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REVIEW ARTICLE

Intravesical radiofrequency-induced hyperthermia combined with chemotherapy for non-muscle-invasive bladder cancer

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Abstract

Although many treatment modalities and schedules for non-muscle-invasive bladder cancer (NMIBC) exist, all yet prove to have limitations. Therefore the search for new forms of therapy continues. One of these forms consists of combining intravesical chemotherapy, typically mitomycin C (MMC), with hyperthermia achieved by a microwave-applicator. We aimed to review the current status of intravesical radiofrequency (RF) induced chemohyperthermia (CHT) for NMIBC with regard to efficacy, adverse-events (AEs) and its future perspective. A search for RF-induced CHT in MEDLINE, Embase, Cochrane and ClinicalTrials.gov databases was performed. Relevant conference abstracts were searched for manually. If applicable, experts on the area were consulted. Papers were selected based on abstract and title. A table of newly published clinical trials since 2011 was constructed. No meta-analysis could be performed based on these new papers. Efficacy proved to be better for RF-induced CHT compared to both MMC alone and bacillus Calmette–Guérin (BCG) instillations, with the latter being based on just one abstract of a randomised controlled trial. The AE rate in CHT is higher compared to MMC instillation, but is similar compared to BCG, albeit different in the type of AE. In almost all studies no severe AEs are reported. Although heterogeneity in methodology exists, RF-induced CHT seems promising. However, alternative methods of applying hyperthermia are starting to present their first results, imposing as effective options too. Intravesical RF-induced CHT may become an alternative for BCG instillation, and possibly for cystectomy, although further level 1 evidence is required for both reliable and reproducible data on efficacy and adverse events.

Introduction

Bladder cancer is the most common malignancy of the urinary tract. In the European Union (EU), the age-standardised incidence rate varies from 6 per 100 000 in women to 27 per 100 000 in men [1]. These rates vary per region within the EU. On top of the high incidence, bladder cancer was the eighth most common cause of cancer-specific mortality in 2008.

On presentation, about 75% of patients are diagnosed with non-muscle-invasive bladder cancer (NMIBC). In these patients urothelial cell carcinoma is confined to the mucosa (stage Ta, carcinoma in situ (CIS)) or invades the lamina propria only (stage T1). The remaining patients present with muscle-invasive disease ($T \geq 2$) which can be treated with radical cystectomy (RC), radiotherapy or systemic chemotherapy, depending on the presence and extent of regionally or distantly spread disease.

Fortunately, both incidence and mortality are decreasing in some registries, possibly reflecting a decreased prevalence of smoking, less occupational exposure to causative agents, and improved care. As opposed to muscle-invasive bladder cancer (MIBC), NMIBC has a high prevalence due to relatively low progression rates (5-year progression rate of 1–45% (0–30% in the Club Urológico Español de Tratamiento Oncológico (CUETO) risk tables), depending on grade, stage, tumour size, number of tumours, presence of CIS, previous recurrences according to the European Organization for Research and Treatment of Cancer (EORTC) risk tables [2] and additionally sex and age according to the CUETO risk tables [3]) and thus has a long patient survival. However, 5-year recurrence rates can be as high as 78%, necessitating a frequent and long-term follow-up with outpatient clinic visits, cytology tests, and invasive cystoscopies. This imposes a significant burden on the patient and on the healthcare system in both financial and logistic way.

To prevent recurrence and progression from occurring, adjuvant treatment after trans-urethral resection of a bladder tumour (TURBT) is given. According to the EAU guideline on NMIBC, a single post-operative instillation (SPI) with chemotherapy, a 1-year protocol with chemotherapy or immuno-therapy with bacillus Calmette–Guérin vaccine (BCG), or

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instillations with BCG for 3 years should be given for low, intermediate and high risk disease, respectively [1]. However, in the above-mentioned CUETO risk tables for recurrence and progression, these instillation protocols were already taken into account, and still recurrence rates are high. Moreover, a worldwide shortage in BCG has currently evolved. The shortage is even more stringent because of the importance of BCG in patients at high risk for progression to MIBC.

For these reasons, extensive research has been performed to improve therapies in both adjuvant and neo-adjuvant settings to prevent recurrence and progression, reduce the intensity of follow-up, and to maximise bladder preservation rates, thus prolonging the patient's quality of life and survival. A new treatment modality is electromotive drug administration (EMDA) [4], in which iontophoresis is being used for improving tissue penetration by the chemotherapeutic drug. Another strategy is photodynamic therapy (PDT), which uses the interaction between absorbed light and a retained photosensitising agent to destroy tissue, although it is infrequently applied. A final new and promising strategy is hyperthermia combined with intravesical chemotherapy.

Hyperthermia

The potential value of hyperthermia in treating cancer was first suggested in 1866 by a German physician after he noted disappearance of a sarcoma with a high fever due to erysipelas. The use of hyperthermia in the management of bladder cancer had not received much attention until halfway through the 20th century. During this period, hyperthermia was tested as a solitary treatment by recirculating hot fluid in the bladder. It proved to be marginally effective in reaching complete response (CR) even with temperatures of up to 80 °C [5]. Therefore, combinations of hyperthermia with radio- or chemotherapy were explored.

Techniques of establishing intravesical hyperthermia have developed since. At present, four main techniques exist. All of these combine hyperthermia with intravesical chemotherapy. The first technique makes use of the before-mentioned recirculation of fluid heated outside of the body, such as the UniThermia [6] or Combat BRS systems [7] do. Secondly, a relatively new technique which is still in the pre-clinical phase uses magnetic fluid in combination with magnetic resonance for heating [8]. The third and fourth more extensively investigated techniques make use of radiofrequency (RF)-induced hyperthermia. This can be applied from outside of the body (deep external hyperthermia, e.g. a BSD-2000 device [9]) or, as is discussed in this manuscript, with an intravesical RF-emitting antenna (Synergo® [10]) device.

The goal of this review is to provide an overview and reflection on the current status of RF-induced chemo-hyperthermia (CHT). Since a systematic review covering literature up to January 2011 exists [11], we intend to give an update based on the newly acquired knowledge.

Evidence acquisition and synthesis

A literature search in MEDLINE, Embase and Cochrane databases was performed on 30 September 2015, resulting in papers published from 1950 to 29 September 2015. Key search terms used (as well as synonyms, abbreviations, and entry terms/MeSH terms) were 'bladder cancer', 'hyperthermia', 'chemohyperthermia', and 'radiofrequency'. Only titles and abstracts were searched. Searches with these key terms were combined with the appropriate Boolean operators. Relevant conference abstracts were also searched for manually. ClinicalTrials.gov identified only one additional relevant study regarding overactive bladder symptoms after Synergo® treatment which is currently recruiting.

Although this review is not a systematic review, it is based on a very sensitive search. Titles and abstracts of the search result were subsequently scanned for relevance. Where applicable, authors and experts were asked for additional information. Manuscripts were selected for further review if an English abstract was available, if it concerned RF-induced CHT, or in some cases, if it concerned intravesical hyperthermia with a very similar rationale such as conductive heating or deep external RF-induced hyperthermia.

Clinical trials regarding intravesical RF-induced CHT were evaluated and ordered in an overview to facilitate a comprehensive comparison. This overview focuses on clinical trials published after the systematic review of Lammers et al., and thus can be seen as a sequel of the table presented in that publication [11].

No meta-analysis was performed because the newly published manuscripts since January 2011 did not compare RF-induced CHT with other treatments, or were too few for pooling data [11]. Since most chemo-hyperthermia treatments are performed with mitomycin C (MMC), the abbreviation CHT in this manuscript is used for the combination of hyperthermia with MMC unless otherwise stated.

Technical implementation (the Synergo® device)

The only currently available device applying intravesical RF-induced hyperthermia is the Synergo® system, which has been described in detail previously [10]. In short, local hyperthermia is accomplished by a 915-MHz intravesical microwave applicator heating the bladder wall. This applicator is located in the distal end of a three-way transurethral 20F catheter with Tiemann tip, containing a lumen for inflation of the balloon, a lumen for fluid introduction, and another lumen for outflow of fluid. Three thermocouples are tangentially distended from the catheter tip to measure temperature at the bladder neck, and the dorsal and lateral bladder walls. Two additional thermocouples are incorporated more distantly from the tip, measuring temperature in the proximal urethra (Figure 1).

A bladder wall temperature between 41–44 °C is preferable [12]. Temperatures and RF power are monitored and regulated on an external computerised unit to which the catheter is connected, resulting in a closed circuit. This unit also regulates the speed of the peristaltic pump and the cooling of the fluid being pumped into the bladder. The latter is done for urethral thermal protection.

Due to its favourable safety profile and the substantial experience in combination with hyperthermia, MMC is being used as the drug of first choice in chemo-hyperthermia treatment. If MMC is not an option, epirubicin has been accepted as a safe and efficient alternative. Typically, treatment is given in two sessions of 20–30 min in which the
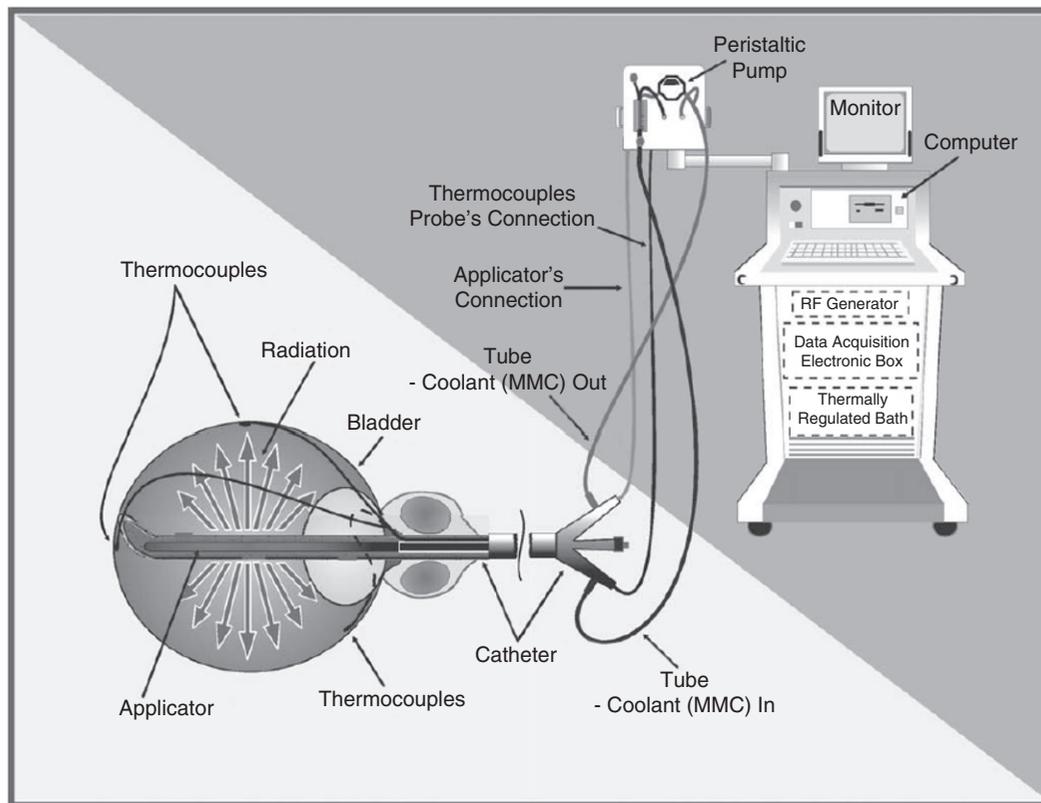
Figure 1. Schematic illustration of the Synergo® SB-TS 101 system during treatment.

aim is to achieve a temperature above 41 °C during at least 20 min per session. Chemo-hyperthermia is most commonly applied in a prophylactic protocol of 2×20 mg MMC or 2×25 mg epirubicin, also described as an adjuvant treatment, or alternatively in an ablative protocol of 2×40 mg MMC or 2×50 mg epirubicin, also known as neo-adjuvant treatment. Dosages are dissolved in 50–60 mL of saline or distilled water. Reasons for changing the instilled fluid after 20–30 min are dilution by newly produced urine and serum exudation, disintegration of the solution, and that MMC absorption occurs mainly during the first 22 min [6,13]. After initial catheter insertion the bladder is emptied. For minimisation of drug dilution patients are instructed to limit fluid intake as much as possible before each treatment.

For induction 6–8 weekly instillations are administered, after which a maintenance period follows consisting of instillations every 4–6 weeks for up to a year. During the second year the interval is widened if no recurrence or progression was seen. Follow-up cystoscopies are usually performed every 3 months. Strictly taken, treatment can be stopped after a disease-free period of 2 years, although no studies have been performed to find the optimal treatment duration. Nonetheless, many patients in our centres continue treatment with longer intervals after a period of 2 years from the first instillation.

Rationale and assumed mechanism

Although some *in vitro* and *in vivo* studies have been performed to unravel the mechanism through which hyperthermia contributes to the anti-tumour effect, no uniform theory yet exists. Nonetheless, results give direction to the rationale for using hyperthermia in combination with intravesical chemotherapy.

When hyperthermia alone is applied, this results in direct damage to the DNA, RNA and proteins, and additionally inhibits their synthesis resulting in a decreased proliferation rate [4,7,14–16]. If subsequently repair mechanisms fail due to altered intracellular metabolism, cell death and apoptosis are accelerated [17]. These changes can be seen from temperatures of 40.5 °C and beyond, with magnitude inclining with temperature [4,18]. Due to a change in intracellular metabolism and resulting acidic and hypoxic micro-environment, a further sensitisation to both hyperthermia and cytotoxic agents occurs. Beside these direct effects, the immune system seems to be boosted [4,19], resulting in increased cellular immune response and autovaccination against tumour cells. Lastly, hyperthermia may increase blood flow in normal surrounding tissue due to vasodilatation, increasing MMC exposure. However, tumour vasculature is less responsive and thus less efficient in dissipating heat, resulting in a higher local temperature than in non-cancerous cells. This possibly results in a higher treatment specificity for cancerous cells. The same seems to be the case at cellular level, since normal urothelial cells demonstrate more resistance to CHT [15,17,20,21], although conflicting results are reported [22].

By introducing chemotherapy to hyperthermia, this additionally damages the vital cellular molecules in the absence of a properly functioning repair mechanism, resulting in an otherwise absent clinically relevant effect [16,17]. Thus, hyperthermia leads to drug potentiation. This is demonstrated by several *in vitro* studies which show a synergistic instead of

just an additive effect on cytotoxicity [18,23]. A possible role in this synergy exists for p53 [16,17] and heat-shock proteins [4]. Lastly, an increased tissue and cellular membrane penetration is presumed but has not yet been confirmed.

Although an increased penetration is an intuitive hypothesis, Wallner et al. [24] found that hyperthermic potentiation of MMC activity was maximal if heating was done simultaneously to exposure, or up to 3 h following MMC exposure. The fact that heating cells after MMC has been removed from the medium still potentiates MMC cytotoxicity argues against the importance of permeability or activation changes at elevated temperatures; rather, it points to the importance of alterations in damage repair processes. Moreover, RF-induced CHT does not result in toxic plasma levels which might be expected in increased tissue penetration [13].

At present, reason for choosing intravesical RF-induced CHT instead of other ways of heating is the assumption that a more controlled and effective heating, including a more precise temperature measurement can be achieved, although no good comparative studies have been performed. RF-induced CHT has the advantage of being the most extensively investigated form of applying intravesical hyperthermia, and thus has a broader base of evidence. Fortunately, studies regarding other forms of chemo-hyperthermia are emerging.

Clinical indications

Currently, RF-induced CHT can be discussed in NMIBC patients at intermediate to high risk for recurrence and progression. Roughly, three main indications exist, namely 1) highly recurrent NMIBC under standard therapy, 2) therapy-resistant CIS or other NMIBC, which means the tumour is BCG-refractory, and severe co-morbidity or the explicit desire of the patient for bladder sparing treatments, and 3) contra-indications for BCG. As already mentioned in the introduction, these indications have been extended temporarily to overlap the indications for BCG (high risk disease) in light of the current BCG-shortage. Patients should not be given RF-induced CHT if bladder volume is less than 150 cm^3 (severe bladder spasms and pain), if urinary bladder diverticulum with a cumulative diameter of larger than 1 cm is present (risk of perforation and MMC diffusion intraperitoneally), or if catheterisation problems are expected.

The setting of RF-induced CHT can be prevention of tumour recurrence (prophylactic, or adjuvant therapy), or eradication of bladder tumour (ablative, or neo-adjuvant therapy). Both have been used in studies, and results are promising (described below).

Efficacy

Chemo-hyperthermia alone

Only a few comparative studies of RF-induced CHT with MMC alone or with BCG exist. Most papers describe experience with CHT alone, as a single-arm study. Nonetheless, this does provide an impression of its general efficacy. Regarding recurrence, for example, rates vary from 16–89%, see also Table 1 in this paper as well as Table 1 from the systematic review of Lammers et al. [11,25–33]. Two outliers are seen in this range, both representing studies with

patients not suitable and/or unwilling for cystectomy [29,34]. If these are excluded, a recurrence rate of 16~50% remains (22.6~50% if follow-up is at least 2 years). Moreover, recurrence rates in the earliest studies are different from the later studies performed, since the principal exploratory studies all made use of CR or partial response scoring with subsequent recurrence rates, regardless of dose and treatment schedule [10,35], whereas later studies used specific ablative or prophylactic treatment protocols.

Progression is reported less often than recurrence, since it requires a longer follow-up of NMIBC. Nonetheless, some figures are published: overall 0–36% show progression, and when only studies with a follow-up of >2 years are considered, the same figures apply [11,25–33]. Most of these studies define progression as occurrence of MIBC. Remarkable is the wide spread of progression rate, mostly caused by the results of more recent publications [29,30,32]. These papers have a definition of progression which is much broader than just the occurrence of MIBC. Sooriakumaran et al. [30], for example, also include in the definition patients with initiation of further treatment (BCG, cystectomy, radiotherapy, diverticulectomy), extravesical disease, or distant metastases, reaching a progression rate of 36%. The study of Kiss et al. used a cohort of patients who were not fit for, or had refused cystectomy. Moreover, most patients did not complete the treatment protocol due to adverse events [29]. If these studies are excluded, a progression rate of 0–11.9% remains [11,25–28,33].

Most studies published allow comparison of prophylactic therapy with\ ablative therapy. CR after ablative therapy ranges from 42–85.5%, with subsequent recurrence rates of 16–30.4% (follow-up ranging from 16–38 months). Progression rate for complete responders varies from 0% to 27% [11,25,26,30–32]. See also Table 1. For prophylactic therapy, recurrence rate varies from 15.6–56% and progression rate from 0–11.9% (follow-up ranging from 10–38 months) [11,25–28,31,33].

Although results in patients that have previously failed intravesical therapy for NMIBC are contradictory, some patients do seem to have additional benefit from CHT treatment. For example, Lammers et al. [11] report on a multicentre Italian project in which patients who have been treated *de novo* with CHT do significantly better than those who had previous intravesical instillations (2-year recurrence-free survival (RFS) of 91% and 62% respectively, $p = 0.006$). This finding is supported by a previous study showing a RFS of 75.4–58.8%, respectively [36]. However, in a different paper no difference in response rate was seen in CIS patients failing or responding to BCG [37]. Also in intermediate and high risk patients in general, studies show no effect of previous BCG failure [38,39]. Arends et al. describe their 10-year experience in a cohort of 160 patients in which 81% of the subjects was previously treated with BCG. Although not analysed separately, the overall 2-year RFS was 47% [28]. Thus, a substantial proportion of pre-treated patients still benefits from treatment.

Bladder preservation rates have been described previously, reaching a pooled rate of 89.4% [11]. In agreement with the previous literature, more recent studies vary from 71–100% in bladder preservation rate, depending on the treatment protocol used [25,27,29–32].

Table 1. Overview of all clinical trials since January 2011 concerning initial response, recurrence and progression chances after RF-induced chemo-hyperthermia in non-muscle-invasive bladder cancer patients.

Reference	Study type	No. of patients	Patient population	Study description	Duration (min)	Temperature (°C)	Dose	No. of treatments	Maintenance	Follow-up median (range)	Outcome		
											Recurrence	Progression	Cystectomy
Moskovitz et al., 2012 [25]	Retrospective	88	Intermediate and high risk NMIBC (EAU criteria)	Single centre Adjuvant (n=64) and neo-adjuvant (n=24) treatment with MMC	2×30=60	42±(N/A)	Adjuvant: 20+20 mg Neo-adjuvant: 40+40 mg Both in 50 mL	Adjuvant: 6× weekly Neo-adjuvant: 8× weekly	Adjuvant or if CR in neo-adjuvant: 6× every 6 weeks, 1 year	23 months (3 months up to 7 years)	Adjuvant: Recurrence in 18/64 (28%) Neo-adjuvant: CR in 19/24 (79%) Recurrence: 3/19 (16%)	Adjuvant: 3/64 (4.7%) Neo-adjuvant: 0/19 (0%)	Adjuvant: 3/64 (4.7%) Neo-adjuvant: 2/24 (8.3%)
Volpe et al., 2012 [26]	Prospective	30	Ta/1 G2/3 or Tis	Single centre CHT with MMC Prophylactic (n=16) and ablative (n=14) treatment. Both had TURBT before start (n=30)	2×20−30 =40−60	42±2	Prophylactic: 20+20 mg Ablative: 40+40 mg Both in 50 mL	Prophylactic: 6× weekly Ablative: 8× weekly	Yes 6× monthly	Mean: 14±8.48 months	Prophylactic: 9/16 (56.25%) Ablative: CR in 6/14 (42.85%) Overall recurrence: 17/30 (56.7%). Overall DFS: 77% after 12 months, 55% after 24 months	Prophylactic: 0/16 (0%) Ablative: 3/14 (17.64%) Overall: 3/30 (10%)	N/A
Maffezzini et al., 2014 [27]	N/A	42	High risk NMIBC (EAU criteria): EORTC recurrence score ≥5 or progression score ≥7	Single centre CHT with MMC in adjuvant setting. Epirubicin in cases of persistent intolerance to MMC (n=10)	2×30=60	42.5±1.5	MMC: 40+40 mg If epirubicin: 50+50 mg Both in 50 mL	4× weekly, 6 every 2 weeks: total=10	Yes 4× every 3 weeks	38 (4−73) months	32 patients completed protocol. ITT: 1-year DFS before study 14.9% vs 88.8% after CHT. Recurrence 13/42 (30.9%)	ITT: 5/42 (11.9%)	ITT: 7/42 (16.6%)
Arends et al., 2014 [28]	Prospective	160	Intermediate and high risk NMIBC (EAU criteria)	Single centre CHT with MMC in adjuvant setting. Epirubicin in cases of persistent intolerance to MMC (n=20)	2×30=60	42±2	Prophylactic: 20+20 mg MMC or 25+25 mg epi Ablative: 40+40 mg MMC or 50+50 mg epi All in 50 mL	6-8× weekly	Yes, every 6 weeks, up to 1 year	75.6 months(N/A)	Overall 1- and 2-year RFS: 60% and 47%, respectively 1-year RFS: 59% vs 64%, and 2-year RFS: 46% vs 55% for MMC and epirubicin, respectively (p=0.30)	7/160 (4%)	N/A
Nair et al., 2014, conference abstract EAU [44]	Prospective	103+51	High risk NMIBC (EAU criteria) Overlap in patients with Sooriakumaraan 2015 [30]	Single centre CHT (n=103) matched with RC (n=51) 5-year survival	2×30=60	42±2	MMC: 40+40 mg in 50 mL saline	6-8× weekly, median: 6×	If CR or PR: 20 mg MMC in 50 mL, every 6 weeks (year 1) and every 8 weeks (year 2)	40 (4-92) months	5-year DSS, RC vs CHT: 74.6% vs 85.2% 5-year OS, RC vs CHT: 68.4% vs 61.9% 90-day mortality: 4% RC, 0% CHT Significant AE: RC 21%, CHT 0%	N/A	N/A
Kiss et al., 2015 [29]	Prospective	21	Intermediate and high risk	Single centre CHT in	2×30=60	42±2	Prophylactic: 20+20 mg	Prophylactic: 6× weekly	N/A	50 (1−120) months	0%	4/21 (19%)	6/21 (29%) due to

Table 1. Continued

Reference	Study type	No. of patients	Patient population	Study description	Treatment					Follow-up median (range)	Outcome		
					Duration (min)	Temperature (°C)	Dose	No. of treatments	Maintenance		Recurrence	Progression	Cystectomy
			NMIBC (EAU criteria)	prophylactic (n = 10) and ablative (n = 11) setting			Ablative: 40 + 40 mg All in 50 mL	Ablative: 12× weekly Overall median: 6×			Overall: 15/21 (71%) DSS: 19/21 (90%) OS: 14/21 (67%)		multifocal recurrence or progression
Sooriakumaran et al., 2015 [30]	Prospective	97	High risk NMIBC (EAU criteria)	Observational cohort study. time-to-progression study in ablative protocol	2 × 30 = 60	41–44	MMC: 40 + 40 mg In 50 mL saline	6–8× weekly, median: 6×	CR or PR: 20mg MMC in 50 mL every 6 weeks (year 1) and every 8 weeks (year 2)	27 (16–47) months	OS: 80/97 (82) DSS: 90/97 (93)	35/97 (36)	18/97 (19)
Lüdecke et al., 2013, conference abstract, Genitourinary Cancers Symposium [31]	Prospective	138	High risk NMIBC (EAU criteria)	Multi-institutional study on long-term effects of CHT, for both the adjuvant (n = 52) and ablative (n = 86) protocol. 69/86 evaluable, because of protocol violations or extra-vesical UCC or second simultaneous malignancy	N/A	N/A	N/A	6–8× weekly	6× every 6 weeks	Mean: 2.9 years (range 3.6 months – 6.9 years)	Adjuvant: 10/52 (19.2) Recurrence free: 78.3% Ablative: 59/69 (85.5) CR at week 11 persisting for 21.6 months in mean	Adjuvant: 0/52 (0) Ablative: 11/69 (15.9)	Adjuvant: 0/52 (0) Ablative: 8/69 (11.6)
Lüdecke et al., 2013, conference abstract, EAU	Prospective	86	High risk NMIBC (EAU criteria) Overlap in patients with other 2013 abstract	First-line CHT in high risk patients, and in extremely high risk patients failing BCG (22/86)	N/A	N/A	MMC: 40 + 40 mg N/A mL	8× weekly	6× every 6 weeks with 2×20 mg MMC if tumour free	Mean: 24.1 months (1.7 months to 11.8 years)	Ablative: 59/69 (85.5) CR at week 11 persisting for 21.6 months in mean. 48/69 (69.6) tumour free during follow-up.	N/A	8/69 (11.6)

(continued)

Reference	Study type	No. of patients	Patient population	Study description	Treatment					Follow-up median (range)	Outcome		
					Duration (min)	Temperature (°C)	Dose	No. of treatments	Maintenance		Recurrence	Progression	Cystectomy
Lüdecke et al., 2015, conference abstract, EAU [49]	Prospective	271	High risk NMIBC (EAU criteria) Overlap in patients with other two abstracts likely	Multi-institutional (n = 7) study on long-term effect of CHT	N/A	N/A	MMC: 40+40mg N/A mL	8× weekly	6× every 6 weeks with 2×20 mg MMC if tumour-free on re-TURBT	Mean: 2.2 years (range 28 days to 12.9 years)	206/271 (76.1) CR 21/271 (7.6) PR 2-year recurrence: 52/271 (19.4) Thus recurrence: 21/69 (30.4)	N/A	N/A
Arends et al., 2015, conference abstract, EAU [33, personal communication]	Prospective	190	Intermediate and high risk NMIBC (EAU criteria)	Multi-institutional (n = 11) Randomised controlled clinical trial comparing RF-induced CHT vs BCG in adjuvant setting over 1 year	2 × 30 = 60	42 ± 2	MMC: 20 + 20 mg in 50 mL	6× weekly	6× every 6 weeks	25.7 (3.9-34) months	24 months RFS per protocol: 81.8% vs 64.8% (CHT vs BCG, p=0.0216). Recurrence: 18.2% vs 35.2% CR in CIS after 3 months: 88.9% vs 85.7% (CHT vs BCG, p>0.1)	1.7% in CHT 2.8% in BCG (p = n.s.)	N/A
Kelly et al., 2015, conference abstract, BAUS [42]	Prospective	104	Recurrence after BCG, but unfit/unwilling for RC	Randomised controlled phase III, multicentre study. CHT after BCG vs second course BCG/institutional standard therapy	2 × 30 = 60	42 ± 2	MMC: 20+20mg in N/A mL	6× weekly	Every 6 weeks in year 1, every 8 weeks in year 2	N/A, but goal was 24 months	No difference in DFS. Improved DFS in papillary disease alone (HR 0.40, p = 0.05) CR in CIS patients (n = 71) at 3 months: 81% vs 86%. Worse DFS (HR 2.17, p = 0.02)	N/A	N/A

AE, adverse event; BAUS, British Association of Urological Surgeons; BCG, bacillus Calmette–Guérin; CHT, chemo-hyperthermia; CIS, carcinoma in situ; CR, complete response; DFS, disease-free survival; DSS, disease-specific survival; EAU, European Association of Urology; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; ITT, intention-to-treat analysis; MMC, mitomycin C; N/A, not available; NMIBC, non-muscle invasive bladder cancer; OS, overall survival; PR, partial response; RC, radical cystectomy; RF, radio-frequency; RFS, recurrence free survival; TURBT, transurethral resection of bladder tumour.

Of further interest, Arends et al. evaluated the difference in efficacy between MMC and epirubicin, both in a prophylactic and an ablative protocol [28]. They found a pooled 2-year RFS of 46% and 55% for MMC and epirubicin, respectively ($p = 0.30$). No other groups have investigated efficacy of chemotherapeutics other than MMC in CHT [17].

It needs to be noted that in all the above-mentioned rates, a high level of methodological heterogeneity (mostly in patient characteristics, treatment schedule and follow-up time) exists, hampering the generalisability of these figures. Therefore, cautious interpretation is warranted.

Chemo-hyperthermia vs. MMC alone

Up to this moment, four studies have been performed comparing RF-induced CHT versus MMC alone. All four were performed by the same author (although patients did not overlap according to the author except for the long-term results paper) and have been clustered in a meta-analysis in a recent systematic review [11,20,21,40,41]. However, several drawbacks are presented. One of these studies was a non-randomised study; allocation in three treatment groups (i.e. CHT, MMC alone, or EMDA) was according to patient preference [40]. Moreover, different treatment duration and drug concentrations were used. Three out of four studies were performed in intermediate to high risk NMIBC patients, the fourth in single, small (<2 cm) stage Ta/T1 G1–2 patients.

In total, 26/93 patients (28%) had a recurrence in the clustered CHT group, vs. 67/99 (67.7%) in the MMC alone group. After meta-analysis this was corrected for different weighting of studies, resulting in an overall risk ratio of 0.410 (95% CI, 0.290–0.579), indicating 59% less risk of recurrence after CHT compared to MMC alone [11]. Although heterogeneity in the studied populations and methodological shortcomings are present, this outcome does indicate a substantial benefit of CHT over MMC alone.

CR rates were only reported in two studies comparing CHT with MMC alone, showing 66% in both for CHT, vs. 22% ($p = 0.001$) and 27.7% (p-value not reported) in MMC alone [20,40]. Progression, bladder preservation, and overall survival were derived from two studies using the same cohort, in which the latest paper reports the long-term outcomes of the same intermediate to high risk patient cohort [21,41]. Over a median follow-up of 90 months (range 6–154), 2/35 patients (5.7%) treated with CHT and 3/40 (7.5%) treated with MMC alone progressed. Bladder was preserved in 86.1% vs. 78.9%, respectively ($p = 0.129$), and overall survival was 29/35 (82.9%) vs. 31/40 patients (77.5%), respectively ($p = 0.558$). No disease-specific deaths occurred.

Chemo-hyperthermia vs. BCG

Until now, no publications on the comparison of RF-induced CHT vs. BCG exist, although an abstract of Arends et al. [33] was presented at the latest conference of the European Association of Urology (EAU) in 2015. In this abstract a randomised controlled clinical trial comparing 1 year of RF-induced CHT with 1 year of BCG in the adjuvant setting was discussed. The study population consisted of 190 patients with intermediate to high risk NMIBC, recruited over 11 centres between 2002 and 2012. A 24-month RFS of 81.8% in

the RF-induced CHT group, compared to 64.8% in the BCG group was found on the per-protocol (PP) analysis ($p = 0.0216$). The intention-to-treat analysis, however, did not result in a significant difference (78.1% vs. 64.8% respectively, $p = 0.0803$). In a specific analysis for CIS patients only, a CR rate of 88.9% and 85.7% was found for CHT and BCG, respectively ($p > 0.1$). Progression was described in less than 3% in both groups (personal communications).

Another interesting yet unpublished project is the HYMN trial (ClinicalTrials.gov; NCT01094964). In this two-arm, randomised, open-label and multicentre study from the UK, RF-induced CHT is compared with BCG or standard therapy as a second-line therapy in 104 patients with recurrent NMIBC after a first-line induction or maintenance BCG treatment. Whether a patient receives BCG maintenance or standard therapy depends on the response to the first-line BCG treatment. Primary outcomes were disease-free survival time (DFS) in all patients, and CR rate at 3 months in patients with CIS. Secondary outcomes will be RFS, progression-free survival, overall survival (OS), disease-specific survival (DSS), safety and tolerability, quality of life, and cost effectiveness. Lastly, biomarkers of response to standard and investigational treatment will be assessed. An abstract was presented recently showing no difference regarding CR and overall DFS [42]. The DFS in patients with papillary disease alone at randomisation ($n = 33$), however, had an improved DFS for RF-induced CHT compared to BCG or standard therapy (HR 0.40, 95% CI 0.16–0.98, $p = 0.05$), whereas with any CIS at randomisation ($n = 71$), DFS was worse (hazard ratio (HR) 2.17, 95% confidence interval (CI) 1.15–4.08, $p = 0.02$). No difference in adverse events was found.

The concept of CHT with a different technique has been compared with BCG solely by Ekin et al. [43]. They compared conductive CHT ($n = 40$) with BCG ($n = 142$) in a retrospective propensity score-matched study in high risk NMIBC patients and found a 2-year RFS in conductive CHT and BCG groups of 76.2% and 93.9%, respectively ($p = 0.020$). Conductive CHT treatment (HR 5.42; 95% CI 1.11–26.43; $p = 0.036$) and high-grade tumour (HR 4.60; 95% CI 1.01–20.88; $p = 0.048$) were associated with an elevated odds of tumour recurrence. In multivariate Cox regression analysis, there was no significant difference between conductive CHT and BCG in the odds of recurrence ($p = 0.054$). There were no differences in progression.

Chemo-hyperthermia vs. radical cystectomy

Radiofrequency-induced CHT has also been compared with the other gold standard, i.e. radical cystectomy (RC), by Nair et al. [44]. This prospective single-centre review matched 103 high risk NMIBC patients treated with RF-induced CHT to 51 patients undergoing a RC. Patients in the CHT group had a higher mean age and were more frequently treated with BCG before therapy. Results are only available in an abstract, showing a 5-year DSS of 85.2% and 74.6% in the CHT and RC cohorts, respectively, and an OS of 61.9% vs. 68.4%. For survival rates, a median follow-up of 40 months (4–92 months) was accomplished. More complications

(Clavian-Dindo score >2) were seen after RC (21%) compared to CHT (0%), as well as more deaths (90-day mortality of 4% vs. 0%, respectively). These results seem to promote CHT over RC, although it needs to be noted that this is not a randomised controlled and blinded trial, but a matched design in which patient groups might have differed significantly. Moreover, results regarding deaths and complications are not expected to be worse in CHT with this short follow-up anyway.

Chemo-hyperthermia long-term efficacy

Just as studies comparing CHT with BCG are needed, studies regarding long-term effects of RF-induced CHT are too. A few studies have been performed with a median follow-up of at least 60 months (5 years, Table 1) [28,29,32,41], although only two of these studies were designed to study long-term efficacy [32]. Colombo et al. [41] described an estimated 10-year DFS of 52.8% for RF-induced CHT compared to 14.6% for MMC alone ($p < 0.0001$). The estimated 5-year DFS for CHT and MMC alone was 61.7% and 21.3%, respectively. Both progression and RC rates did not differ significantly between treatment groups (CHT 2/35 and 1/35, respectively; RC 3/40 and 3/40, respectively).

Kiss et al. [29] had a median follow-up of 50 months, although efficacy analysis was hampered by the high fall out rate due to severe adverse events. They reported 6/21 patients (29%) without recurrence after this follow-up period. Also 6/21 patients underwent a cystectomy. Regarding mortality, 2/21 died due to metastatic disease, and 5/21 due to other non-cancer-related causes. Progression was not specified. At the EAU conference 2015, Lüdecke et al. [32] presented their data regarding long-term efficacy of ablative RF-induced CHT in 271 high risk NMIBC patients from 7 centres, with a median follow-up of only 2.2 years (28 days–12.9 years), but in some patients up to 12.9 years. CR was achieved in 76.1%, and 76.8% remained tumour free for a mean of 28 months (2.4 months–10.8 years). Halachmi et al. [38], with a retrospective study in 56 T1G3 NMIBC patients, found a 4-year recurrence chance of 51%.

Last but not least, an as yet unpublished Italian multi-centre, non-randomised, patient-for-patient matched study was promoted and sponsored by the health provider (Lombardy Region Health Care System) in order to compare the outcomes of patients receiving adjuvant RF-induced CHT or the current treatment according to the EAU guidelines. Between January 2005 and July 2011 consecutive patients were recruited into the treatment arm at 6 centres while for the control arm the archived records of patients treated at a single centre between January 2005 and December 2008 were used. Only intermediate or high risk patients according to the EORTC tables were accepted for comparative analysis. In all, 189 RF-induced CHT and 180 control patients were available for the analysis of outcomes. At a minimum of 24 months of follow-up, 24.9% and 38.3% of patients experienced a recurrence in the RF-induced CHT and in the control arm, respectively ($p < 0.006$). During the whole follow-up period (median of 55.3 months), a sixfold rate of radical cystectomies was registered in the control group compared to the RF-induced CHT arm (20 and 3 cystectomies, respectively;

$p = 0.0015$) (Lombardia project, unpublished data, R. Colombo, Milan, Italy).

Adverse events

An important factor in determining the value of RF-induced CHT is the type and quantity of adverse events (AEs). For RF-induced CHT, these can be divided into AEs seen during treatment and AEs which prolong after treatment. Most frequently seen AEs during treatment consist of bladder spasms and pain (21.6% and 17.5%, respectively) [11]. Lower urinary tract symptoms (LUTS) of storage (frequency, dysuria, urgency, nocturia) (25.6%) and haematuria (6.0%) are the AEs most commonly seen after treatment. Other commonly observed AEs include cystitis-like symptoms (definitions vary greatly, and overlap with LUTS) and allergic reactions/rash (0–24%, with rashes included in the higher percentage). Urethral strictures occur in only 0–10% of cases, with 3.5% being mentioned in the recent systematic review [11,25–33]. Most adverse events are reported to be self-limiting and reversible. Adverse event related drop-out rate is about 3.8% [11], although one study reported a substantially higher drop-out rate of 38%. In this study not all patients were fit for or had refused cystectomy, implying that this was a highly selected cohort with possibly a worse starting point [29].

During follow-up cystoscopy, an asymptomatic posterior wall thermal reaction (PWTR) can be seen in almost all patients [11,28]. Histological damage mainly occurs in the tumour tissue, though leaving normal epithelium relatively unharmed [35]. In the study by Rath-Wolfson et al. [45] using anaesthetised sheep, histological changes in both RF-induced CHT and control groups showed foci of oedema and haemorrhage with inflammation in the lamina propria and serosa. Foci of desquamation of the epithelium were noticed in the treated sheep. Histological analysis of the treated group showed no significant differences compared to the control group.

Influence on endocrine homeostasis has also been tested, in 11 patients receiving external RF-induced CHT, showing none of the tested hormones (i.e. the thyroid, cortisol and sex hormones) to be altered significantly [46]. Moreover, Paroni et al. [13] investigated the plasma MMC concentrations after 20 mg and 40 mg of MMC with CHT, vs. both concentrations without hyperthermia. They found a maximum plasma concentration of 67.9 ng/mL after 45–60 min of treatment, which was seen in the 40 mg MMC with CHT group. Median value of systemic absorption for this group was 19.4 ng/mL, compared to 5.56 ng/mL in the 20 mg MMC with CHT-group. These values were significantly higher than those after MMC alone with the same dose. All measured plasma concentrations were well below the threshold for myelosuppression (i.e. 400 ng/mL).

In comparison with MMC instillations, and based on the four previously mentioned papers comparing MMC alone to RF-induced CHT, local toxicity was slightly higher in CHT, although the difference was not significant [20,21,40,41]. Only one of these four studies found significantly more pelvic pain and PWTR in the CHT group [21].

When comparing RF-induced CHT with BCG instillation, more allergic reactions, pain, bladder spasm, strictures, catheter issues and PWTR are found for CHT, compared to

more fever, fatigue, arthralgia, haematuria, incontinence and frequency in BCG treatment [33].

Altogether, it seems that toxicity after CHT is higher than after MMC alone, whereas inadequate reporting hampers comparison with other treatments. Based on just one conference abstract, toxicity in CHT compared to BCG is not necessarily higher, but is mainly characterised by different, instead of more frequent, AEs.

Critical appraisal and future perspectives

With 15 years of experience, RF-induced CHT has become a commonly applied treatment modality in our centres. Nonetheless, few properly designed randomised, controlled clinical trials have been performed to date. As a consequence, high level evidence for efficacy and adverse events remains limitedly available and RF-induced CHT is still considered an experimental form of therapy. This is one of the reasons why centres hesitate to use this modality. Randomised controlled clinical trials are being executed though, with some being submitted and others being presented at conferences (which are described earlier in this review).

Another conceivable reason for reservations regarding intravesical RF-induced CHT could be the amount of adverse events seen during and after treatment. However, within the current indications, patients often have BCG or radical cystectomy as the only alternatives. Logically, adverse events and complications due to radical cystectomy are more severe than in the case of RF-induced CHT [44]. Regarding BCG instillations, patients suitable for RF-induced CHT often failed BCG or were BCG-intolerant. In deciding which treatment modality should be used, one must be conscious of the, albeit different, potentially serious or frequent adverse events of BCG.

Costs of intravesical RF-induced CHT are regarded as being substantial, although previously mentioned costs in other papers are outdated [47]. One study on conductive heating with the UniThermia device mentions device costs of about €42 000 compared to €90 000 for the Synergo® console. Disposable UniThermia catheters cost about €200 each, compared to €600 for the three-way catheters used in the treatment with Synergo® [6]. However, this estimation for Synergo® costs is too high. Total costs per treatment vary from about €650 to €850 in our centres, depending on the drug and dose used (MMC or epirubicin), and include dispersed acquisition costs.

No studies on cost-effectiveness in RF-induced CHT have yet been published. However, the Lombardia project mentioned above attempted for the first time to assess the cost–benefit ratio of RF-induced CHT. The cost-related model was designed in order to simulate treatment outcome and cost in 100 patient pairs over a period of 10 years. One of the patients in each pair was treated by RF-induced CHT and the second according to current EAU guideline recommendations. Based on this model, RF-induced CHT is expected to reduce the overall cost for treatment of intermediate and high risk NMIBC at long-term (5-10 years) follow-up compared to current treatments. The cost/effectiveness of RF-induced CHT treatment is currently under evaluation from the health provider in view of its possible total reimbursement in the routine clinical practice (Lombardia project, unpublished data, R. Colombo, Milan, Italy).

Besides costs, some important obscurities in current knowledge remain. For starters, it would be informative to have data on the effect on quality of life in CHT-treated patients compared to BCG or MMC treated, or even radical cystectomised, patients. As written in the Evidence acquisition and synthesis section above, most of the research has been performed with MMC. Epirubicin has been described in only a few studies, and no good comparison with MMC was possible [28]. Moreover, no evidence yet exists regarding treatment duration. Although consensus exists for starting treatment with an induction course and subsequently giving a maintenance scheme of a combined total of 2 years, many patients are treated for longer periods [11]. Studies addressing all these issues would be most valuable.

Studies on different forms of achieving hyperthermia are being performed, and authors have been increasingly publishing their results in the past 2 years. Almost all make use of the conductive heating technique, reaching an efficacy of 18–41% for recurrence rates, 10.3–18% for progression rates, and have about 50% of grade 2 adverse events, with 9.2–14.3% showing grade 3 AEs (Common Terminology Criteria for Adverse Events (CTCAE) version 6) [6,7,43,48]. Nonetheless, comparative studies of RF-induced CHT with these new forms of (conductive) heating are important for determination of the superior hyperthermic treatment in the future.

The place of RF-induced CHT in future NMIBC management will partly be shaped by conclusions on the above-mentioned issues. However, more ways of improving pharmacokinetics, drug exposure and pharmacodynamics will likely have an important share as well.

Conclusion

Radiofrequency-induced chemo-hyperthermia remains a promising treatment modality which appears to be a potential alternative to BCG immunotherapy. It can also be used in patients unfit to undergo radical cystectomy, or to prolong bladder preservation time. Adverse events and safety profile seem to be acceptable in the context of the indication for RF-induced CHT. Nonetheless, a more solid scientific basis is needed to define the position of RF-induced CHT in relation to other hyperthermic treatment modalities and in relation to the newly emerged non-hyperthermia treatments.

Declaration of interest

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