Intravesical device-assisted therapies for non-muscle invasive bladder cancer

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Abstract | Non-muscle-invasive bladder cancer (NMIBC), the most prevalent type of bladder cancer accounts for approximately 75% of bladder cancer diagnoses. This disease has a 50% risk of recurrence and 20% risk of progression within 5 years , despite the use of intravesical adjuvant treatments (such as BCG or mitomycin C (MMC)) that are recommended by clinical guidelines. Intravesical device-assisted therapies, such as radiofrequency-induced thermochemotherapeutic effect (RITE), conductive hyperthermic chemotherapy, and electromotive drug administration (EMDA), have shown promising efficacy. These device-assisted treatments are an attractive alternative to BCG , as issues with supply has been a problem in some countries. RITE might be an effective treatment option in patients who have experienced BCG failure and are not candidates for radical cystectomy. Data from trials using EMDA suggest it is effective in high risk disease but require further validation and results of randomised trials are eagerly awaited for conductive hyperthermic chemotherapy. Considerable heterogeneity in patient cohorts, treatment sessions, use of maintenance regimens, and single-arm study design makes it difficult to draw solid conclusions, although randomized controlled trials have been reported for RITE and EMDA.

[H1] Introduction

Bladder cancer is the ninth most common cancer worldwide and is the thirteenth most common cause of cancer-associated mortality.[1] Non-muscle-invasive bladder cancer (NMIBC) is the most frequently diagnosed type of bladder cancer; approximately 75% of bladder cancers are NMIBC. The main stay of NMIBC management is by transurethral resection of bladder tumour (TURBT). NMIBC is stratified into low-risk, intermediate-risk, and high-risk categories using clinical and pathological factors. In the UK, intermediate-risk NMIBC is treated with adjuvant chemotherapy while high-risk NMIBC is treated with adjuvant immunotherapy.[2] Neoadjuvant chemoablation has been described but is not standard of care within NMIBC guidelines due to limited level one evidence.[3,4]

A single post-TURBT instillation of chemotherapy as adjuvant therapy within 24 hours, but ideally within 6 hours, reduces the relative risk of recurrence by 35% (HR: 0.65, 95% CI 0.58-0.74) in an individual patient data meta-analysis of low, intermediate and high-risk NMIBC.[5] A course of intravesical chemotherapy is recommended for intermediate-risk NMIBC and reduces the relative risk of recurrence by 44% (HR: 0.56, 95% CI: 0.48-0.65).[6] Mitomycin C (MMC) is the most commonly used intravesical chemotherapy.[7]. MMC is a cytotoxic antibiotic that induces cell death by alkylation and cross linking of DNA.[8] Its molecular weight of 334 kDa minimizes the risk of systemic absorption and toxic effects such as myelosuppression and pulmonary toxicity.[8] Adverse events following intravesical delivery of MMC are predominantly local irritative voiding symptoms, which are reported in up to 39% of patients.[9] Evidence exists for alternative agents including gemcitabine, epirubicin, and Adriamycin, which have not been as commonly adopted as MMC due to less compelling evidence although recent studies have suggested that gemcitabine is efficacious and may be an alternative to MMC.[10-12]

Intravesical BCG is recommended for high-risk NMIBC as a 6 once weekly induction course followed by a maintenance regime of 3 once weekly instillations at 3 and 6 months followed by every subsequent 6 months for up to 3 years.[13] Maintenance BCG has been shown to increase absolute survival advantage by 5% at 5 years compared with induction BCG alone, supporting the use of maintenance treatment.[13] However, up to 65% of patients treated with BCG report local toxicities and 12% of patients do not complete maintenance therapy.[14] Since 2012, availability of BCG has become an issue in some countries and the production of the Connaught strain is expected to cease in 2019 further limiting availability.[15] Thus, the development of alternative intravesical treatments for bladder cancer is imperative.

Despite use of adjuvant therapies, up to 52% of patients with high-risk NMIBC will have disease recurrence and 20% will progress to muscle-invasive bladder cancer (MIBC) within 5 years.[16] Radical cystectomy is the standard-of-care treatment after BCG failure, although rechallenging with further BCG remains an option according to National Comprehensive Cancer Network guidelines..[2,17]

Developments for the treatment of NMIBC have focused on optimizing the delivery of established therapies or potentiating the effects of chemotherapy using intravesical device-assisted technology to deliver hyperthermia to the bladder wall or circulating chemotherapy and ionisation of chemotherapy to improve drug tissue penetration. The three most used

82 devices are radiofrequency-induced thermochemotherapeutic effect (RITE), conductive
83 hyperthermic chemotherapy, and electromotive drug administration (EMDA) chemotherapy.
84 Depot delivery devices, where slow releasing formulation of chemotherapy over an extended
85 period of time, have been reported and are in early phase development.[18,19] In this Review,
86 we describe the evidence for intravesical device-assisted technologies and summarize
87 efficacy, safety, and tolerability outcomes. We also highlight other potential devices that are
88 promising for the treatment of NMIBC.

89

90 **[H1] Hyperthermia as a treatment**

91 The use of hyperthermia to treat bladder cancer is based on the concept that heat can
92 potentiate the effect of chemotherapy. [20]   In vitro studies demonstrated that hyperthermia
93 results in the denaturation of cytoplasmic structures and enzymatic proteins, inducing cell
94 death by apoptosis and necrosis.[21-23] Temperature elevation enhances cell membrane
95 permeability resulting in increased drug absorption.[24,25] Hyperthermia also causes the release
96 of heat shock proteins (HSP), in particular HSP70, during cellular necrosis, which stimulates
97 an adaptive T-cell response to induce the innate and adaptive immune system, despite
98 promoting thermotolerance[26,27]. Furthermore, at 42°C exponential cell death seems to occur;
99 above this temperature the benefit of hyperthermia might be minimal, but toxic effects might
100 become apparent.[21] Cancer cells are more susceptible to hyperthermia than nonmalignant
101 cells and, in clinical practice, hyperthermia is usually delivered at 42°C, although 45°C has
102 been described.[28] Data from cell lines demonstrates synergism, whereby the effect of
103 hyperthermia plus chemotherapy is greater than the combined additive effect.[29,30]
104 Hyperthermia might also chemosensitize tumours to alkylating agents such as MMC via HSP
105 mediated pathways.[26]

106 In the clinical setting, hyperthermia has been used in combination with chemotherapy for the
107 treatment of NMIBC.[31,32] [33]   Hyperthermia can be either delivered by intravesical
108 radiofrequency-induced hyperthermia or conductive heat via energy transfer from heated
109 circulating fluid.[31,32] [33] Deep regional hyperthermia by radiofrequency is feasible and has been
110 reported but is not in widespread use in clinical practice, although it might be effective in MIBC
111 as well as NMIBC.[34]

112

113 **[H1] RITE**

114 Radiofrequency-induced hyperthermia is an established therapy for a number of cancers
115 including hepatocellular carcinoma,[35] Barrett's oesophagus,[36] breast cancer[37], and lung
116 cancer.[38] Radiofrequency is delivered to tissues with high perfusion and poor electrical and
117 thermal conductivity at a frequency of 350-500 kHz for the treatment of localized solid organ
118 tumours.[39,40] In contrast, RITE is delivered to the entire bladder at a frequency of 915 MHz
119 using microwave which does not require conductive delivery of energy and penetrate low-
120 conductive tissues.[40] This is ideal for the delivery of heart energy directly to the tissue to
121 enable an efficient effect on the full bladder wall thickness . Pharmacokinetic analysis showed
122 that RITE with 40 mg MMC over 60 minutes resulted in >10-fold higher MMC concentration
123 in bladder cancer tissue than passive intravesical MMC (median 665 ng/g versus

124 64 ng/g, $P = 0.018$).[41] Plasma concentrations of MMC in patients treated using RITE plus MMC

125 increased rapidly within 15 minutes and continued to increase and peak between 45 to 60

126 minutes.[42] In comparison, there was a dose response increase in patients treated with passive

127 mitomycin and MMC plasma concentration peaks at 15 minutes and remained stable over 60

128 minutes.[42] In addition, a report by Ware et al.[43] suggest that radiofrequency promotes the

129 formation of tunnelling nanotubes within cancer cells, which might increase drug diffusion and

130 increase efficiency.[43]

131 RITE therapy for bladder cancer is the most established device-assisted therapy and the

132 Synergo system was first reported in 1995.[44] The Synergo system comprises a microwave

133 radiofrequency source generating energy at 915 MHz from an antenna located at the tip of a

134 Foley catheter (Fig. 1). The specialized triple lumen 18/20 Fr Foley catheter consists of the

135 inflow and outflow lumen, the energy source antenna, and intravesical thermocouples at the

136 catheter tip and proximal urethra that are used to monitor bladder wall temperature.[44] The

137 radiofrequency antenna delivers hyperthermia at 42 ± 2°C to the bladder wall by direct

138 radiation, while the inflow and outflow channel recirculate chemotherapy at room temperature

139 (22ºC) within a closed system.

140 Treatment comprises two 30-minute sessions; between each session the bladder is emptied

141 and a new solution of MMC is instilled, reducing the dilutional effect of diuresis.[45] An adjuvant

142 treatment protocol consists of two 30-minute sessions of 20 mg MMC instillations dissolved in

143 40 ml of saline or water. An ablative protocol of two 30-minute sessions of 40 mg MMC in 40

144 ml of saline or water is recommended in the manufacturer's protocol.[46] The requirement for

145 intravesical administration of MMC midway of treatment session with RITE requires additional

146 nursing input. An induction protocol of 6-8 once weekly treatments is administered followed

147 by a maintenance protocol of one treatment every 6 weeks for the first year and one treatment

148 every 8 weeks for the second year.[47] An alternative protocol of six once weekly induction

149 protocol with a maintenance protocol of three once weekly instillations at 3, 6, and 12 months

150 has been reported.[31] No comparisons between the two protocols because they have been

151 used in different patient cohorts.

152

153 [H2] Treatment efficacy

154 To date, 21 reports from 20 studies on the efficacy of RITE for NMIBC have been published

155 (Table 1); five studies report outcomes for RITE delivered in the pre-TURBT ablative

156 setting,[44,48-51] nine studies in the adjuvant setting[47,52-60] and six studies had a mixture of

157 patients treated with adjuvant therapy or pre-TURBT ablative treatment.[61-66] Only four

158 randomized controlled trials (RCTs) investigating RITE have been conducted; three as

159 adjuvant treatment[47,53,56,60] and one in the ablative setting.[50]

160 Reported recurrence free survival (RFS) differs between studies , reflecting the heterogenous

161 patient cohorts, follow-up duration, and different treatment regimens and presence of CIS In

162 studies including patients with papillary-only disease, RFS ranges from 53%–91% with 9.6–

163 24-month follow-up duration.[47,53,58-60,65,66] However, in patients who had isolated or concurrent

164 CIS (13–68%), RFS can range from 29%–88.6% at 14–38-months follow-up

165 duration.[47,54,55,57,61-64] A substantial number of patients treated with RITE had developed

166 recurrence after previous intravesical therapy and disease progression occurs in 0–38% of
167 patients. [47,49,52,53,55-65]

168

169 In the pre-TURBT ablative setting, data from nine studies reporting outcomes from 211
170 patients suggest a complete response rate of 65.4%.[44,48-51,62,63,65,66] Subsequent studies have
171 used an increased dose of MMC for ablative therapy (two 30-minute cycles of 40 mg MMC vs
172 20 mg MMC), which might be beneficial for patients with widespread concurrent or isolated
173 carcinoma *in situ* (CIS) .[61,62 63-65 66] In one RCT of 52 patients, RITE resulted in significantly
174 higher complete response rates than MMC alone (66% versus 22%, *P*< 0.01).[50]

175 Three RCTs compared RITE with either passive MMC or BCG ; two trials in the setting of first-
176 line therapy and one in patients who had experienced BCG failure. Colombo et al.[60] conducted
177 a RCT involving 83 patients comparing RITE plus MMC with passive MMC in intermediate-
178 risk or high-risk disease. Patients in both arms (42 RITE vs 41 passive MMC) had complete
179 TURBT followed by an induction schedule of 8 once weekly intravesical instillations and a
180 maintenance schedule of four once-monthly instillations. Patients in the RITE arm received
181 two 30-minute sessions of MMC (20 mg in 40 ml saline) and patients in the passive MMC arm
182 received 40 mg of MMC in 40 ml for 1 hour. At 24 months RFS was significantly improved in
183 patients who received RITE (RITE: 82.9% versus passive MMC: 42.5%, *P* = 0.002) with no
184 significant difference in disease progression between treatment arms.[60] Subsequently, a
185 longer-term follow-up of a median of 91 months suggested that the RFS superiority of RITE
186 over passive MMC is sustained (RITE: 60% versus passive MMC: 20%, *P* <0.001).[56]

187 Arends et al.[31] later reported a RCT of 190 patients with intermediate-risk or high-risk NMIBC
188 (92 RITE plus MMC vs 98 BCG). Patients in the RITE arm received a 6 once weekly induction
189 course of two 30-minute sessions of 20 mg of MMC in 50 ml of water followed by a three once
190 weekly   maintenance course at 3, 6, and 12 months, whereas patients in the BCG arm
191 received full dose OncoTICE for 120 minutes per session for six once weekly induction
192 instillations and three once weekly maintenance instillations at months 3, 6 and 12 months.
193 The trial closed early owing to slow recruitment. Intention-to-treat results for the whole patient
194 cohort were not reported. At the 24-month follow-up point, a trend towards significance in RFS
195 was observed in the RITE arm (*n* = 71) compared with the control arm (*n* = 76) for patients
196 with papillary-only disease (RITE: 78.1% versus 64.8%, *P* = 0.08). The per-protocol analysis
197 suggested that the RFS was significantly higher in the RITE arm than the BCG arm for patients
198 with papillary disease (RITE: 81.8% versus BCG: 64.8%, *P* = 0.02). At 3 months, the complete
199 response rate for patients with CIS was not significantly different between the two arms. This
200 study was the first to compare RITE plus MMC with BCG therapy and, although the primary
201 outcome was not met in the intention-to-treat analysis, the results suggest that RITE is an
202 effective treatment for papillary NMIBC. These results are promising, but the outcomes for
203 patients with CIS-only disease or concurrent CIS were not reported.

204 Tan et al. [47] reported the results of the HYMN study, a multicentre phase III trial of 104 patients
205 with intermediate-risk or high-risk NMIBC who developed recurrence after induction with or
206 without maintenance BCG. Patients were randomized to RITE plus MMC or institutional
207 standard practice. Patients in the RITE arm received 6 once weekly instillations of two 30-

minute sessions of 20 mg MMC in 50 ml of sterile water as part of induction treatment and three once weekly instillations at months 3, 6, 12, 18 and 24 months as part of maintenance treatment. Institutional standard practice comprised either rechallenge with BCG (59%), passive MMC (18%), or EMDA with MMC (23%). At the 24-month follow-up point , no overall difference in intention-to-treat disease-free survival (DFS) was observed between the two treatment arms (HR 1.33; 95% CI: 0.84-2.10, P = 0.23) or in 3-month complete response rate in patients with CIS (RITE plus MMC arm: 30% versus control: 47%, P = 0.15). There was a non-significant higher intention-to-treat DFS in papillary-only disease (HR 0.50; 95% CI: 0.22-1.17, P = 0.11) treated with RITE compared to control However, patients with CIS with/without papillary disease who received RITE had significantly higher disease recurrence than those who received treatment according to institutional standard practice (HR 2.06; 95% CI: 1.17-3.62, P = 0.01), which resulted in the premature closure of the trial. A subsequent study reported an ablative protocol for patients with CIS comprising two 30-minute sessions of 40 mg MMC.[64] DFS in patients who received this protocol was 43% at a median of 22 months.[64] The requirement for an increased MMC dose in ablative setting might explain results observed in the HYMN study.

The rate of disease progression in the HYMN trial was low (6%) at a median follow-up duration of 35 months, which should be compared with the 5% risk of 90-day mortality of radical cystectomy in these patients who have comorbidities.[68] Despite limited RCT data, emerging evidence suggests that RITE plus MMC is a suitable alternative intravesical treatment option to passive MMC. Moreover, this modality could be considered for patients with high-risk papillary NMIBC as an alternative to BCG in the first-line setting. Results following RITE plus MMC treatment in patients with papillary-only disease who experienced BCG failure suggest this modality may be promising, but evidence is currently insufficient to support its use in patients with CIS. In fact, the FDA defined that a RFS of ≥25-30% at 18-24 months as clinically meaningful in BCG refectory patients.[67] Both treatment arms in HYMN achieved a RFS >35% which was above the threshold for clinically meaningful effect although BCG failure patients recruited to HYMN had a better prognosis as BCG intolerant and relapsing patients were also included.

[H2] Adverse events

The reported adverse event rates following RITE suggest that it is well tolerated, with 92% of patients completing induction treatment.[69] The most commonly reported adverse events during treatment are cystitis and/or storage lower urinary tract symptoms (LUTS) (32%), suprapubic pain (30%), and bladder spasm (20%).[47,52,6144,50,51,55,57-60,62,65,66] Storage LUTS such as incontinence (12.6%) and nocturia (23.9%) and haematuria (17.2%) are the most common adverse events after treatment and 3.3% of patients had urethral stricture (Table 2). However, most adverse events are self-limiting and short lived.[31,47] RITE recirculates room temperature MMC, hence, no thermal reaction to the urethra occurs which would theoretically minimise the risk of urethral strictures.[70] Iatrogenic urethral injuries owing to catheter insertion might have contributed to the development of the urethral strictures reported. Thermal reaction on the posterior bladder wall, which is commonly observed following RITE treatment, can look suspicious for CIS owing to urothelium erythema and prompt unnecessary bladder biopsies

although they are benign and does not cause long term damage.[44] Indeed, animal studies suggest that the thermal reaction represent focal oedema, haemorrhage, and oedema of the lamina propria and serosa, which resolves completely.[71]

Adverse events reported in RCTs enable comparison of adverse event rates following RITE plus MMC or other standard-of-care treatment (Supplementary Table 1). RITE resulted in significantly more pain (P <0.001) and bladder wall erythema (P <0.001) than passive MMC, but no difference in dysuria, haematuria, urethral stenosis, or allergic reaction was observed.[60] Patients who received RITE plus MMC had a significantly increased risk of bladder pain during treatment (OR: 26.3; 95% CI, 14.3–48.5) or between treatments (OR: 1.6; 95% CI, 1.2–2.3), bladder spasms (OR: 15.5; 95% CI, 9.7–25.0), difficulty with catheterisation (OR: 16.7; 95% CI, 5.1–54.0), urethral strictures (OR: 2.3; 95% CI, 1.3–4.1), bladder wall erythema (OR: 5.8; 95% CI, 4.0–8.3), and allergic reaction (OR: 2.7; 95% CI, 1.6–4.6) compared with BCG. However, significantly less 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) were reported than for patients who received BCG.[53]

In summary, RITE treatment for bladder cancer has been shown to be efficacious in intermediate or high risk papillary only BCG naïve NMIBC in a randomised setting. In the BCG failure setting, subgroup analysis of papillary only patients showed better efficacy in RITE treated patients compared to control, but this was not significant suggesting that this may be a treatment option in this patient cohort with limited options. There is limited data specifically in the BCG refractory setting and in patients with isolated or concurrent CIS disease and future planned trials will hopefully address this question. A single-arm study, RITE-Europe which will recruit patients with BCG-refractory CIS with or without papillary NMIBC is being planned . Treatment will consist of RITE with two 30-minute sessions of 40 mg MMC.

[H1] Conductive hyperthermic chemotherapy

Conductive hyperthermic chemotherapy is an alternative technology for delivering localized hyperthermia. The chemotherapy solution is externally heated and recirculated at a constant temperature via a catheter irrigation channel to deliver hyperthermia to the bladder wall by conduction.[72] Previous to its application in the treatment of NMIBC, conductive hyperthermia was adopted as hyperthermic intraperitoneal chemotherapy (HIPEC), which is an approved treatment used in combination with cytoreductive surgery for peritoneal metastasis in ovarian, gastric, and colorectal cancer.[73-75]

Two conductive hyperthermic chemotherapy systems for bladder cancer have been reported, both of which use MMC: the Combat Bladder Recirculating System (BRS) and the Unithermia system. Minimal nursing 'hands-on' time is required once the system is set-up as a mid-treatment repeat instillation of MMC is not required compared to the RITE system allowing. This allows for a lower nurse to patient ratio when treatment is being administered. The Combat BRS system uses a 16 Fr three-way Foley catheter, which recirculates MMC in a close system with a bubble trap (Figure 2). MMC is heated to 43°C using an aluminium heat

293   exchanger that enables efficient heat transfer and accurate temperature control within ± 0.5

294   °C. Each treatment uses 40 or 80 mg MMC in 50 ml of water for adjuvant and ablative

295   treatment respectively recirculating for a continuous 60 minutes. [32,72,76] The Unithermia system

296   uses a conical heat exchanger with a high recirculation rate to deliver hyperthermic MMC to

297   the bladder via an 18 Fr Foley catheter. MMC is heated to 46.5 °C to deliver it at 44.5 °C to

298   the bladder wall. The system is primed with 40 mg of MMC in 50 ml of water, which is

299   recirculated for a continuous 50 minutes.[33,76] Results of a pharmacokinetics study suggested

300   that peak plasma MMC concentration is achieved around 45 minutes after MMC instillation.

301   [77]

302   Aqueous doxorubicin has been shown to efficacious for the treatment of NMIBC.[78] The

303   synergism between hyperthermia and temperature activated liposomes have been shown to

304   enable a much higher dose of drug to be delivered at the target organ of treatment.[79]

305   ThermoDox is a heat-activated liposomal encapsulation of doxorubicin that is a promising

306   alternative to MMC. At 40-45°C; the liposomes release doxorubicin directly at the heated

307   source, which enables a targeted approach.[80] An in vivo study in pigs showed that intravenous

308   ThermoDox with localized conductive hyperthermia delivered to the bladder resulted in the 10-

309   fold higher concentration of doxorubicin within the bladder than when ThermoDox was not

310   heated or intravenous doxorubicin.[80] Although heat-activated, ThermoDox is infused

311   intravenously and patients with a history of cardiac disease may not be suitable candidates

312   for this therapy owing to the cardiotoxic nature of doxorubicin although reports suggest that

313   this is less apparent in the liposomal based formulation.[81,82]

314   Five studies have reported results for conductive hyperthermia,[32 72 76 33 83] and, although RCTs

315   are in progress, level 1 evidence reporting outcomes for conductive hyperthermia for the

316   treatment for NMIBC is lacking.

317

318   [H2] Efficacy

319   All reports to date are single-arm observational studies; two using the HIVEC system[32,72] and

320   three using the Unithermia system[33,76,83], all of which use MMC (Table 3). All studies conducted

321   to date included patients with predominantly intermediate-risk NMIBC and were proof-of-

322   concept studies with a limited sample size of between 15 and 43 patients. Studies using the

323   HIVEC system report a RFS of 87.5% at the 24-month follow-up point in an adjuvant setting

324   (n=16) [32] and a complete response rate of 60-63% after 8 once weekly ablative intravesical

325   treatments (n=39).[32,72] The three studies using the Unithermia system included 117 patients

326   and report RFS of 65-70% at follow-up points between 24-41 months.[33,76,83] These studies

327   included one retrospective propensity score matched comparison[83], which reported that BCG

328   treated patients had a better RFS compared to conductive hyperthermia (89.5% versus

329   70.1%, P = 0.054).[83] No difference in disease progression was reported.

330

331   [H2] Adverse events

332   Similar to RITE, conductive hyperthermia therapy is well tolerated and most adverse events

333   are short lived (Table 4).[86] Reliable adverse event data are available for the HIVEC system.

An interim analysis of adverse events in 307 patients recruited into HIVEC-I and HIVEC-II reported that 89% of patients completed a minimum of induction therapy compared with 95% of patients treated with passive MMC.[86] In the patients treated with HIVEC, the most common adverse events were urinary frequency (15%), suprapubic pain (13.1%), haematuria (11.8%), and urinary urgency (11.8%).[86] HIVEC was associated with significantly increased incidence of urinary frequency (15.0% versus 5.8%, p=0.008), haematuria (11.8% versus 3.9%, p=0.010), and bladder spasm (6.5% versus 0.6%, p=0.006). No significant difference in grade III adverse events between HIVEC (2.3%) and passive MMC (1.5%) were observed, and these were predominantly caused by allergic reactions. No urethral strictures occurred in either treatment arm.[86]

The safety and efficacy data for the Unithermia system is not well reported and at present the grade III adverse event rate is 12% (Table 5). Non-infective cystitis (37.2%) is the predominant reported adverse event followed by suprapubic pain (23.3%) and bladder spasm/ urinary urgency (22.1%). Notably, one incidence of bladder perforation occurred following Unithermia treatment, resulting in a grade IV adverse event, which was reported by Ekin and colleagues.[33] Reasons for this remained uncertain but may be related to the higher circulation rate of fluid and temperature used.

Prospective randomised data are eagerly awaited. HIVEC-I (EudraCT: 2013-002628-18)[84] and HIVEC-II (ISRCTN: 23639415)[85] are two multicentre, open-label, phase II RCTs recruiting patients from 12 Spanish and 13 UK centres respectively.. HIVEC-I will randomize 303 patients with intermediate-risk disease to passive MMC, conductive hyperthermic MMC for 30 mins, or conductive hyperthermic MMC for 60 minutes.[84] HIVEC-II will randomize 259 patients with intermediate-risk disease to passive MMC or conductive hyperthermic MMC for 60 mins.[85] Both studies have completed patient recruitment at the end of 2017 and results are eagerly awaited.

[H1] EMDA MMC

EMDA enhances the delivery of chemotherapy by electro-osmosis, iontophoresis, and electroporation whereby an electrical charge is generated between a catheter electrode and a cutaneous electrode to aid the transport of drug molecules into tissues.[87,88] In vitro studies have shown that EMDA MMC delivers a sixfold greater concentration of MMC to the bladder wall than passive diffusion, reaching a peak concentration of MMC within 15 minutes of initiating treatment .[87,88] MMC was detected in all layers of the bladder wall in both treatments modalities; however, MMC concentration in the urothelium was 30 times greater using EMDA MMC than passive MMC, and threefold greater in the lamina propria and muscularis.[87]

Intravesical EMDA MMC is administered using a battery-powered generator to deliver a controlled electric current of up to 30 mA.[48] The electrical current passes between the intravesical active electrode at the tip of a catheter to a dispersive ground electrode positioned on the lower abdomen (Figure 3). The specialized 16 Fr catheter is in inserted and the bladder is washed with water, after which 40 mg MMC in 100 ml of water is instilled with the operating current maintained at 20 mA pulsed electrical current. Treatment time is 30 minutes per session, which is shorter than RITE and conductive hyperthermia and cadaveric studies

375   suggest that the peak concentration of MMC in the bladder wall is achieved after 15 minutes

376   of initiating treatment.[89]

377

378   [H2] Efficacy

379   To date, seven studies have reported on the efficacy of EMDA MMC for bladder cancer, three

380   of which investigated neoadjuvant EMDA MMC as monotherapy or in combination with

381   BCG[48,90,91] and a four studies in the adjuvant setting[92-95] (Table 6). Four studies reported

382   outcomes for monotherapy EMDA MMC,[48,90,91,94,95] including one RCT in the neoadjuvant

383   setting[90] and one in the adjuvant setting.[94]

384   Alternating BCG with EMDA MMC is a more established regimen than EMDA MMC as

385   monotherapy, and promising results from a RCT and another single-arm study have been

386   reported.[92,93] Di Stasi et al. [93] randomized patients with high-risk NMIBC to either sequential

387   BCG plus EMDA MMC or BCG alone. DFS was higher in the BCG plus EMDA MMC group

388   than the BCG alone group at 88 months (58.1% versus 42.1%, $P = 0.0012$).[93] Progression-

389   free survival (90.7% versus 78.1%, $P = 0.004$) and overall survival (78.5% versus 67.6%, $P =$

390   0.045) were also significantly improved in BCG plus EMDA MMC cohort. However, the BCG

391   plus EMDA MMC arm had an induction protocol of 9 once weekly treatment compared with

392   the 6 once weekly treatments in the BCG alone arm and the increased number of induction

393   treatments might have improved efficacy. A subsequent single-arm study using the same BCG

394   plus EMDA MMC treatment regimen reported a 71% RFS and 95% PFS at 24 months.[92] The

395   proposed hypothesis for combination therapy is that instilling BCG first results in BCG-induced

396   inflammation, which might increase urothelium permeability to MMC. The results for BCG plus

397   EMDA MMC are impressive, but further validation is required before it is accepted as standard

398   of care.

399   In the monotherapy setting, a three-arm study randomized patients to either EMDA MMC,

400   BCG, or passive MMC.[94] Patients treated with EMDA MMC had a significantly longer time to

401   recurrence than those who received passive MMC or BCG (EMDA MMC: 35 months versus

402   MMC: 20 months versus BCG: 26 months, $P = 0.013$). However, no difference in time to

403   disease progression was observed. Complete response rate at 6 months was higher in the

404   EMDA MMC (58%) and BCG (64%) groups than in passive MMC group (31%) ($P = 0.012$).

405   Di Stasi et al.[90] reported outcomes of a trial in which patients were randomized to either

406   TURBT alone, preoperative EMDA MMC followed by TURBT, or TURBT with a single

407   postoperative instillation of passive MMC.[90] At a median follow-up point of 86 months, patients

408   in the preoperative EMDA MMC group had significantly higher RFS than those in the TURBT

409   alone and TURBT with postoperative passive MMC groups (62% versus 36% versus 41%, P

410   <0.0001).[90] Colombo et al.[48] compared ablative treatment with RITE, passive MMC, and

411   EMDA MMC in a nonrandomized study, which showed that complete response rate was 66%,

412   27.7%, and 40% respectively.[48]

413

414   [H2] Adverse events

Similar to hyperthermia delivery systems, 90% of patients complete adjuvant induction treatment of EMDA MMC (Table 7). In a RCT comparing EMDA MMC, passive MMC, and BCG, significantly more local and systemic adverse events occurred in patients who received BCG than those in the two MMC arms.[94] EMDA MMC had lower drug-related cystitis incidence (36% versus 67%, p=0.001), haematuria (22% versus 72%, p=0.001), frequency (19% versus 58%, p=0.001), and fatigue (2.5% versus 44.4%, p=0.001) than BCG.[94] Pooled adverse events from 73 patients suggest that drug related cystitis and/or storage LUTS (23%), bladder spasm (19%), and haematuria (12%) were the most common adverse events and no urethral strictures were reported.[91,94,95] The most common reason for stopping EMDA MMC treatment was allergic reaction.[93] Compared with RITE plus MMC , EMDA MMC has an increased rate of suprapubic pain and dysuria, and patients who received RITE patients experienced less urinary frequency .[48] Anecdotally, subcutaneous burns have been reported to develop where the ground electrode pad is placed.

No difference in reported adverse events were seen when sequential therapy of BCG-EMDA MMC was compared with BCG.[93] Between 3% and 28% of patients treated with combination BCG and EMDA MMC could not tolerate the complete course of nine induction instillations.[92,93] LUTS, haematuria, and inability to tolerate catheter were the most frequent reasons for early termination of treatment.[92]

Despite level one evidence reporting the superiority of EMDA, particularly when used in combination with BCG, compared to BCG and MMC, the use of EMDA has been limited in the treatment of NMIBC. A Cochrane review highlights that the quality of evidence in these studies were low and data on time to recurrence and progression as well as adverse events remains inconclusive suggesting that further studies are warranted.[96]

[H1] Comparison of cost between treatments

Comparison of the estimated cost of treatment (disposables and drugs) between the different intravesical device assisted therapies based on end-user price suggest that that RITE treatment is the most costly followed by EMDA and conductive hyperthermia systems (Table 8). Estimated cost of treatment was based on published treatment protocols. Cost of precuring the different devices itself as well as the service contract if applicable are normally the subject of separate negotiation and has not been reported herein. Physician and nurse cost to deliver treatment and other associated cost have been excluded.

The disposables for the RITE and EMDA systems are more costly than those for conductive hyperthermic chemotherapy owing to the requirement of specialized catheters such as a radiofrequency antenna with thermocouples in the RITE catheter or active electrode at the catheter tip in the EMDA catheter . The different maintenance protocols used between different treatment devices makes comparison of cost difficult.

The only cost-effectiveness analysis that has been performed was reported in the RCT comparing BCG plus EMDA MMC with BCG alone.[93] Based on a Markov model, sequential therapy was more costly than BCG therapy alone , but it was more efficacious with a 5-year increment cost-effectiveness ratio (ICER) of   Can$27,815 per life-year gained (US$21,173, assuming Can$1=US$0.76).[97] This figure is below the maximum acceptable ICER of £20,000-£30,000 (US$26,472-US$39,709, assuming £1=US$1.32)   per quality-adjusted life-year

457 (QALY) used by the UK National Institute for Health and Care Excellence (NICE) and the
458 US$50,000 QALY used as a benchmark of acceptability when evaluating new technology.[98,99]

459

460 **[H1] Novel agents**

461 Several novel technologies have been reported and are at an early phase development. Two
462 devices augment the cytotoxic effects of chemotherapy by prolonging exposure time. GemRIS
463 is an intravesical gemcitabine depot delivery system (225 mg), which is constructed from
464 silicone tubing and nitinol wire. [18] GemRIS is delivered into the bladder using an 18 Fr ureteric
465 catheter-like inserter. The 5 cm-long device, which folds into a pretzel shape, remains in the
466 bladder and releases gemcitabine by passive diffusion over a 7-day period (Figure 4).[18] The
467 device can be removed 7 days later by grasping forceps and flexible cystoscopy.[18] In a phase
468 1b study (NCT02722538) ,[100] the GemRIS pretzel was well tolerated by all 10 patients with
469 MIBC. Neoadjuvant GemRIS treatment for 14 days before radical cystectomy for all 10
470 patients resulted in a reduction of tumour size in 80% of patients with 40% having pT0 disease
471 after treatment.[18]

472 VesiGel is a reverse-thermal gelation hydrogel compound combined with high-dose MMC that
473 is liquid at room temperature and fully solidifies to a gel state at body temperature within 15
474 minutes after instillation. VesiGel can be delivered using a standard Foley catheter and
475 gradually dissolves over several hours while releasing MMC. This slow release preparation
476 might be more effective than a single 1 hour instillation of aqueous MMC. In a study of 64
477 patients with low-grade NMIBC treated with either VesiGel 0.06% (40 mg at 64 ml), VesiGel
478 0.12% (80 mg at 64 ml), or MMC 0.1% (40 mg in 40 ml) as chemoablation therapy, VesiGel
479 80 mg had a higher complete response rate (87.5%) than aqueous MMC 40mg (63.6%) and
480 VesiGel 40 mg (35.3%).[19] The results of this proof-of-concept study are promising and future
481 studies will be necessary to determine the effect of drug delivery and RFS in the adjuvant
482 setting.[19] Although results for VesiGel 80 mg are promising, interestingly, aqueous MMC 40
483 mg had a better complete response rate than VesiGel 40 mg, suggesting that a slow-release
484 formulation might take longer to reach peak chemotherapy concentration and this delay might
485 negate the advantage of prolonged drug exposure, requiring an increased drug concentration.
486 Early safety and tolerability data suggest that VesiGel is well tolerated with similar reports of
487 allergic reaction to aqueous MMC, although the incidence of dysuria was higher (40% versus
488 13%).[101]

489

490 **[H1] Conclusions**

491 Intravesical hyperthermia-inducing device-assisted therapies are attractive treatment options
492 for augmenting the efficacy of intravesical chemotherapy for the treatment of NMIBC.
493 Prospective randomized trials for RITE suggest that it might be superior to BCG in papillary
494 only-disease both in the BCG-naive and BCG-failure cohorts. However, results remain
495 inconclusive for patients with isolated CIS or papillary disease with concurrent CIS. RCTs
496 comparing conductive hyperthermia plus MMC with passive MMC alone have reached their
497 recruitment target and results are eagerly awaited before adoption of intravesical device-
498 assisted therapies in clinical practice can be recommended. Results of RCTs of BCG-EMDA

MMC, both in the ablative (neoadjuvant) and adjuvant setting, are impressive but this modality has not been widely adopted and will require further validation. Reported adverse events suggest that they are short lived and not significantly worse than intravesical BCG. Hence, these treatments are normally administered in a nurse-led environment. The induction regime of these treatments is now standardized to mirror traditional intravesical chemotherapy and BCG, but the maintenance treatment requirement and protocol has considerable variation. Other novel treatment options that increase intravesical chemotherapy contact time have shown promising results in phase I trials. With the issues with BCG supply in some countries the use of device-assisted therapies is expected to increase.

Key points

- Intravesical chemotherapy and BCG is the recommended adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC) to reduce the risk of disease recurrence.
- The combination BCG supply shortage and alternative bladder-sparing approaches in patients with BCG-refractory disease have led to the development of hyperthermia-inducing device-assisted therapies for NMIBC.
- Radiofrequency induced thermotherapy (RITE), hyperthermic conductive chemotherapy, and electromotive drug administration (EMDA) chemotherapy are the most widely used devices to augment intravesical chemotherapy.
- Randomized controlled trials suggest that RITE and alternating BCG and EMDA mitomycin C is more efficacious than BCG alone . Data on patients with concurrent carcinoma in situ treated with RITE is currently inconclusive.
- Adverse events from RITE, hyperthermic conductive chemotherapy, and EMDA chemotherapy are short lived and better tolerated than BCG.
- Other novel therapies that improve the delivery of chemotherapy by prolonging chemotherapy exposure time or targeted local therapy are promising.

Review criteria

A comprehensive literature review was performed using Medline Pubmed and Google Scholar. The following MESH words were used: 'non-muscle invasive bladder cancer', 'hyperthermia', 'chemohyperthermia', 'hyperthermia', 'radiofrequency induced thermotherapy', 'RITE', 'EMDA', 'electromotive drug administration', 'mitomycin', 'MMC', 'intravesical chemotherapy', 'device assisted' and 'novel agents'. Original research, review articles, editorials, commentaries and letters to the editor which were in English were used for this review. The reference list of articles was screened to identify additional articles.

Author contributions

W.S.T. performed the researched data for and wrote the manuscript. JDK contributed substantially to writing, reviewing, and editing of the manuscript before submission

Competing interests statement

J.D.K. is chief investigator for HYMN and HIVEC-II, which are trials using hyperthermia delivery systems to treat bladder cancer, and is a consultant for Combat Medical. W.S.T. declares no completing interests

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552 **Tables**

553 Table 1: Overview of studies reporting outcomes using RITE for the treatment of NMIBC

554

Study	Patient entry	Number of patients	Risk group (previous intravesical treatment)	Carcinoma in situ	Median follow up, months (Interquartile range)	Induction treatment details	Maintenance	RFS and complete response rate (where specified)	Progression-free survival	Refs
RCT of adjuvant RITE versus institutional standard practice	2010- 2013	104: RITE: 48 Control: 56	Intermediate-risk (10%) or high-risk (90%) with recurrence following BCG, unwilling or unfit for cystectomy (previous intravesical treatment: 100%)	68%	35.1 (23.1-44.5)	RITE: 6 once weekly with 20 plus 20 mg MMC in 50 ml water for 60 mins Control: 6 once weekly BCG in 50 ml saline or standard of care at institution (EMDA chemotherapy, gemcitabine, re-challenge with MMC)	RITE: 20 plus 20 mg MMC in 50 ml water once 6 weekly (year 1) then once 8 weekly (year 2) Control: 3 weekly instillations at 3, 6, 12, 18, and 24 months	Overall 2 year RFS: RITE: 34% Control: 32% (p=0.24) 3 month CR: RITE: 30% Control: 47% (p=0.15)	RITE: 83% Control: 87%	47
Single-arm adjuvant RITE	2006- 2013	97	High-risk (previous intravesical treatment: 90.7%)	75%	27 (16-47)	6-8 once weekly 40 mg MMC in 50 ml saline for 60 mins	20 mg MMC in 50 ml saline 6 once weekly (year 1) then once 8 weekly (year 2)	NA	61.9%	52

RCT of adjuvant RITE versus BCG	2002 - 2011	190: RITE: 92 BCG: 98	Intermediate-risk (69%) or high-risk (31%) risk BCG-naive (previous intravesical treatment: 11.1%)	23%	24 (24)	RITE: 6 once weekly 20 plus 20 mg MMC in 50 ml water for 60 mins BCG: 6 once weekly OncoTICE full dose for 2 hours	RITE: 20 plus 20 mg MMC in 50 ml once weekly at 6 week intervals BCG: 3 once weekly at 3, 6, and 12 months	Papillary only RFS : RITE:81.8%, BCG: 64.8% (p=0.08) CR for CIS at 3 months: RITE: 88.9%, BCG: 85.6% (p=1)	RITE: 0% BCG: 1.4%	[53]
Single-arm adjuvant or ablative RITE	2003-2009	21: 11 ablative 10 adjuvant	Intermediate-risk or high-risk (>57%) recurrent NMIBC (previous intravesical treatment: 71%)	38%	50 (range: 1-120)	Ablative: 12 once weekly 40 plus 40 mg MMC in 50 ml saline over 60 mins Adjuvant: 6 once weekly 20 plus20 mg MMC in 50 ml saline over 60 mins	NA	Overall RFS: 29%	Overall: 62%	[61]
Single-arm adjuvant RITE	NA	26	High-risk (previous intravesical treatment not recorded)	23%	16.4 (6-48)	6 once weekly 20 plus 20 mg in 50 ml saline for 60 mins	6 once monthly 20 plus 20mg in 50 ml saline	RFS: 88.4%	NA	[54]
Single-arm adjuvant RITE	2006- 2010	42	High-risk (previous intravesical treatment: 64%)	7%	38 (4-73)	4 once weekly then 6 two weekly 40 plus 40 mg of MMC in 50 ml water for 60 mins	4 once monthly 40 plus40 mg MMC in 50 ml water	RFS: 57.1%	88%	[55]

Study type	Years	Number	Risk	%	Follow-up	Induction	Maintenance	Response	Survival	Ref
Single-arm adjuvant or ablative RITE	2006- 2009	30: 14 ablative 16 adjuvant	High risk (previous chemotherapy57%, previous BCG 43%)	13%	Mean: 14±8.5	Ablative: 8 once weekly 40 plus 40 mg MMC in 50 ml water over 60 mins Adjuvant: 6 once weekly 20 plus 20 mg MMC in 50 ml water over 60 mins	Ablative: 6 once monthly 40 plus 40 mg MMC in 50 ml Adjuvant: 6 once monthly 20 plus 20 mg MMC in 50 ml water	Ablative CR: 42.9% Adjuvant RFS: 43.8%	Ablative: 82.4% Adjuvant: 0%	62
Single-arm adjuvant and ablative RITE	2001-2011	92: 26 ablative 66 adjuvant	Intermediate-risk (27%) or high-risk(73%) (previous intravesical treatment: 76%)	28%	23 (range: 3- 84)	Ablative: 8 once weekly 40 plus 40 mg MMC in 50ml water over 60 mins Adjuvant: 6 once weekly 20 plus 20 mg MMC in 50 ml water over 60 mins	Adjuvant: 6 once every 6 weeks 20 plus 20 mg MMC in 50 ml water	Ablative CR: 79% Adjuvant RFS: 72%	Ablative: NA Adjuvant: 95.3%	63
RCT of adjuvant RITE versus MMC	1994-1999	83: RITE: 42 MMC: 41	Intermediate-risk and high-risk (>61%) (previous intravesical treatment: 58%)	1.2%	91 (range: 6-154)	8 once weekly 20 plus 20 mg MMC 50 ml water over 60 mins	4 once monthly 20 plus 20 mg MMC in 50 ml water or 60 mins	RITE RFS:60%, MMC: 20% (p<0.001)	RITE: 95.1% MMC: 92.9%	56
Single-arm adjuvant RITE	2000-2007	56	High-risk (previous intravesical treatment: 43%, previous BCG: 33.9%)	16%	18 (range: 2-49)	6 once weekly 20 plus 20 mg MMC over 60 mins	4-6 once weekly 20 plus 20 mg MMC for 6 treatments	RFS: 64.7%	92.9%	57
Single-arm adjuvant RITE	2001-2008	111	High-risk papillary recurrence after BCG	0%	16 (range: 2-74)	6 once weekly 20 plus 20 mg MMC in 50 ml over 60 mins	4-6 once weekly 20 plus 20 mg MMC for 6 treatments	12 months RFS: 85% 24 months RFS: 56%	97%	58

Design	Years	N	Risk (previous BCG)	%	Follow-up (months)	Induction	Maintenance	Outcomes	%	Ref
Single-arm adjuvant or ablative RITE	1997-2005	51: 33 ablative 18 adjuvant	High-risk: CIS with or without papillary NMIBC (previous BCG: 66.7%)	100%	22 (range: 3-77)	Ablative (papillary lesion and/or wide-spread CIS): 8 once weekly 40 plus 40 mg MMC in 50ml water over 60 mins Adjuvant: 6 once weekly 20 plus 20 mg MMC in 50 ml water over 60 mins	Ablative: 6 once monthly 40 plus 40 mg MMC in 50 ml water Adjuvant: 6 once monthly 20 plus 20 mg MMC in 50 ml water	All-patient RFS: 55% All-patient CR at 4 months: 92%	90%	64
Single-arm adjuvant or ablative RITE	2000-2004	47: 10 ablative 22 adjuvant	Intermediate-risk (16%) or high-risk(84%) (previous prophylactic BCG: 59%; previous ablative BCG: 80%)	0%	9.6	Ablative: 8 onceweekly 40 plus 40 mg MMC in 50 ml water Adjuvant: 6-8 once weekly 20 plus 20 mg MMC in 50 ml water	Ablative: 4 once monthly 40 plus 40 mg MMC in 50 ml water Adjuvant:4-6 once monthly 20 plus 20 mg MMC in 50 ml water	Ablative CR: 80% Adjuvant RFS: 91%	Ablative NA Adjuvant 0%	65
Adjuvant single arm RITE	1994 -2003	90	Intermediate-risk (59%) or high-risk (41%) (previous BCG: 46%)	0%	18 (range: 4-24)	Adjuvant: 6-8 once weekly 20 plus 20 mg in 50 ml water	Adjuvant: 4-6 once monthly treatments	RFS: 84%	0%	59
Single-arm adjuvant and ablative RITE	NA	52: -28 ablative -24 adjuvant	High-grade	0%	15.2 (range: 6-90), mean: 35.3 months	Ablative: 8 once weekly 40 plus 40 mg MMC in 50 ml water over 40 mins Adjuvant: 8 once weekly 20 plus 20 mg MMC in 50 ml water over 40 mins	Ablative: 4 once monthly 40 plus 40 mg MMC in 50 ml water over 40 mins Adjuvant: 4 once monthly 20 plus 20 mg MMC in 50 ml water over 40 mins	Ablative CR: 75% Adjuvant RFS: 62.5%	NA	66

RCT of adjuvant RITE vs MMC	1994-1999	83 (RITE: 42 versus MMC: 41)	Intermediate-risk or high-risk (>61%) (previous intravesical treatment: 58%)	1.2%	24	Both treatment arms: 8 once weekly 20 plus 20 mg MMC 50 ml water over 60 mins in both RITE and MMC arms	Both treatment arms: 4 monthly 20 plus 20 mg MMC in 50 ml water over 60 mins	RFS: RITE: 82.9% MMC: 42.5% (p=0.0002)	RITE: 100% MMC: 97.6%	[60]
Single-arm ablative RITE	1996-1998	80: 29 RITE 36 MMC 15 EMDA	Low-risk	0%	7-10 days after treatment	All 4 once weekly: MMC: 40mg in 50 ml saline RITE: 40 mg in 50 ml water EMDA: 40 mg 150 ml water	None	CR: MMC: 27.7%, RITE: 66% EMDA: 40%	NA	[48]
Single-arm ablative RITE	1992-1996	19	High-risk (previous intravesical treatment 100%)	0%	CR: 2 weeks after treatment	8 once weekly 40 mg in 40 ml water for 40 mins	None	CR: 47%	100%	[49]
RCT of ablative RITE versus MMC	1989-1993	52: RITE: 29 MMC: 23	Intermediate-risk and high-risk (>7%) %) (previous intravesical treatment: 80.8%)	0%	38 36	Both treatment arms: 6-8 once weekly 40+40 mg MMC in 50 ml water for 60 mins	None	E CR: RITE: 66%, MMC: 22% (p<0.01) RFS: RITE: 73%, MMC 61% (p>0.3)	NA	[50]
Single-arm ablative RITE	1988 -1992	44	Intermediate-risk or high-risk (>27%) (previous intravesical treatment: 63.6%)	0%	TURBT <3 weeks	8 twice weekly (within 6 weeks) 30 mg MMC in 60 ml water for 60 mins	None	CR: 70.4%	NA	[44]
Single-arm ablative RITE	NA	12	Not known	0%	TURBT 1-3 weeks	6-8 once weekly 30 mg MMC in 60 ml	None	CR: 41.7%	NA	[51]

CIS, carcinoma in situ; CR, complete response; DFS, disease-free survival; EMDA, electromotive drug administration; MMC, mitomycin C; NA, not applicable; NMIBC, non-muscle-invasive bladder cancer; NS, not significant; RCT, randomized control trial; RITE, radiofrequency-induced thermochemotherapeutic effect; RFS, recurrence-free survival; TURBT, transurethral resection of bladder tumour;

559   Table 2 | Adverse events in patients with NMIBC treated with RITE

First author	Number of patients	Complete treatment (%)	Grade ≥3 adverse events (%)	Haematuria (%)	UTI or sepsis (%)	Suprapubic pain (%)	Non-infective cystitis (%)	Bladder spasmor urgency (%)	Stricture (%)	Allergic reaction (%)	Incontinence (%)	Nocturia (%)	Reduced bladder capacity (%)	Refs
Tan et al., 2016	48	90	10	48	23	58	54	61	6	15	21	60	NR	47
Sooriakumaran et al., 2016	97	93	7	14	14	1	44	25	0	0	NR	NR	NR	52
Kiss B et al., 2015 61	21	62	52	24	0	38	52	24	10	10	NR	NR	NR	61
Maffezzini et al., 2014 55	42	88	0	62	0	29	71	12	0	0	29	NR	NR	55
Volpe et al., 2012	30	100	NR	27	7	3	23	30	0	13	NR	NR	7	62
Moskovitz et al., 2012	92	96	4	7	1	29	3	22	5	1	4	9	NR	63
Halachmi et al., 2011 57	56	91	NR	4	00	13	18	23	2	12.5	NR	NR	NR	57
Nativ et al., 2009 58	111	95	8	19	2	27	16	31	5	8	10	8	NR	58
Moskovitz et al., 2005	47	NR	4	17	00	66	6	17	6	4	NR	NR	NR	65
van der Heijden et al., 2004 59	90	100	NR	9	00	37	24	0	4	9	NR	NR	NR	59
Gofrit et al., 2004	52	96	NR	2	10	23	58	15	2	10	NR	NR	10	66
Colombo et al., 2003	42	69	NR	7	0	20	24	0	7	12	NR	NR	NR	60
Colombo et al., 1996	29	93	NR	NR	NR	NR	100	NR	0	NR	NR	72	NR	50
Colombo et al., 1995	44	NR	NR	NR	NR	NR	NR	NR	2	2	NR	NR	NR	44
Rigatti et al., 1991	12	NR	NR	NR	NR	25%	NR	42	0	NR	NR	NR	NR	51
Total	813	92.0	98.3	17.2	4.8	29.5	32.0	20.3	3.6	5.7	12.6	23.9	8.5	NA

560   NMIBC, non-muscle-invasive bladder cancer; RITE, radiofrequency-induced thermochemotherapeutic effect; UTI, urinary tract infection.

561   Note: Total percentages have been calculated by the sum of patients observing a specific adverse event divided by the total number of patients of each study where the specific adverse event
562   is report

563 Table 3 | Outcomes of conductive hyperthermia for the treatment of NMIBC

Setting	Patient entry	Number of patients	Risk group	Carcinoma in situ	Median follow up, months (IQR)	Induction treatment details	Maintenance	RFS and complete response rate (where specified)	Progression free survival	Refs
HIVEC										
Single-arm adjuvant or ablative	2010 -2015	40: 24 ablative 16 adjuvant	Intermediate-risk (35%) and high-risk (65%) (previous intravesical treatment: 73%)	15%	Ablative: 37 (95% CI: 12-52) Adjuvant: 24 (95% CI: 9-32)	Ablative: 8 once weekly 80 mg in 50 ml (43°C) in 50 ml water for 60 mins Adjuvant: 4 once weekly 40 mg in 50 ml (43°C) 50 ml water for 60 mins	Ablative: NA Adjuvant: 6 monthly 40 mg in 50 ml	Ablative: CR:62.5% 48 month RFS: 79.2% Adjuvant: RFS: 87.5%	NA	32
Single-arm ablative	2010- 2011	15	Intermediate (27%) and high (73%) risk (73% previous intravesical treatment)	0%	TURBT 7-15 days after neoadjuvant treatment, 29 months (95% CI: 26-32) follow-up duration	8 once weekly 80 mg in 50 ml water (43°C for 60 mins)	NA	CR: 60% RFS: 86.7%	NA	72
Unithermia										
Single-arm adjuvant	2009- 2011	34	Low-risk, intermediate-risk, or high-risk (24%) (all had recurrence after induction BCG)	0%	41	6 once weekly 40 mg MMC in 50 ml saline (43-45°C) for 45 mins	NA	RFS: 64.7%	76.5%	76
Single-arm adjuvant	2011- 2013	43	Treatment-naive, high-risk	23%	30 (9-39)	6 once weekly 40 mg MMC in 50 ml of saline (43-45 C) for 60 mins	3 once weekly instillations at 3 and 6 months	RFS: 67.5%	NA	33

| Adjuvant propensity scored matched cohort (versus BCG) | 2004- 2014 | 182:
CH: 40
BCG: 142 | Treatment-naive, high-risk | 18% | 24 | CH: 6 once weekly 40 mg in 50 ml saline (43-45°C) for 60 mins
BCG: 6 weekly | CH: 3 once weekly instillations at 3 and 6 months
BCG: determined by clinician or patient | RFS: CH: 70.1%, BCG: 89.5%
(univariate: p=0.006, multivariate: p=0.054) | CH: 87.2%
BCG: 94.9% | [83] |

CH, conductive hyperthermia; CR, complete response; DFS, disease-free survival; RFS, recurrence-free survival; MMC, mitomycin C; NA, not applicable; RFS, recurrence free survival; TURBT, transurethral resection of the bladder tumour.

581   Table 4: Adverse events in patients with NMIBC treated with conductive hyperthermia using HIVEC.

First author	Number of patients	Complete treatment (%)	Grade ≥ 3 adverse events (%)	Haematuria (%)	UTI or sepsis (%)	Suprapubic pain (%)	Non-infective cystitis (%)	Bladder spasm or urgency (%)	Stricture (%)	Allergic reaction (%)	Urinary retention (%)	Bladder calcification (%)	Refs
Sousa et al., 2016	40	98	8	23	23	28	40	33	3	3	8	3	32
Sousa et al., 2014	15	NR		20	13	27	33	27	0	7	0	7	72
Total	55	98	5.5	21.8	20.0	27.3	38.2	30.9	1.8	3.6	5.5	3.6	NA

582   NA, not applicable; NMIBC, non-muscle-invasive bladder cancer; NR, not reported; UTI, urinary tract infection.

583   Note: Total percentages have been calculated by the sum of patients observing a specific adverse event divided by the total number of patients of each study where the specific adverse event
584   is report

585   Table 5 | Adverse events in patients with NMIBC treated with conductive hyperthermia using Unithermia.

First author	Number of patients	Complete treatment (%)	Grade ≥ 3 AE (%)	Haematuria (%)	UTI or sepsis (%)	Suprapubic pain (%)	Non-infective cystitis (%)	Bladder spasm or urgency (%)	Stricture (%)	Allergic reaction (%)	Incontinence (%)	Frequency (%)	Bladder perforation (%)	Refs
Soria et al., 2016	34	88	12	NR	4	NR	NR	24	NR	6	3	15	0	76
Ekin et al., 2015	43	93	12	9	0	23	37	21	0	7	2	26	2	33
Ekin et al., 2015	40	95	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	83
Total	117	94.0	11.7	9.3	3.9	23.3	37.2	22.1	0	6.5	2.6	20.8	1.3	NA

586   NA, not applicable; NMIBC, non-muscle-invasive bladder cancer; NR, not reported; UTI, urinary tract infection.

587   Note: Total percentages have been calculated by the sum of patients observing a specific adverse event divided by the total number of patients of each study where the specific adverse event
588   is report

589

590 Table 6: Outcomes using EMDA MMC as monotherapy or in combination with BCG for the treatment of NMIBC

Setting	Patient entry	Number of patients	Risk group	Carcinoma in situ	Median follow up, months (IQR)	Induction treatment details	Maintenance	RFS and complete response rate (where specified)	Progression-free survival	Refs
Single-arm adjuvant sequential BCG and EMDA MMC	2009- 2013	107	New or recurrent high-risk	32%	24	BCG weekly for week 1 and 2 plus EMDA MMC (40 mg and 20 mA for 30 mins) for week 3. This was repeated three times.	3 once weekly BCG 3 months after induction and every 6 months for 3 years.	RFS: 68%	3%	[92]
RCT of TURBT versus TUBRT plus immediate postoperative MMC (adjuvant) versus neoadjuvant EMDA MMC plus TURBT	1994- 2003	374: 124 TURBT 126 TUBRT plus immediate postoperative MMC 124 neoadjuvant EMDA MMC plus TURBT	Low-risk (6%), intermediate-risk (66%),or high-risk (28%) (no previously intravesical treatment)	0%	86 (57-125)	TURBT alone TURBT plus immediate postoperative MMC 40 mg MMC in 50 ml water (60 minutes) Neoadjuvant EMDA plus TURBT 40 mg MMC in 100 ml water (20 mA for 30 mins).	All groups Intermediate-risk: 6 once weekly40 mg MMC in 50 ml water High-risk: 6 once weekly 81 mg BCG (ImmuCyst) in 50 ml saline for 120 mins	RFS: TURBT: 36%, TURBT plus MMC: 41%, Neoadjuvant EMDA MMC plus TURBT: 62% (p≤0.0001)	PFS TURBT: 79% TURBT plus MMC: 81% Neoadjuvant EMDA MMC plus TURBT: 94%	[90]
RCT of adjuvant BCG versus BCG and EMDA	1994- 2002	212: 105 BCG 107 BCG and EMDA	High-risk- all pT1 (previous intravesical treatment: 42%)	27%	88 (63-110)	BCG alone: 81 mg BCG over 120 mins weekly for 6 once weeks BCG and EMDA: 81 mg BCG over 120 mins weekly for 2 weeks then 40 mg EMDA (20 mA for 30 mins) weekly repeated 3 times (9 instillations in total) plus maintenance	BCG alone: once monthly for 10 months BCG and EMDA: 40 mg EMDA monthly for 2 months then 81 mg BCG for month 3. Repeated for three cycles	RFS: BCG alone: 42.1%, BCG plus EMDA: 58.1% (p=0.0012)	PFS: BCG alone: 78.1%, BCG and EMDA: 90.7% (p=0.004) OS: BCG alone: 67.6%, BCG and EMDA: 78.5% (p=0.045) CSS: BCG alone: 89.4%, BCG and EMDA: 94.4% (p=0.01)	[93]

Study	Years	N	Risk		Prior treatment	Timing	Treatment regimen	Maintenance	Outcome	Progression	Ref
RCT of adjuvant EMDA MMC versus MMC alone versus BCG	1994- 2001	108: 36 EMDA MMC 36 MMC 36 BCG	High-risk CIS ± pT1 (previous intravesical treatment not specified)	100%	6 (6)	All: 6 once weekly: EMDA MMC 40 mg (20 mA) in 100 ml water for 30 mins MMC: 40 mg in 100 ml water for 60 mins BCG: 81 mg in 50 ml saline for 120 mins.	All: 10 monthly instillations if response Non-responders at 3 months re-challenged with another 6 weeks induction.	Time to recurrence: EMDA MMC: 6 month, MMC alone: 20 months, BCG: 26 months, (p=0.013) CR: EMDA MMC: 58%, MMC alone: 31%, BCG: 64%(p=0.012)	No difference in progression	[94]
Ablative non-randomized comparative study of RITE, MMC, and EMDA MMC	1996- 1998	80: 29 RITE 36 MMC 15 EMDA	Low-risk	NA	7-10 days after treatment	All: 4 once weekly: MMC 40mg in 50 ml saline for 60 mins RITE: 40 mg MMC in 50 ml water (42.5C) for 60 mins EMDA MMC: 40 mg MMC (20 mA) in 150 ml water for 20 mins	NA	CR MMC: 27.7% RITE: 66%, EMDA: 40%	NA	[48]
Single-arm adjuvant EMDA MMC	NA	22 EMDA MMC	Low-risk (5%), intermediate-risk (67%), or high-risk (28%) (previous intravesical treatment not specified)	9%	14.1	4 once weekly EMDA MMC 40 mg in 100 ml saline (15 mA) for 20 mins	NA	RFS: 56.3%	NA	[95]
Non-randomized comparison study of adjuvant EMDA MMC versus MMC	1993- 1995	28: 13 MMC 15 EMDA MMC	Low-risk (36%), intermediate-risk (14%) and high-risk (50%) (previous intravesical treatment not specified)	0%	MMC: 10.5 EDMA MMC: 14.5	MMC: 8 once weekly 40 mg 50 ml water for 120 mins EMDA MMC: 8 once weekly 40 mg MMC (15 mA) for 20 mins	NA	CR: MMC: 41.6%, EMDA MMC: 40% RFS: MMC: 15.4%, EMDA MMC: 26.7	NA	[91]

CR, complete response; DFS, disease-free survival; EMDA, electromotive drug administration; MMC, mitomycin C; NA, not applicable; NMIBC, non-muscle-invasive bladder cancer; RCT, randomized control trial; RITE, radiofrequency induced thermochemotherapeutic effect; RFS, recurrence-free survival; TURBT, transurethral resection of bladder tumour.

597   Table 7: Adverse events in NMIBC treated with EMDA MMC monotherapy

598

First author	Number of patients	Complete treatment (%)	Grade ≥ 3 adverse events (%)	Haematuria (%)	UTI or sepsis (%)	Suprapubic pain (%)	Non-infective cystitis (%)	Bladder spasm or urgency(%)	Allergic reaction (%)	Refs
Di Stasi et al., 2003	36	92	8	8	19	0	36	0	8	94
Riedi et al., 1998	22	86	NR	5	5	18	9	63	0	95
Brausi et al., 1998	15	93	NR	0	0	0	13	0	13	91
Total	**73**	**90.4%**	**8.3%**	**12.7%**	**11.0%**	**5.5%**	**23.3%**	**19.2%**	**5.5%**	**NA**

599

600   EMDA, electromotive drug administration; MMC, mitomycin C; NA, not applicable; NMIBC, non-muscle-invasive bladder cancer; NR, not reported; UTI, urinary tract infection.

601   Note: Total percentages have been calculated by the sum of patients observing a specific adverse event divided by the total number of patients of each study where the specific adverse event
602   is report

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606 Table 8: Estimated end-user cost of intravesical device-assisted therapies for bladder cancer

Factor	Synergo	HIVEC	Unithermia	EMDA
Estimated end-user cost (£) of disposables per treatment	650	195	150	260
Number of treatments	6 once weeklyinduction plus maintenance of 1 treatment every 6 weeks for year one (6 treatments) and 1 treatment every 8 weeks for year two (7 treatments)= 19 treatments total[47] 6 weekly induction plus 3 weekly at 3, 6, and 12 months, 15 treatments total[31]	6 weekly plus 6 monthly treatments, 12 treatments total [32] 6 weekly plus 9 monthly treatments, 15 treatments total	6 weekly plus 3 weekly instillations at 3 and 6 months, 12 treatments total[33, 83]	BCG and EMDA: 9 weekly treatments (2 BCG treatments plus1 EMDA treatments repeated 3 times) plus 9 monthly (2 X EMDA plus 1 X BCG repeated 3 times), 9 EMDA plus 9 BCG total[93] EMDA: 6 weekly plus 10 monthly EMDA, 16 treatments total[94]
Time for each treatment session (min)	30 plus 30	60	50	30
Estimated end-user cost of disposables for 6 weekly induction treatment	3,900	1,170	900	BCG and EMDA: 780 EMDA: 1,560
Total cost of MMC for induction (£80/unit) ‡	480	480	480	BCG and EMDA: 240 EMDA: 480
Total cost of BCG for induction (£120/unit) ‡	NA	NA	NA	BCG and EMDA: 720
Estimated total end-user cost for 6 weekly induction treatment	4,380	1,650	1,380	BCG and EMDA: 1,740 EMDA: 2,040
Estimated end-user cost of disposables for induction and maintenance treatment	9,750-12,350	2,340-2,925	1,800	BCG and EMDA: 2,340 EMDA: 4,160
Total cost of MMC for induction and maintenance (£80/unit) ‡	1,200-1,520	960-1,200	960	BCG and EMDA: 720 EMDA: 1,280
Total cost of BCG for induction and maintenance (£120/unit) ‡	NA	NA	NA	BCG and EMDA: 1,080
Estimated end-user cost for induction and maintenance treatment	10,950-13,870	3,300-4,125	2,760	BCG and EMDA: 4,140 EMDA: 5,440

607 ‡ Prices according to the British National Formulary

608 EMDA, electromotive drug administration; MMC, mitomycin C; NA, not applicable.

Figures

610 Figure 1: Schematic diagram of the Synergo system. The Synergo system comprise of a radiofrequency generator which delivers radio-frequency energy at 915 MHz, a drug
611 circulation unit which promotes the circulation of chemotherapy from the device to the bladder within a close system and vice versa and a computer system with application
612 specific software. The specialised triple lumen silicon catheter has a lumen to fill the balloon at the catheter tip, an inflow and outflow channel. At the distal end of the catheter,
613 thermocouples are on contact with the bladder wall for accurate temperature measurement as well as the miniaturised antenna which delivers radiofrequency to the bladder
614 wall. Reproduced with permission
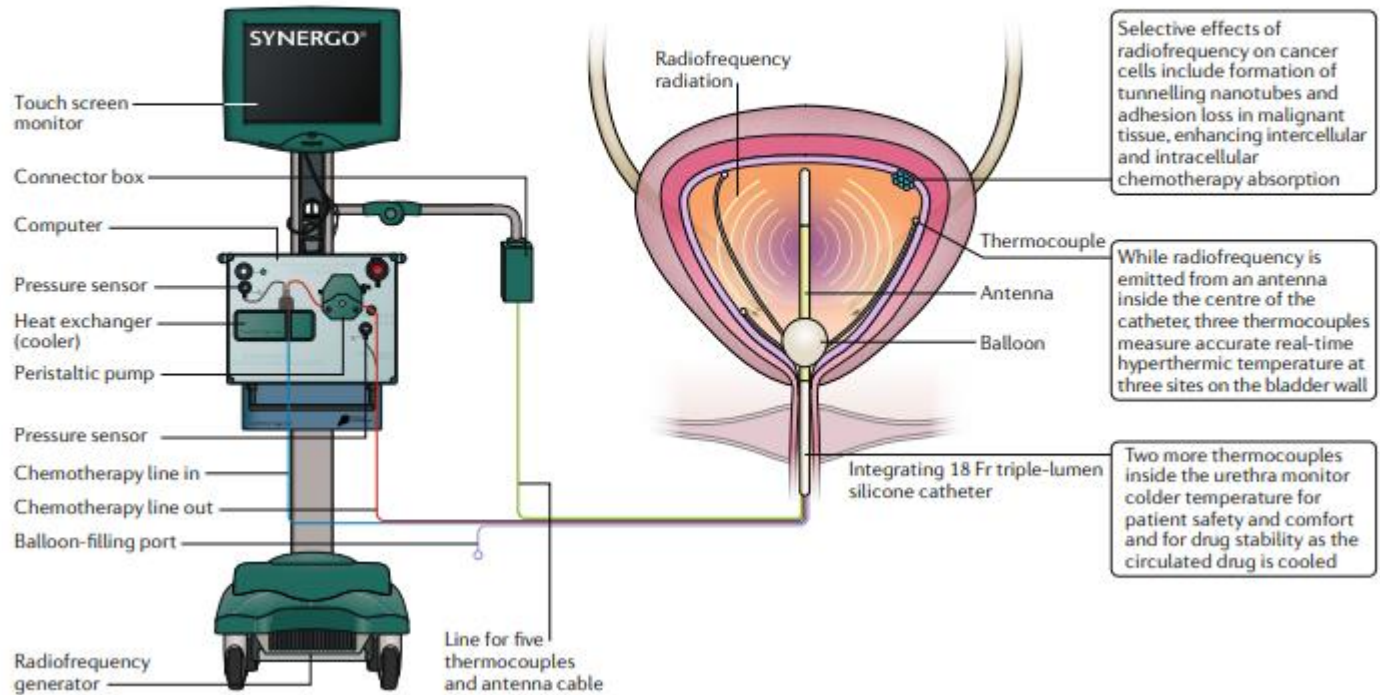
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616 Figure 2: Schematic diagram of the Combat BRS system. The Combat BRS system uses an aluminium heat exchange to allow efficient heat transfer. Circulating
617 chemotherapy is then recirculated within a close system at a rate of 200 ml per minute. The triple lumen catheter comprises a lumen to fill the balloon at the catheter tip, an
618 inflow and outflow channel, as well as a temperature probe.   Reproduced with permission

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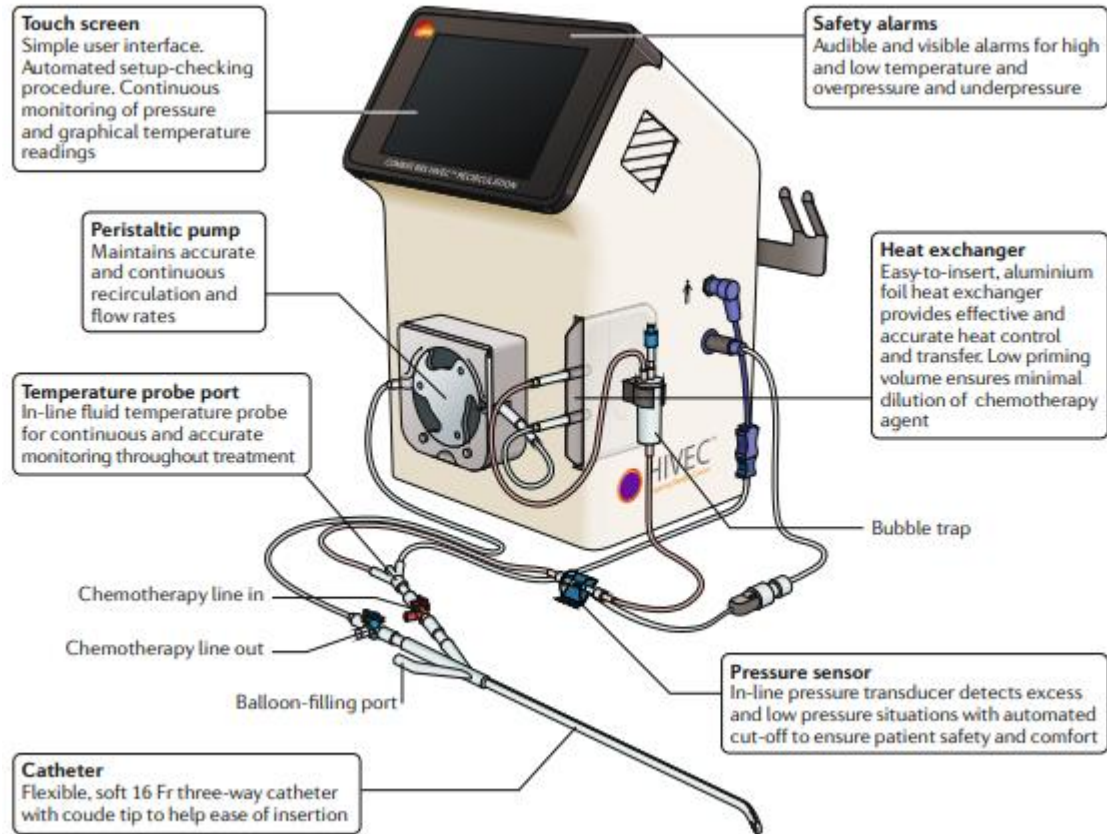
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623   Figure 3: Schematic diagram of the EMDA system. The EMDA system comprise of a battery- powered generator, a specialised triple lumen catheter with a lumen for the
624   catheter tip balloon, inflow and outflow channel as well as an active electrode at the tip of the catheter. Two dispersive electrodes a positioned at the suprapubic area which
625   acts as dispersive ground electrodes.   Reproduced with permission
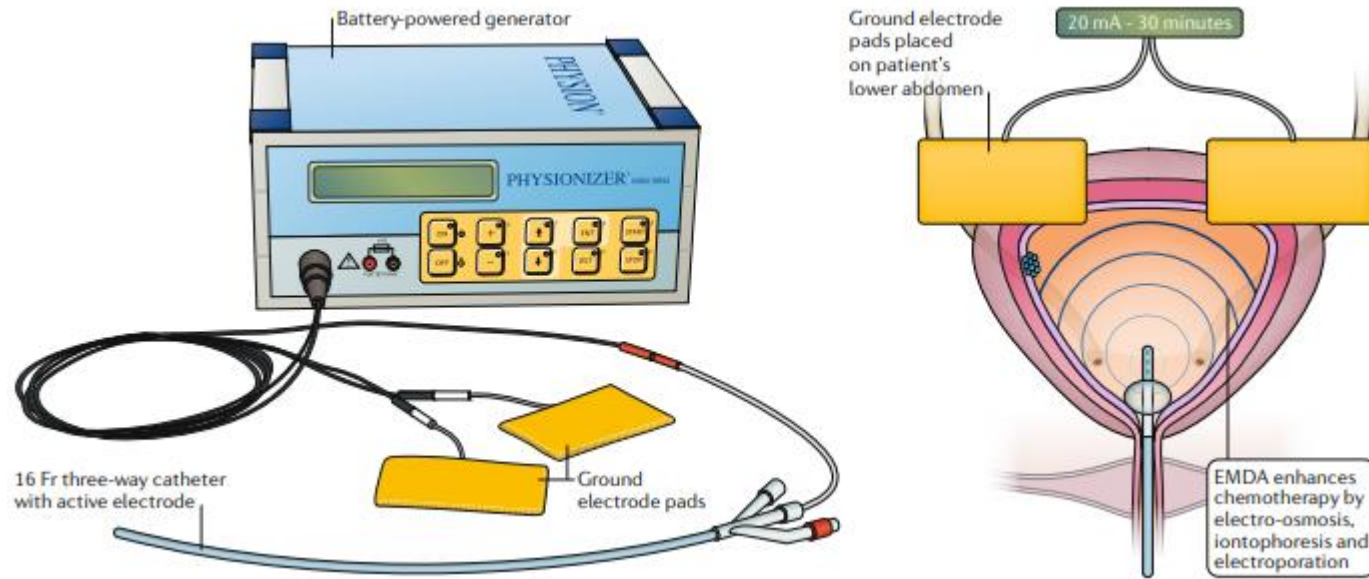
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634 Figure 4: GemRIS intravesical gemcitabine depot delivery system. The GemRIS system comprise of a 5 cm dual silicon tube which a Gemcitabine core to allow continuous
635 drug release over days. Nitinol wiring within the silicon tube preforms the device into a 'pretzel' like shape preventing the risk of expulsion from the bladder. Reproduced with
636 permission
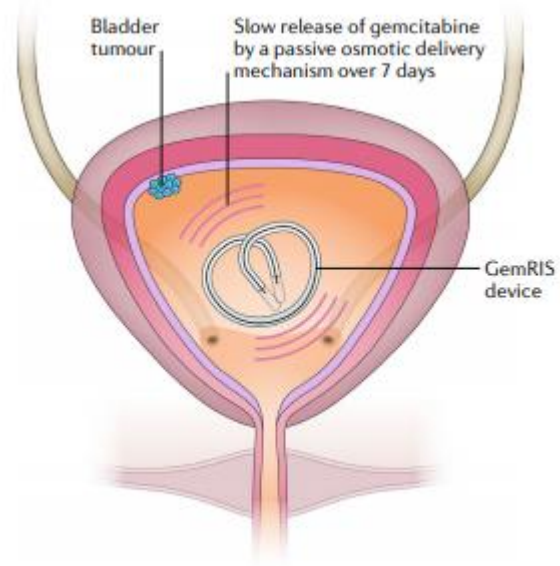
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644   Appendix

645   Supplementary Table 3: Comparison of reported adverse events in RCTs between RITE, BCG and MMC alone

BCG	RITE	MMC alone	Refs
NA	Increased pain, bladder wall erythema No difference in dysuria, haematuria, urethral stenosis, or allergy	No difference in dysuria, haematuria, urethral stenosis, allergy	60
Increased urinary frequency, nocturia, incontinence, haematuria, fever, fatigue, arthralgia, and cystitis No difference in urinary tract infection or residual urine volume	Increased bladder pain, bladder spasm, catheterisation difficulty, urethral stricture, bladder wall erythema, and allergic reaction No difference in urinary tract infection or residual urine volume	NA	53

646   MMC, mitomycin C; RCT, randomized control trial; RITE, radiofrequency-induced thermochemotherapeutic effect.

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