disease to confirm absence MIBC, age ≥ 18 yr,

Author, year	Arends, 2016 [5]	Colombo, 1996 [38]	Colombo, 2003 [6] and 2011 [7]	Tan, 2018 [39]
Inclusion criteria *(continuation)*	All patients required TURBT, confirmed by negative cytology and cytoscopy with negative biopsies before intravesical therapy. In high-risk NMIBC patients, re-resection of the tumour bed and random biopsies were mandatory. In CIS patients, positive cytology and/or CIS-positive biopsies were allowed. WHO performance status ≤ 2, life expectancy > 24 months.			WHO performance status ≤ 4, patients unfit or unwilling to have radical cystectomy, exclusion of upper tract disease ≤ 12 months, normal haematological and biochemical blood tests
Exclusion criteria	Histology other than UC, another primary malignancy, UC involving the urethra or upper urinary tract, previous history of UC stage T2 or higher, intravesical MMC treatments during the previous 12 months, any previous BCG therapy < 48 months, previous pelvic radio-therapy or systemic chemotherapy, partial cystectomy, bladder diverticulum > 1 cm, residual urin > 100 ml, bladder volume < 150 ml, urinary incontinence, urethral stricture impeding 20F catheterisation, persistent haematuria, active intractable or uncontrollable urinary tract infection, active tuberculosis or BCG infection, patients with previous BCG life-threatening sepsis, known MMC or BCG allergy, known impaired immune response, positive HIV serology, receipt of systemic steroids or immunosuppressives, haematological disorders, leukocytes < 3500, platelets < 100 000, kidney or liver function disorders (> 1.5 times upper normal limit), and pregnant/lactating women.	NR	Low-risk TCC bladder cancer (Ta, G1, single, primary cancer), stage higher than T1, residual tumor after completed TURBT, transitional tumor of the bladder involving the prostatic urethra, primary CIS, distant or lymph nodes metastases, urethral stricture, large benign prostatic hyperplasia or big middle lobe, postvoid residual urine level more than 100 ml, bladder capacity < 150 ml, urinary tract infection unresponsive to treatment, neurogenic, hypotonic bladder, allergy to MMC, pretreatment with either local or systemic chemotherapy or radiotherapy during the last three months, WHO performance status > 2	Non-urothelial carcinoma, low-grade NMIBC recurrence, treatment with intravesical chemotherapy ≤ 6 months (single post-TURBT instillation allowed), prostatic urethra or upper tract disease, known MMC allergy, active/intractable urinary tract infection, urethral stricture, small bladder capacity (< 250 ml), significant urinary incontinence, history of pelvic radiotherapy
Patients receiving previous treatment (MMC or BCG) (%), free interval (months)	IG: Chemo (including MMC): 13/95 (13.7%); MMC: 6/95 (6.3%); BCG: 6/95 (6.3%) CG: Chemo (including MMC): 8/89 (9.0%); MMC: 6/89 (6.7%); BCG: 4/89 (4.5%)	IG: Chemotherapy: 16/29 (55.2%); BCG (alone and in combination): 8/29 (27.6%) CG: Chemotherapy: 13/23 (56.5%); BCG (alone and in combination): 5/23 (21.7%)	IG: Chemotherapy (> 3 months ago): 42.9%; MMC: 16,6% CG: Chemotherapy (> 3 months ago): 41.5%3; MMC: 26.8%	IG: BCG: 48/48 (100%); CG: Chemotherapy (MMC): 23/56 (41.1%); BCG: 56/56 (100%)
Mean age of patients, yrs (SD or M)	IG: 65.2 (SD 10.67); CG: 67.4 (SD 10.08)	64.3	NR	IG: 77 (M; IQR: 72-82); CG: 76 (M; IQR: 67-81)

Author, year	Arends, 2016 [5]	Colombo, 1996 [38]	Colombo, 2003 [6] and 2011 [7]	Tan, 2018 [39]
Sex (% female)	IG: 15/95 (15.8%); CG: 15/89 (16.9%)	8/52 (15.4%)	IG: 7/42 (16.7%); CG: 7/41 (17.1%)	IG: 14/48 (29.2%); CG: 12/56 (21.4%)
Follow-up (months)	25.6 (M, range: 0-34)	IG: 38 (M); CG: 36 (M)	tumor-free patients: IG 90 (M, range 6-154); CG 87 (M) to recurrence: IG: 29 (M); CG: 10 (M)	24; for patients without DFS events: 36 (M)
Loss to follow-up, n (%)	190 patients were randomised; 184 were available for analysis, NR[3]	NR	8/83 (9.6%); withdrew: IG: 3/42 (7.1%); CG: 5/41 (12.2%)	IG: 4/48 (8.3%); CG 3/56 (5.4%)
Outcomes				
Efficacy				
Overall survival (OS), n (%)	NR	At 38 months (IG) and 36 months (CG): No significant differences between the two groups (p> 0.30)[4]	At 90 months (M): no significant differences between treatment groups	24 months rate[2]: IG: 85%; CG: 90%; HR 1.64 (95% CI: 0.79-3.39); p=0.18
Disease-specific survival (DSS)	NR	NR	NR	24 months rate[2]: IG: 89%; CG: 96%; (HR 3.02; (95% CI: 1.04-8.76)); p=0.04
Quality of life	NR	subjective symptom score: mean (SD) before therapy: IG: 10.5 (SD 1.6); CG: 9.8 (SD 1.4) after therapy:IG: 12.6 (2.1); CG: 10.7 (1.8) p=NR	subjective symptom score: mean (SD) before therapy: IG: 9.1 (SD 1.8); CG: 9.4 (SD 1.7) after therapy: IG: 12.7 (SD 1.5); CG: 12.2 (SD 1.5) p=NR	EQ-5D no difference in scores[4]
Disease-free survival (DFS)	NR	NR	IG: 60.0%, CG: 20.0%; p < 0.001 in favour of IG Estimated 10-year survival rat: IG: 53%; CG: 15%; p<0.001 (2011)	24 months: IG: 35%; CG: 41%; HR: 1.33 (95% CI: 0.84-2.10); p=0.23
Progression-free survival (%)/time to progression	At 24 months: IG: 100.0%; CG: 98.6%; p=1	NR	At 24 months: IG: 39/39 (100%; CG: 35/36 (97.2%); p=NR At 90 months: IG: 33/35 (94.3%); CG: 37/40 (92.5%); p=NR [7]	24 months[5,6]: IG: 83%; CG: 87%, (HR 1.64; 95% CI: 0.82-3.27); p=0.16
Recurrence-free survival (%)/time to recurrence	At 24 months: IG: 78.1 (95% CI: 65.2-86.7); CG: 64.8 (95% CI: 52.2-74.9); p=0.08)	At 38 months (IG) and 36 months (CG): IG: 21/29 (73%); CG: 14/23 (61%); p>0.30	At 24 months: IG: 33/39 (84.6%); CG: 13/36 (36.1%); p<0.001 At 90 months (M): IG: 21/35 (60%); CG: 8/40 (20%) [7]; p=NR	24 months rates[5,6]: IG: 23%; CG: 40%; (HR: 1.01; 95% CI: 0.53-1.91); p=0.98
Complete response (CR)	At 3 months (CIS patients only) IG: 88.9%; CG: 85.7%; (p=1)	At 38 months (IG) and 36 months (CG): IG: 19/29 (66%) vs. 5/23 (22%); p<0.01	NR	At 3 months: Subgroup CIS): IG: 30%; CG: 47%; OR 0.43 (95% CI: 0.18-1.28); p=0.15

Author, year	Arends, 2016 [5]	Colombo, 1996 [38]	Colombo, 2003 [6] and 2011 [7]	Tan, 2018 [39]
Radical cystectomy/Bladder preservation rate	NR	NR	Radical cystectomy IG: 2/35 (5.7%); CG: 3/40 (7.5%) (due to tumor progression)[8]; p=0.129 Bladder preseration rate (10 year estimat) IG: 86.1%; CG: 78.9; p=NR	NR
Safety				
complications, n (%)	IG: 1431 AEs/1540 treatments (92.9%) Most prevalent AEs: bladder spasms (14.4%), pain (14.1%), dysuria (11.7%), nocturia (10.3%), urinary frequency (9.9%); 5 SAE (contracted bladder (n=1), urethral bleeding (n=1), fever (n=3) CG: 1525 AEs/1923 treatments (79.3%) Most prevalent AEs: urinary frequency (18.0%), dysuria (15.0%), nocturia (14.9%) haematuria (11.2%), fatigue (8.5%); 4 SAEs (retention, haematuria, urinary tract infection, fever) IG had significantly less urinary frequency, nocturia, incontinence, haematuria, fever, fatigue, arthalgia but significantly more cathetarisation difficulties, urethral strictures, bladder tissue reaction, bladder spasms, bladder pain during sessions and allergy.	No major complications reported in either group. IG: cystitis syndrom: 29/29 patients (100%), mild to moderate urge and nocturia: 21/29 (72%) CG: Most patients experienced mild urgency and urethral burning; cystitis syndrome (less prevalent, but not statistically significant)[1]	IG: 69 AEs; no side effects among 5/42 patients (12%) (2003): AEs per treatment group: Tissue reaction: 21; pain: 17; Dysuria: 10; Hematuria: 3; urethral stenosis: 3; posterior-wall thermal reaction: 10; skin allergy: 5; reduced bladder capacity with urge incontinence: 1; 6 deaths (other causes) (2011) CG 30 AEs; no side effects among 15/41 patients (37%); AEs per treatment group: Tissue reaction: 20; pain: NR; Dysuria; 4; Hematuria: 2; urethral stenosis: 1; posterior-wall thermal reaction: 1; skin allergy: 2; Pain and posterior-wall thermal reaction were significantly more likely in the IG 1 death (due to bladder cancer) (2003); 9 deaths (other causes) (2011)	IG (per treatment): Pain: (46(%); Dysuria: (54%); Increased frequency (52%); increased urgency (42%); incontinence (23%); nocturia (33%); Haematuria (48%); Fatigure (33%); Fever (13%); urinary tract infection (27%); rash (15%); stricture (6%) CG (per treatment): Pain (56%); Dysuria (59%); Increased frequency (54%); increased urgency (48%), incontinence (18%), nocturia (38%); Haematuria (36%); Fatigure (38%), Fever (25%); urinary tract infection (18%); rash (25%); stricture (%4)

Abbreviations: ***AE*** *– adverse event;* ***BCG*** *– bacillus Calmette-Guérin;* ***CG*** *– control group;* ***CIS*** *– carcinoma in situ;* ***DFS*** *– disease-free survival;* ***EAU*** *– European Association of Urology;* ***HR*** *– hazard ratio,* ***IG*** *– intervention group;* ***M*** *– median;* ***IQR*** *– inter quartile range,* ***M*** *– median,* ***MMC*** *– mitomycin C;* ***NMIBC*** *– non-muscle invasive bladder cancer;* ***NR*** *– not reported,* ***SD*** *– standard deviation;* ***TCC*** *– transitional cell carcinoma;* ***TURBT*** *– transurethral resection of the bladder tumour;* ***UC*** *– urothelial carcinoma;* ***SAE*** *– serious adverse event*

Footnotes

[1] *the original sample size required by the study protocol was 158 patients. Due to an interim analysis that supported the superiority of the combined treatment, the study was terminated after a total of 83 patients enrolled*

[2] *the original sample size calculations anticipated 242 patients with 81 events per arm and an embedded subgroup analysis of CIS patients with at least 27 patients per arm (depending on the outcome DFS)*

[3] *the study was closed prematurely due to slow accrual. Original sample size calculations suggested a total of 300 patients (based on the outcome RFS)*

[4] *numbers not given*

[5] *per-protocol analysis*

[6] *among patients receiving equal to or more than 6 treatments*

[7] *the absolute numbers regarding the denominator differed between the publication of 2003 and 2011 (IG:39 and CG: 36 vs. IG: 35 and CG: 40)*

[8] *additional four patients underwent radical cystectomy for recurrent high-risk NMIBC.*

Table A-2: Radiofrequency-induced intravesical chemohyperthermia: Results from non-randomised controlled trials

Author, year	Colombo, 2001 [35]
Country	Italy
Sponsor	NR
Study design	NRCT
Number of pts	80 (IG: 29; ICT: 36; EMDA: 15)
Intervention/Product	Synergo system (SB-TS 101- with 40 mg MMC in 4 weekly sessions (à 60 min),local hyperthermia with mean temperature of 42.5°C
Comparator(s)	Intravesical chemotherapy (ICT): Standard chemotherapy using intravesical instillations of 40 mg MMC in four weekly sessions (à 60 min) EMDA: intravesical MMC (40 mg) solution according to the EMDA procedure with 4 weekly session (à 20 min)
Inclusion criteria	Patients with superficial (Ta –T1), low grade (GI-GII), recurrent, single, small (<2cm) bladder tumors, previously untreated by MMC; the tumor was left intact as indicator lesion (post-treatment: TURBT of residual or suspected areas)
Exclusion criteria	NR
Patients receiving previous treatment (MMC or BCG) (%), free interval (months)	MMC: 0/80 (0.0%)
Mean age of patients, yrs (SD)	NR
Sex (% female)	NR
Follow-up (months)	10 days (0.3)
Loss to follow-up, n (%)	NR
Overall survival (OS), n (%)	NR
Disease-specific survival time (DSS)	NR
Quality of life (subjective symptom score: mean (SD))	before therapy: IG: 11.6 (SD 1.8); ICT: 10.3 (SD 1.2); EDMA: 9.4 (SD 1.7) after therapy: IG: 12.7 (SD 1.5); ICT: 11.0 (SD 0.8); EDMA: 12.2 (SD 1.5) p=NR
Disease-free survival (DFS)	NR
Progression-free survival (%)/time to progression	NR
Recurrence-free survival (%)/time to recurrence	NR
Complete response (CR)	IG: 66.0%; ICT: 27.7%; EDMA: 40.0%; P=NR
Radical cystectomy/Bladder preservation rate	NR
complications, n (%)	No major complications registered.

Abbreviations: ***CG*** *– control group;* ***EMDA*** *– electromotive drug administration;* ***ICT*** *– intravesical chemotherapy,* ***IG*** *– intervention group;* ***MMC*** *– mitomycin C;* ***NR*** *– not reported,* ***NRCT*** *– non randomised controlled trial;* ***SD*** *– standard deviation;* ***TURBT*** *– transurethral resection of the bladder tumour*

Table A-3: Radiofrequency-induced intravesical chemohyperthermia: Results from single-arm trials (part 1)

Author, year	Colombo, 1995 [42]	Colombo, 1998 [43]	Erturhan, 2015 [8]
Country	Italy	Italy	Turkey
Sponsor	NR	NR	NR
Study design	Single-arm	Single-arm	Single-arm
Number of pts	44	19	26
Intervention/Product	Synergo system SB-TS 101 (neoadjuvant therapy) 30 mg MMC per session, hyperthermia at 42.5 to 44.5°C for at least 40 min 8 sessions (à 60 min) twice a week with an overall treatment period of ≤ 6 weeks;	Synergo system SB-TS 101 (neoadjuvant therapy); 40 mg MMC within a medium temperature range of 42.5 to 46°C for at least 40 min. per session; 8 weekly sessions for a maximum of 2 months	Synergo system SB-TS 101 (adjuvant therapy) using 2x 20 mg MMC, hyperthermia at 41 to 44°C for a total of 60 min once a week during 6 weeks, followed by once a month for 6 months
Comparator	none	none	none
Inclusion criteria	Patients with superficial transitional cell carcinoma of the bladder, first episode or recurrent, single or multifocal (clinical stage and histological confirmed Ta or T1 transitional tumors)	Patients with multifocal recurrent superficial transitional cell carcinoma of the bladder (at least one stage T1 tumor recurrence); tumors up to 3 cm; 5 patients also had vegetations on bladder neck; 3 patients involvement of prostatic urethra.	Patients with primary tumor, diagnosed with high-risk NMIBC (T1 or Grade III or CIS or multiple-recurrent > 3 cm Ta Grade I/II)
Exclusion criteria	NR	NR	Patients with previous bladder cancer or additional malignancy, concurrent upper urinary system urothelial carcinoma, who were not tumor-free in TURBT, who had a bladder capacity of < 150 cc, or bladder diverticulum
Patients receiving previous treatment (MMC or BCG) (%), free interval (months)	Intravesical chemotherapy: 20/44 (44.5%); BCG: 8/44 (18.2%)	MMC: 8/19 (42%); MMC + bCG 4/19 (21%); BCG: 6/19 (32%); Epirubicin: 1/19 (5%)	NR
Mean age of patients, yrs (SD)	57.3 (range 34 to 78)	58.3 (range 36-86)	62.4 (range 51-78)
Sex (% female)	NR	3/19 (15.8%)	2/26 (7.7%)
Follow-up (months)	average 24 months (range 3-57)	Median 33 months (M; range 12 to 60)	16.4 (M; range 6-48)
Loss to follow-up, n (%)	NR	NR	None (0.0%)
Outcomes			
Efficacy			
Overall survival (OS), n (%)	NR	NR	NR
Disease-specific survival time (DSS)	NR	NR	NR

Author, year	Colombo, 1995 [42]	Colombo, 1998 [43]	Erturhan, 2015 [8]
Quality of life (subjective symptom score: mean (SD))	before therapy: daytime frequency: 2.6 (SD 0.8); nocturia: 2.8 (SD 1.0); dysuria: 1.9 (SD 1.2); urgency: 2.2 (SD 0.8); Hematuria: 0.9 (SD 0.6); urethrorhagia: 0.2 (SD 0.2); urethral pain: 1.8 (SD 0.8) after therapy: daytime frequency: 2.8 (SD 0.6); nocturia: 3.3 (SD 0.4); dysuria: 2.1 (SD 0.8); urgency: 2.2 (SD 0.4); Hematuria: 0.8 (SD 0.6); urethrorhagia: 0.3 (SD 0.6); urethral pain: 2.1 (SD 0.8)	NR	NR
Disease-free survival (DFS)	NR	NR	NR
Progression-free survival (%)/time to progression	NR	NR	NR
Recurrence-free survival (%)/time to recurrence	NR	NR	23/26 (88.4%)
Complete response (CR)	31/44 (70.4%)	9/19 (47.0%)	NR
Radical cystectomy/Bladder preservation rate	3/44 (6.8%)	3/19 (15.8%)	0/19
Safety			
complications, n (%)	subjective intolerance: 12/352 sessions (3.4%); urge incontinence during application: 9/44 patients (20.5%); allergy to MMC (skin rash): 1/44 patients (2.3%); stricture of the external meatus of the urethra: 1/44 patients (2.3%)	severe detrusor instability: 6/152 sessions (3.9%); severe cystitis symptoms: 3/19 patients (16%); unilateral vesicoureteral reflux: 1/19 (5.3%); contracted bladder: 1/19 (5.3%); 2/19 deaths (10.5%)	Dysuria: 11/26 patients (42.3%); storage functions: 5/26 (19.2%); hematuria: 4/26 (15.3%); pain of procedure: 10/26 (38.4%); allergic reactions: 2/26 (7.6%); thermal reaction of the posterior wall: 7/26 (26.9%)

Abbreviations: ***BCG*** *– Bacillus Calmette-Guérin;* ***CIS*** *– carcinoma in situ;* ***EORTC*** *– European Organisation for Research and Treatment of Cancer;* ***M*** *– median;* ***MMC*** *– mitomycin C;* ***n*** *– number;* ***NR*** *– not reported;* ***pts*** *– number of patients,* ***SD*** *– standard deviation;* ***TCC*** *– transurethral cell carcinoma;* ***TURBT*** *– transurethral resection of the bladder tumour; yrs – years,* ***WHO*** *– World Health Organization*

Table A-3: Radiofrequency-induced intravesical chemohyperthermia: Results from single-arm trials (part 2)

Author, year	Gofrit, 2004 [40]	Kiss, 2015 [44]	Maffezzini, 2014 [45]	Moskovitz, 2005 [46]
Country	Multicentre trial (Italy, Israel, Germany, the Netherlands)	Switzerland	Italy	Israel
Sponsor	NR	NR	NR	NR
Study design	Single-arm	Single-arm	Single-arm	Single-arm
Number of pts	52	21	42	47 (32 patients included in the efficacy analysis)
Intervention/Product	Synergo system SB-TS 101 2x 20 mg (prophylactic therapy) and 2x 40 mg (ablative therapy) MMC, respectively; (Epirubicin given to 4 patients allergic to MMC); each session with a total period of 40 min of effective heating (with a mean bladder wall temperature greater than 41°C); 8 weekly sessions, followed by 4 monthly sessions.	Synergo SB-TS 101; curative: 2x 40 mg MMC combined with hyperthermia at 42 ±2°C for two 30 min cycles; 12 weeky sessions prophylactic: 2x 20 mg MMC for two 30 min cycles; weekly for 6 weeks	Synergo SB-TS 101; adjuvant therapy: 2x 40 mg MMC for a total of 60 min; (in case of intolerance, 50 mg Epirubicin were adminstered; 4 weekly sessions, followed by 6 sessions every 2 weeks and finally by 4 monthly sessions for a total of 14 session over 8 months;	Synergo SB-TS 101; Prophylatic therapy: 2x 20 mg MMC for 60 min; 6-8 weekly sessions followed by 4-6 monthly session for a total of 12 sessions; Ablative therapy: 2x 40 mg MMC for 60 min; 8 weekly sessions followed by 4 monthly sessions (if inadaequate response after the fourth weekly session, patients were classified as non-responders and referred to other therapies)
Comparator	none	none	none	none
Inclusion criteria	Patients with Ta or T1 G3 tumors Prophylactic: patients who had G3 stage Ta or T1 tumors with neither visible tumor nor CIS (biopsy) ablative:remaining patients (if inadequate response after fourth treatment: patients referred to alternative forms of therapy)	Histologically confirmed recurrent NMIBC; curative (in 11/21 patients (52%) with positive cytology after TURBT); pophylactic (in 10/21 patients (48%) with negative cytology)	Patients with high-risk NMIBC; minimum scores of 5 for recurrence and 7 for progression using the EORTC scoring system were required, WHO performance status 0-2, adequate bone marrow function (white blood count ≥ 3,000/µl, absolute neutrophil count ≥ 1,500/µl, platelet count ≥ 100.000/µl, normal serum creatinine ≤ 1.2 mg/dl, normal serum transaminases und bilirubin levels	Patients with recurrent stage Ta and T1, grade G1-G3 TCC of the bladder (intermediate or high-risk superficial transitional cell carcinoma of the bladder) Prophylatic: complete transurethral resection of all tumors, confirmed by cystoscopy, biopsies and negative urine cytology ablative: patients in whom complete tumor eradication could not be achieved by single TURBT and patients unable to undergo anaesthesia

Author, year	Gofrit, 2004 [40]	Kiss, 2015 [44]	Maffezzini, 2014 [45]	Moskovitz, 2005 [46]
Exclusion criteria	NR	History of muscle-invasive bladder cancer (T2 or higher), local (cN+) or distant (cM+) spreading, variant histology (other than urothelial), residual urine > 100 ml, urethral stricture, pregnancy, age < 18 years, active urinary tract infection	Presence of muscle-invasive transitional cell carcinoma, tumors located at the prostatic urethra, bladder capacity ≤ 150 ml, voiding disturbances, presence of urethral strictures, bladder diverticula	Low risk bladder cancer, stage higher than T1, bladder tumour other than TCC, TCC involving the urethra or upper urinary tract, urinary bladder diverticulum > 1 cm in diameter, patients after partial cystectomy and any situation impending a 20F catheterisation
Patients receiving previous treatment (MMC or BCG) (%), free interval (months)	BCG:29/52 (55.8%); intravesical chemotherapy: 23/52 (44.2%)	BCG: 12/21 (57%); MMC: 10/21 (48%); Farmorubicin: 4/21 (19%)	Chemotherapy: 19/42 (45.2%), BCG: 8/42 (19.0%)	BCG: 21/32 (65.6%); MMC: 11/32 (34.4%); other chemotherapy: 7/32 (21.9%)
Mean age of patients, yrs (SD)	Prophylactic: 68 (SD 9); ablative: 69 (SD 15)	70 (M, range 35-95)	at enrollment: median 74 (r 40-82)	Prophylactic: 69 (mean; range: 44-98); ablative: 68 (mean; range 43-97)
Sex (% female)	Prophylactic: 3/24 (12.5%); ablative: 8/28 (28.5%)	5/21 (24%)	15/42 (35.7%)	5/32 (15.6%)
Follow-up (months)	15.2 (M; range 6-90)	50 (M, range 1-120)	Median 38 months (range 4-73)	Prophylactic: mean 289 days Ablative: mean 169.4 days
Loss to follow-up, n (%)	NR	NR	2/42 (4.8%)	7/47 (excluded from analysis)
Outcomes				
Efficacy				
Overall survival (OS), n (%)	NR	NR	NR	NR
Disease-specific survival time (DSS)	NR	NR	NR	NR
Quality of life (subjective symptom score: mean (SD))	NR	NR	NR	NR
Disease-free survival (DFS)	NR	NR	24/42 patients (57.1%)	NR
Progression-free survival (%)/time to progression	0 cases of tumour progression	NR	NR	Prophylactic: no progression observed
Recurrence-free survival (%)/time to recurrence	71%	NR	NR	Prophylactic: 20/22 (91%)
Complete response (CR)	NR	6/21 (29%)	NR	Ablative: 8/10 (80%)
Radical cystectomy/Bladder preservation rate	7/52 (13.5%)	6/21 (29%)	7/42 patients (16.7%)	NR

Author, year	Gofrit, 2004 [40]	Kiss, 2015 [44]	Maffezzini, 2014 [45]	Moskovitz, 2005 [46]
Safety				
complications, n (%)	Posterior wall thermal reaction: 33/52 patients (63.5%); Dysuria: 30/52 (57.7%); Pain during treatment: 12/52 (23.1%); Bladder spasms: 8/52 (15.4%); urinary tract infection: 5/52 (9.6%); reduced bladder capacity: 5/52 (9.6%); palmar or plantar rash: 4/52 (7.7%)	AEs in 18/2621 patients (86%): pain and bladder spasms during intervention: 12/21 (57%); of those severe pain: 7/21 (33%); severe AEs: 8/21 patients (38%) of these pain: 3; bladder spasms 2; allergic reaction: 2; iatrogenic urethral perforation: 1 Common Toxicity Criteria of the National Cancer Institute of Canada: Grade 0-2=10; Grade 3-4=11 7/21 (33%) deaths	Bladder spasms resulting in treatment discontinuation: 5/42 patients (11.9%); Symptoms of toxicity (CTCAE Grade 1 & 2): Frequency: 20 & 18; cystitis: 16 & 14; Haematuria: 25 & 1; incontinence: 8 & 4; bladder/pelvic pain: 10 & 2; urinary retention: 1 & 0 1 death	Cystitis: 2/47 patients (4.3%); posterior wall thermal reaction: 9/47 (19.1%); skin allergy: 2/47 (4.3%) (4.8%); urethral stenosis: 6/47 (12.8%);

Abbreviations: ***BCG*** *– Bacillus Calmette-Guérin;* ***CIS*** *– carcinoma in situ;* ***EORTC*** *– European Organisation for Research and Treatment of Cancer;* ***M*** *– median;* ***MMC*** *– mitomycin C;* ***n*** *– number;* ***NR*** *– not reported;* ***pts*** *– number of patients,* ***SD*** *– standard deviation;* ***TCC*** *– transurethral cell carcinoma;* ***TURBT*** *– transurethral resection of the bladder tumour; yrs – years,* ***WHO*** *– World Health Organization*

Table A-4: Radiofrequency-induced intravesical chemohyperthermia: Results from single-arm trials

Author, year	Rigatti, 1991 [47]	Sooriakumaran, 2016 [48]	Van der Heijden, 2004 [41]	Volpe, 2012 [49]
Country	Italy	UK	Multicentre trial (the Netherlands, Israel, Italy, Germany)	Italy
Sponsor	NR	NR	NR	NR
Study design	Single-arm	Single-arm	Single-arm	Single-arm
Number of pts	12	97	90	30
Intervention/Product	Synergo system SB-TS 100, (neoadjuvant therapy) 30 mg MMC for a 60 min session; temperature of 41.5 -43.5°C for at least 40 min; 6-8 sessions once or twice per week, overall treatment period no more than 6 weeks	Synergo SB-TS 101 (prophylactic therapy) 40 mg MMC, induction regimen with weekly 60 min treatments for 6-8 weeks with a median of 6 cycles; those with CR or partial response continued on a 2-year regimen of 20 mg MMC every 6 weeks for the first year and every 8 weeks for the second year	Synergo SB-TS 101 (adjuvant therapy), 2 x 20 mg MMC, with and a temperature range of 41-44°C 6 to 8 weekly sessions followed by 4 to 6 monthly sessions à 60 min	Synergo SB-TS101; prophylatic therapy: 2 x 20 mg MMC for a total of 60 min; 6 weekly sessions followed by 6 monthly session for a total of 12 sessions with; Ablative therapy: 2x 40 mg MMC for a total of 60 min; 8 weekly sessions followed by 6-montly session for a total of 14 sessions

Author, year	Rigatti, 1991 [47]	Sooriakumaran, 2016 [48]	Van der Heijden, 2004 [41]	Volpe, 2012 [49]
Comparator	none	none	none	none
Inclusion criteria	Patients with superficial transitional cell carcinoma of the bladder with tumor categories Ta (G1-G3); T1 (G1-G3) and CIS, first or recurrent tumor, monofocal or plurifocal, bladder capacity > 150 ccm, life expectancy > 18 months	Patients with high-risk NMIBC (EAU guidelines 2013) as well as patients with prostatic urethral CIS, if cystectomy was contraindicated or refused and after full transurethral resection of the prostatic urethra	Patients with histologically confirmed Ta or T1 multilple or recurrent superficial transitional cell carcinoma of the bladder, complete resection of all visible papillary tumors (Ta/T1), WHO performance status 0-2, life expectancy > 24 months; max 2 times treated with 20 mg MMC	NMIBC unresponsive to consecutive chemotherapy and/or immunotherapy and suitable for radical cystectomy Prophylactic: complete TURBT confirmed by cystoscopy, biopsies and negative urine cytology; patients with history of recurrence-free time > 3 months Ablative: patients with CIS (Tis) or patients in whom the the rapid rate of recurrence did not allow a 'free bladder' at the last cystoscopy before treatment
Exclusion criteria	Tumor categories > T1, previous BCG intravesical instillation, previous pelvic radiation, large benign prostatic hypertrophy or urinary residual volume > 100 cm^2, neurogenic bladder, positive urine culture, known MMC allergy, persistent hematuria not due to the tumor, urethral pathology, patient unable to collaborate	Patients with ablative treatment regimen (n=3), if less than 4 instillations were received; patients with disease progression during induction course (n=1); due to intolerable side-effects (n=3),	Bladder capacity < 150 ml, concomitant malignancy, extravesical TCC, presence of a diverticle of the bladder; patients without follow-up cystoscopy or with less than 6 treatments were excluded from the analysis	Stage higher than T1, bladder tumor other than TCC, TCC involving the urethra or upper urinary tract, urinary bladder diverticulum arger than 1 cm in diameter, patients after partial cystectomy an any situation impeding a 20-Fr catheterization
Patients receiving previous treatment (MMC or BCG) (%), free interval (months)	NR	BCG: 67/97 (69.1%), BCG+other: 13/97 (13.4%);	BCG: 22/90 (24.4%); MMC: 7/90 (7.8%), Epirubicin: 5/90 (5.6%), BCG+Epirubicin 6/90 (6.7%), BCG+MMC: 10/90 (11.1); BCG+Epirubicin+MMC: 3/90 (3.33%)	Mulitple agents: 17/30 (56.7%); BCG: 13/30 (43.3%)
Mean age of patients, yrs (SD)	59.4	73 (M; IQR 12)	64.8	55.4
Sex (% female)	1/12 (8.3%)	16/97 (16.5%)	12/90 (13.3%)	2/30 (6.6%)
Follow-up (months)	16	27 (M, range 16-47)	18 (mean, range 4-24)	14 (SD 8.48)
Loss to follow-up, n (%)	NR	NR	NR	0 (0.0%)

Author, year	Rigatti, 1991 [47]	Sooriakumaran, 2016 [48]	Van der Heijden, 2004 [41]	Volpe, 2012 [49]
Outcomes				
Efficacy				
Overall survival (OS), n (%)	NR	80/97 (82%)	NR	NR
Disease-specific survival time (DSS)	NR	NR	NR	NR
Quality of life (including subjective symptoms of fatigue, arthralgia, fever)	before therapy: 11.8 (SD 2.4); after therapy: 12.5 (SD 3.1) on scale 7 (best) to 21 (worst)	NR	NR	NR
Disease-free survival (DFS)	NR	NR	NR	At 12 months: 77%; at 24 months: 55%
Progression-free survival (%)/time to progression	NR	60/97 (61.9%)	100%	NR
Recurrence-free survival (%)/time to recurrence	At 3 months: 11/12 (91.7%)	NR	76/90 (84.4%);risk at 12 months: 14.3% (SE 4.5%); risk at 24 months: 24.6% (SE 5.9%)	13/30 (43.3%)/mean 10.7 months
Complete response (CR)	5/12 (41.7%)	NR	NR	42.9% (ablative group)
Radical cystectomy/Bladder preservation rate	NR	18/of 35 that progressed (51.4%)	NR	NR
complications, n (%)	Bladder spasms and urethral irritability: 5/12 patients (40%); mild hypogastric pain:3/12 (25%); light urethral buring during application: 8/12 (58%); MMC allergy: 1/12 (8.4%)	severe hematuria: 3/97 patients (3.1%), severe urinary sepsis: 3/97 (3.1%), severe transient non-specific abdominal pain: 1/97 (1.0%); moderate to severe cystitis-type symptoms: 43/97 (44.3%); haematuria: 24/97 (24.7%), urinary tract infection:14/97 (14.4%) Deaths: 17/97 patients (17.5%) (7 due to bladder cancer, 10 due to other causes)	Dysuria: 22/90 patients (24.4%); haematuria: 8/90 (8.9%); pain: 33/90 (36.7%); posterior wall thermal reaction: 23/90 (25.6%); skin allergy: 8/90 (8.9%); urethral stenosis: 4/90 (4.4%); tissue reaction: 22/90 (24.4%)	Prophylactic: Posterior wall thermal reaction (in 58% of the patients), dysuria (21.2%), pain during treatment (30.3%), bladder spasm (27.3%); urinary tract infection (3%); reduced bladder capacity (3.9%); palmar or plantar rash (10%); ablative: Posterior wall thermal reaction (72%), dysuria (24.4%), pain during treatment (31%), bladder spasm (32.1%); urinary tract infection (6%); reduced bladder capacity (4.2%); palmar or plantar rash (16%);

Abbreviations: ***BCG*** *– Bacillus Calmette-Guérin;* ***CIS*** *– carcinoma in situ;* ***EAU*** *– European Association of Urologists;* ***IQR****–interquartile range;* ***M*** *– median;* ***MMC*** *– mitomycin C;* ***n*** *– number;* ***NMIBC*** *– non-muscle invasive bladder cancer;* ***NR*** *– not reported;* ***pts*** *– number of patients,* ***SD*** *– standard deviation;* ***TCC*** *– transurethral cell carcinoma;* ***TURBT*** *– transurethral resection of the bladder tumour;* ***yrs*** *– years,* ***UK*** *– United Kingdom*

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [2] and in the Guidelines of EUnetHTA [3].

Table A-5: Risk of bias – study level (randomised studies), RoB 2.0 see [2]

Trial	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the oucome	Bias in selection of the reported result	Risk of bias – study level
Arends, 2016 [5]	Some concerns[1]	Some concerns[2]	Some concerns[3]	Some concerns[4]	Low	Some concerns
Colombo, 1996 [38]	Some concerns[1]	Some concerns[2]	Some concerns[5]	Some concerns[4]	Low	Some concerns
Colombo, 2003 [6]	Low	Some concerns[6]	Low	Some concerns[4]	Low	Some concerns
Tan, 2018 [39]	Low	Some concerns[6]	Low	Some concerns[4]	Low	Some concerns

Footnotes

[1] *no information available if allocation sequence was random nor if the allocation sequence was concealed until participants were recruited and assigned to interventions*

[2] *Patients and physicians giving the intervention were aware of assignments*

[3] *data from 142 patients (with at least one treatment given) of 190 randomised participants was used for the analysis*

[4] *no information available if outcome assessors were blinded*

[5] *no information available if any outcome data was missing*

[6] *no information available if patients, carers and trial personnel were aware of the intervention*

Table A-6: Risk of bias of non – randomised studies comparing radiofrequency-induced intravesical chemohyperthermia versus comparators ROBINS-I see [3]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in classification of interventione	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias
Colombo, 2001 [35]	No information[7]	Low	Low	Moderate[8]	NA[9]	Moderate[10]	Low	Moderate

Footnotes

[7] *no information on recruitment or baseline characteristics available*

[8] *the authors note that the schedule of administration might not be the most appropriate for clinical routine application*

[9] *no information available*

[10] *the outcome 'subjective symptom score' could be influenced by the knowledge of the intervention received*

Table A-7: Risk of bias – study level (case series), see [4]

Study reference/ID	Colombo, 1995 [42]	Colombo, 1998 [43]	Erturhan, 2015 [8]	Gofrit, 2004 [40]	Kiss, 2015 [44]	Maffezzini, 2014 [45]	Moskovitz, 2005 [46]	Rigatti, 1991 [47]	Sooriakumaran, 2016 [48]	Van der Heijden, 2004 [41]	Volpe, 2012 [49]
Study objective											
1. Was the hypothesis/aim/objective of the study clearly stated?	Partial	Partial	Yes	Yes	Yes	Yes	Yes	Partial	Partial	Partial	Partial
Study design											
2. Was the study conducted prospectively?	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
3. Were the cases collected in more than one centre?	No	Unclear	No	Yes	No	No	No	No	No	Yes	No
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
Study population											
5. Were the characteristics of the participants included in the study described?	Partial[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Partial[2]	Partial[2]	Yes	Partial[2]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Did participants enter the study at similar point in the disease?	No[3]	Yes	No[3]	No[3]	Yes	Yes	No[3]	No[3]	No[3]	No[4]	No[3]
Intervention and co-intervention											
8. Was the intervention clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Partial[5]	Yes	Yes	Partial[6]	Yes	Yes	NA	Partial[5]
Outcome measure											
10. Were relevant outcome measures established a priori?	Yes	Yes	Partial	Yes	Partial	Partial	Yes	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Study reference/ID	Colombo, 1995 [42]	Colombo, 1998 [43]	Erturhan, 2015 [8]	Gofrit, 2004 [40]	Kiss, 2015 [44]	Maffezzini, 2014 [45]	Moskovitz, 2005 [46]	Rigatti, 1991 [47]	Sooriakumaran, 2016 [48]	Van der Heijden, 2004 [41]	Volpe, 2012 [49]
Statistical Analysis											
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	NA	Yes	Yes	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	No[6]	No[6]	Yes	Yes	No[6]	No[6]	Yes	No[6]	No[6]
16. Was the loss to follow-up reported?	No	No	Yes	No	No	Yes	No	Yes	No	No	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	NA	No	Partial	Yes	Yes	Partial	Yes	Yes	Yes	Yes
18. Were adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Unclear	No[7]	No[7]	Unclear	No[8]	No[7]	No[12]	No[8]	No[8]	Yes
Competing interest and source of support											
20. Were both competing interest and source of support for the study reported?	No	No	No	Partial[9]	Partial[9]	Partial[9]	No	No	Partial[9]	No	Partial[9]
Overall Risk of bias	high	high	medium	high	medium	medium	medium	medium	medium	medium	medium

Footnotes

[1] *the gender of the patients was not reported.*

[2] *the exclusion criteria were not defined in the publication.*

[3] *patients with first episodes as well as patients with recurrent tumours were included.*

[4] *previously untreated as well as previously treated patients were included.*

[5] *non-responders were referred to other forms of therapy, which were not described.*

[6] *for studying the efficacy outcomes, a minimum follow-up period of 24 months is recommended.*

[7] *the study design cannot meet the conclusions about effectiveness.*

[8] *the study design cannot meet the conclusions about effectiveness nor safety.*

[9] *Source of support were not clearly reported.*

Table A-8: Evidence profile: efficacy and safety of radiofrequency-induced intravesical chemohyperthermia in patients with NMIBC

Quality assessment							№ of patients		Absolute effect (SD)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IG	CG			
Efficacy											
Overall survival											
3 [7, 38, 39]	RCTs	Not serious[1]	Not serious	Not serious	None	Serious[2,3]	119	120	IG: 85.0% vs. CG: 90% [39] no significant differences in 3/3 studies (p>0.05)	⊕⊕⊕◯ MODERATE	CRITICAL
Disease-specific survival time											
1 [39]	RCT	Not serious[1]	Not applicable	Not serious	None	Serious[2]	48	56	IG: 89 vs. CG: 96%; HR 3.02 (95% CI 1.04-8.76); p=0.04	⊕⊕◯◯ LOW	CRITICAL
Disease-free survival											
2 [6, 7, 39]	RCTs	Not serious[1]	Serious	Not serious	None	Serious[2,3]	90 (42)	97 (41)	At 24 months IG: 35-60% vs. CG: 20-41%; p<0.001 (Colombo, 2003) vs. p=0.23 (Tan, 2018) 10 year-estimate IG: 53%; CG: 15%; p<0.001	⊕⊕◯◯ LOW	CRITICAL
Progression-free survival/time to progression											
3 [5, 6, 39]	RCTs	Not serious[1]	Serious	Not serious	None	Serious[2,3]	185	186	Progression-free survival At 24 months: IG: 83-100% vs. CG: 87%-97.2% At 90 months: IG 33/35 (94.3%) vs. CG 37/40 (92.5%)	⊕⊕◯◯ LOW	CRITICAL
Recurrence-free survival/time to recurrrence											
4 [5-7, 38, 39]	RCTs	Not serious[1]	Serious[4]	Not serious	Serious[5]	None	214	209	Recurrence-free survival (24 months) IG: 23-84.6% vs. CG: 36.1-64.8% in 2 studies p=n.s., in 1 study study (Colombo 2003) p<0.001 Recurrence-free survival (36-38 months) IG: 21/29 (73%); CG: 14/23 (61%); p>0.30 Recurrence-free survival (90 months) IG: 21/35 (60%); CG: 8/40 (20%), p=NR	⊕⊕◯◯ LOW	CRITICAL
Quality of Life (subjective symtom score)											
3 [6, 35, 38]	RCTs (n=2), NRCT (n=1)[6]	Not serious[1]	Not reported	Not serious	Serious[6]	None	71+29	64+51	Before therapy: IG: 9.1-11.6 vs. CG: 9.4-10.3; p=NR After therapy: IG: 12.6-12.7 vs. CG: 10.7-12.2; p=NR	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							№ of patients		Absolute effect (SD)	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IG	CG			
Quality of Life (EQ-5D)											
1 [39]	RCT	Not serious[1]	Not applicable	Not serious	Serious[2]	None	48	56	No difference in HRQoL(-scores) were observed[3].	⊕⊕◯◯ LOW	CRITICAL
Complete response											
4 [5, 35, 38, 39]	RCTs (n=3), NRCT (n=1)	Serious[7]	Not serious	Not serious	Serious[8]	None	29+29 (95+48)	23+51 (89+56)	Total study population[9] IG: 66% vs. CG: 22-40.0% Subgroup CIS patients IG: 30-88.9%; CG: 47-85.7%	⊕⊕◯◯ LOW	IMPORTANT
Radical cystectomy/bladder preservation rate											
1 [6]	RCT	Not serious[1]	Not applicable	Not serious	Not serious	Serious[4]	42	41	Radical cystectomy IG 2/35 (5.7%); CG: 3/40 (7.5%); p=0.129 Bladder preservation rate (10-year estimate) IG: 86.1% vs. CG: 78.9%	⊕⊕◯◯ LOW	IMPORTANT
Safety											
Complications											
16 [5-8, 35, 38-49]	RCTs (n=4), NRCT (n=1), observational studies (n=11)	Serious[10]	Serious[11]	Not serious	Not serious	Serious[13]	723	260	SAEs IG: 42; CG: 7	⊕◯◯◯ VERY LOW	IMPORTANT

Footnotes

[1] *Although RoB was assessed with 'some concerns' due to a lack of information available, this was not considered important enough for downgrading the overall quality*

[2] *Tan (2018) reports that the HYMN trial closed prematurely in February 2014 following a joint decision by the independent DMC and trial steering committee due to a higher than expected CIS recurrence in the radiofrequency-induced thermos-chemotherapy-treated patients.*

[3] *the study reported by Colombo (2003) stopped early, before the planned sample size was searched, as the interim analysis showed superiority of the combined treatment*

[4] *inconclusive results (statistically significant results were reported by two studies, whereas two other studies reported statistically not significant results).*

[5] *due to wide range of sample estimates*

[6] *questionnaire being used was not validated*

[7] *mean EQ-5D scores were depicted in a diagram, but not given in absolute numbers*

[8] *since the overall RoB for both studies reporting the outcome CR for the total study population was assessed with some concerns and moderate, respectively, we classified the RoB for this outcome as serious*

[9] *due to small sample size of studies reporting the outcome CR for the total study population*

[10] *only 2/4 studies reported the outcome*

[11] *due to inclusion of 11 single-arm studies, all of which were assessed with a medium to high RoB*

[12] *results are reported inconclusively*

[13] *11/16 studies were observational trials (single-arm studies)*

Applicability table

Table A-9: Summary table characterising the applicability of a body of studies (controlled studies)

Domain	Description of applicability of evidence
Population	The patient population (n=503, of whom 243 received the intervention) varied considerably in terms of stage of the NMIBC (Ta/T1/CIS), primary tumours versus recurrent lesions and/or a previous treatments. The mean age ranged from 64.3 to 77 years.6.6% to 35.7 % of the participants were female.
Intervention	All studies used radiofrequency-induced intravesical chemotherapy applied by the Synergo® system in combination with mitomycin-C. With the exception of one study, all sessions were executed as 2x20-30 min of hyperthermia either applied once or twice a week during the induction cycles. These were followed by either none or a various number of maintenance cycles.
Comparators	Three studies used either intravesical instillations with MMC (2 study) or BCG (1 study) as comparators. One study investigated the intervention in comparison to either BCG or institutional standard of care, whereas the patients of the non-randomised trial could chose between instillations with MMC or MMC provided via EMDA.
Outcomes	All outcomes defined as crucial for a decision were reported in the included trials. Three studies reported on the overall survival, one study provided data for the disease-specific surival and four studies documented the quality of life. Regarding important outcomes, two studies reported the disease-free survival, three studies documented the progression-free surivival and four studies described the recurrence-free survival. Additonal four studies reported data on the surrogate parameters complete response, while one study included estimates for the radical cystectomy/ bladder preservation rate. All studies reported the outcome complications.
Setting	The trials were conducted in Austria, Belgium, France, Germany, Israel, Italy, the Netherlands, Switzerland, Turkey and the UK and and were published between 1991 and 2018.

List of ongoing randomised controlled trials

Currently, there are no ongoing randomised controlled trials investigating the efficacy of the Synergo® system. However, the search in the clinical trial registries revealed two ongoing single-arm studies: NCT03335059 (with an estimated study completion dates in March 2025) and EUCTR2016-000049-30-ES (no estimated completion date provided).

Literature search strategies

Search strategy for Cochrane

Search Name: intravesical RF-induced Hyperthermia for Bladder Cancer	
Search Date: 20.12.2019	
ID	Search
#1	MeSH descriptor: [Urinary Bladder Neoplasms] explode all trees
#2	MeSH descriptor: [Carcinoma, Transitional Cell] explode all trees
#3	((bladder* OR urinary OR urothelial OR transitional) NEAR (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR neoplasm* OR sarcoma* OR malignan* OR lump* OR masses OR metasta*)) (Word variations have been searched)
#4	(STCCB):ti,ab,kw (Word variations have been searched)
#5	#1 OR #2 OR #3 OR #4 (Word variations have been searched)
#6	MeSH descriptor: [Hyperthermia, Induced] explode all trees
#7	((intravesic* OR endovesic) NEAR (chemo* OR mitomycin*)) (Word variations have been searched)
#8	((hypertherm* OR heat*) NEAR (chemo* OR mitomycin* OR induce* OR deliver* OR insert* OR catheter*)) (Word variations have been searched)
#9	(thermochemo* OR thermo-chemo* OR chemotherm* OR chemo-therm*) (Word variations have been searched)
#10	(chemohypertherm* OR chemo-hypertherm*) (Word variations have been searched)
#11	(thermocouple* OR thermo-couple* OR thermo-therap* OR thermotherap*) (Word variations have been searched)
#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11 (Word variations have been searched)
#13	#5 AND #12 (Word variations have been searched)
#14	(synergo* OR (Combat* NEXT BRS) OR Unithermia OR BSD-2000) (Word variations have been searched)
#15	#13 OR #14 with Publication Year from 2018 to 2019, with Cochrane Library publication date Between Apr 2018 and Dec 2019, in Trials
Total: 45 Hits	

Search strategy for Embase

Search Name: intravesical RF-induced Hyperthermia for Bladder Cancer	
Search Date: 20.12.2019	
ID	Search
#1	'bladder cancer'/exp
#2	'transitional cell carcinoma'/exp
#3	((bladder* OR urinary OR urothelial OR transitional) NEAR/4 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm* OR sarcoma* OR malignan* OR lump* OR masses OR metasta*)):ti,ab,de,kw
#4	stccb:ti,ab
#5	#1 OR #2 OR #3 OR #4
#6	'thermotherapy'/exp
#7	((intravesic* OR endovesic*) NEAR/4 (chemo* OR mitomycin*)):ti,ab,de,kw
#8	((hypertherm* OR 'hyper therm*' OR heat*) NEAR/4 (chemo* OR mitomycin* OR induce* OR deliver* OR insert* OR catheter*)):ti,ab,de,kw
#9	thermochemo*:ti,ab,de,kw OR 'thermochemo*':ti,ab,de,kw OR chemotherm*:ti,ab,de,kw OR 'chemo therm*':ti,ab,de,kw
#10	chemohypertherm*:ti,ab,de,kw OR 'chemo hypertherm*':ti,ab,de,kw
#11	thermocouple*:ti,ab,de,kw OR 'thermocouple*':ti,ab,de,kw OR 'thermotherap*':ti,ab,de,kw OR thermotherap*:ti,ab,de,kw

#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11
#13	#5 AND #12
#14	synergo*:ti,ab,de,kw,dn OR ((combat* NEAR/1 brs):ti,ab,de,kw,dn) OR unithermia:ti,ab,de,kw,dn OR 'bsd 2000':ti,ab,de,kw,dn
#15	#13 OR #14
#16	#15 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)
#17	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#18	#15 AND #17
#19	#16 OR #18
#20	#19 AND [30-4-2018]/sd NOT [21-12-2019]/sd
Total: 73 Hits	

Search strategy for Medline

Search Name: intravesical RF-induced Hyperthermia for Bladder Cancer	
Search Date: 20.12.2019	
ID	Search
#1	exp Urinary Bladder Neoplasms/
#2	Carcinoma, Transitional Cell/
#3	((bladder* or urinary or urothelial or transitional) adj5 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm* or sarcoma* or malignan* or lump* or masses or metasta*)).mp. (95617)
#4	STCCB.ti,ab.
#5	1 or 2 or 3 or 4
#6	exp Hyperthermia, Induced/
#7	((intravesic* or endovesic*) adj5 (chemo* or mitomycin*)).mp.
#8	((hypertherm* or heat*) adj5 (chemo* or mitomycin* or induce* or deliver* or insert* or catheter*)).mp.
#9	(thermochemo* or thermo-chemo* or chemotherm* or chemo-therm*).mp.
#10	(chemohypertherm* or chemo-hypertherm*).mp.
#11	(thermocouple* or thermo-couple* or thermo-therap* or thermotherap*).mp.
#12	6 or 7 or 8 or 9 or 10 or 11
#13	5 and 12
#14	(synergo* or (Combat* adj1 BRS) or Unithermia or BSD-2000).mp.
#15	13 or 14
#16	limit 15 to clinical trial, all
#17	((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.)
#18	15 and 17
#19	16 or 18
#20	limit 19 to ed=20180430-20191220
#21	remove duplicates from 20
Total: 65 Hits	

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