

1 **Intravesical device-assisted therapies for non-muscle invasive**  
2 **bladder cancer**

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

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## 40 [H1] Introduction

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

50 A single post-TURBT instillation of chemotherapy as adjuvant therapy within 24 hours, but  
51 ideally within 6 hours, reduces the relative risk of recurrence by 35% (HR: 0.65, 95% CI 0.58-  
52 0.74) in an individual patient data meta-analysis of low, intermediate and high-risk NMIBC.<sup>5</sup> A  
53 course of intravesical chemotherapy is recommended for intermediate-risk NMIBC and  
54 reduces the relative risk of recurrence by 44% (HR: 0.56, 95% CI: 0.48-0.65).<sup>6</sup> Mitomycin C  
55 (MMC) is the most commonly used intravesical chemotherapy.<sup>7</sup> MMC is a cytotoxic antibiotic  
56 that induces cell death by alkylation and cross linking of DNA.<sup>8</sup> Its molecular weight of 334  
57 kDa minimizes the risk of systemic absorption and toxic effects such as myelosuppression  
58 and pulmonary toxicity.<sup>8</sup> Adverse events following intravesical delivery of MMC are  
59 predominantly local irritative voiding symptoms, which are reported in up to 39% of patients.<sup>9</sup>  
60 Evidence exists for alternative agents including gemcitabine, epirubicin, and Adriamycin,  
61 which have not been as commonly adopted as MMC due to less compelling evidence although  
62 recent studies have suggested that gemcitabine is efficacious and may be an alternative to  
63 MMC.<sup>10-12</sup>

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

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

78 Developments for the treatment of NMIBC have focused on optimizing the delivery of  
79 established therapies or potentiating the effects of chemotherapy using intravesical device-  
80 assisted technology to deliver hyperthermia to the bladder wall or circulating chemotherapy  
81 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.<sup>18,19</sup> 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.

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## 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.<sup>20</sup> 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.<sup>21-23</sup> Temperature elevation enhances cell membrane  
95 permeability resulting in increased drug absorption.<sup>24,25</sup> 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<sup>26,27</sup>. 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.<sup>21</sup> 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.<sup>28</sup> Data from cell lines demonstrates synergism, whereby the effect of  
103 hyperthermia plus chemotherapy is greater than the combined additive effect.<sup>29,30</sup>  
104 Hyperthermia might also chemosensitize tumours to alkylating agents such as MMC via HSP  
105 mediated pathways.<sup>26</sup>

106 In the clinical setting, hyperthermia has been used in combination with chemotherapy for the  
107 treatment of NMIBC.<sup>31,32 33</sup> Hyperthermia can be either delivered by intravesical  
108 radiofrequency-induced hyperthermia or conductive heat via energy transfer from heated  
109 circulating fluid.<sup>31,32 33</sup> 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.<sup>34</sup>

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## 113 **[H1] RITE**

114 Radiofrequency-induced hyperthermia is an established therapy for a number of cancers  
115 including hepatocellular carcinoma,<sup>35</sup> Barrett's oesophagus,<sup>36</sup> breast cancer<sup>37</sup>, and lung  
116 cancer.<sup>38</sup> 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.<sup>39,40</sup> 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.<sup>40</sup> This is ideal for the delivery of heat 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,  $P = 0.018$ ).<sup>41</sup> 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.<sup>42</sup> 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.<sup>42</sup> In addition, a report by Ware et al.<sup>43</sup> suggest that radiofrequency promotes the  
129 formation of tunnelling nanotubes within cancer cells, which might increase drug diffusion and  
130 increase efficiency.<sup>43</sup>

131 RITE therapy for bladder cancer is the most established device-assisted therapy and the  
132 Synergo system was first reported in 1995.<sup>44</sup> 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.<sup>44</sup> The  
137 radiofrequency antenna delivers hyperthermia at  $42 \pm 2^\circ\text{C}$  to the bladder wall by direct  
138 radiation, while the inflow and outflow channel recirculate chemotherapy at room temperature  
139 ( $22^\circ\text{C}$ ) 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.<sup>45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>31</sup> No comparisons between the two protocols because they have been  
151 used in different patient cohorts.

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## 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,<sup>44,48-51</sup> nine studies in the adjuvant setting<sup>47,52-60</sup> and six studies had a mixture of  
157 patients treated with adjuvant therapy or pre-TURBT ablative treatment.<sup>61-66</sup> Only four  
158 randomized controlled trials (RCTs) investigating RITE have been conducted; three as  
159 adjuvant treatment<sup>47,53,56,60</sup> and one in the ablative setting.<sup>50</sup>

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.<sup>47,53,58-60,65,66</sup> 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.<sup>47,54,55,57,61-64</sup> 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.<sup>47,49,52,53,55-65</sup>

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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%.<sup>44,48-51,62,63,65,66</sup> 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).<sup>61,62 63-65 66</sup> In one RCT of 52 patients, RITE resulted in significantly  
174 higher complete response rates than MMC alone (66% versus 22%,  $P < 0.01$ ).<sup>50</sup>

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.<sup>60</sup> 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.<sup>60</sup> 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%,  $P < 0.001$ ).<sup>56</sup>

187 Arends et al.<sup>31</sup> 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.<sup>47</sup> 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-

208 minute sessions of 20 mg MMC in 50 ml of sterile water as part of induction treatment and  
209 three once weekly instillations at months 3, 6, 12, 18 and 24 months as part of maintenance  
210 treatment. Institutional standard practice comprised either rechallenge with BCG (59%),  
211 passive MMC (18%), or EMDA with MMC (23%). At the 24-month follow-up point, no overall  
212 difference in intention-to-treat disease-free survival (DFS) was observed between the two  
213 treatment arms (HR 1.33; 95% CI: 0.84-2.10,  $P = 0.23$ ) or in 3-month complete response rate  
214 in patients with CIS (RITE plus MMC arm: 30% versus control: 47%,  $P = 0.15$ ). There was a  
215 non-significant higher intention-to-treat DFS in papillary-only disease (HR 0.50; 95% CI: 0.22-  
216 1.17,  $P = 0.11$ ) treated with RITE compared to control. However, patients with CIS with/without  
217 papillary disease who received RITE had significantly higher disease recurrence than those  
218 who received treatment according to institutional standard practice (HR 2.06; 95% CI: 1.17-  
219 3.62,  $P = 0.01$ ), which resulted in the premature closure of the trial. A subsequent study  
220 reported an ablative protocol for patients with CIS comprising two 30-minute sessions of 40  
221 mg MMC.<sup>64</sup> DFS in patients who received this protocol was 43% at a median of 22 months.<sup>64</sup>  
222 The requirement for an increased MMC dose in ablative setting might explain results observed  
223 in the HYMN study.

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

237

## 238 [H2] Adverse events

239 The reported adverse event rates following RITE suggest that it is well tolerated, with 92% of  
240 patients completing induction treatment.<sup>69</sup> The most commonly reported adverse events  
241 during treatment are cystitis and/or storage lower urinary tract symptoms (LUTS) (32%),  
242 suprapubic pain (30%), and bladder spasm (20%).<sup>47,52,61,44,50,51,55,57-60,62,65,66</sup> Storage LUTS such  
243 as incontinence (12.6%) and nocturia (23.9%) and haematuria (17.2%) are the most common  
244 adverse events after treatment and 3.3% of patients had urethral stricture (Table 2). However,  
245 most adverse events are self-limiting and short lived.<sup>31,47</sup> RITE recirculates room temperature  
246 MMC, hence, no thermal reaction to the urethra occurs which would theoretically minimise the  
247 risk of urethral strictures.<sup>70</sup> Iatrogenic urethral injuries owing to catheter insertion might have  
248 contributed to the development of the urethral strictures reported. Thermal reaction on the  
249 posterior bladder wall, which is commonly observed following RITE treatment, can look  
250 suspicious for CIS owing to urothelium erythema and prompt unnecessary bladder biopsies

251 although they are benign and does not cause long term damage.<sup>44</sup> Indeed, animal studies  
252 suggest that the thermal reaction represent focal oedema, haemorrhage, and oedema of the  
253 lamina propria and serosa, which resolves completely.<sup>71</sup>

254 Adverse events reported in RCTs enable comparison of adverse event rates following RITE  
255 plus MMC or other standard-of-care treatment (Supplementary Table 1). RITE resulted in  
256 significantly more pain ( $P < 0.001$ ) and bladder wall erythema ( $P < 0.001$ ) than passive MMC,  
257 but no difference in dysuria, haematuria, urethral stenosis, or allergic reaction was observed.<sup>60</sup>  
258 Patients who received RITE plus MMC had a significantly increased risk of bladder pain during  
259 treatment (OR: 26.3; 95% CI, 14.3–48.5) or between treatments (OR: 1.6; 95% CI, 1.2–2.3),  
260 bladder spasms (OR: 15.5; 95% CI, 9.7–25.0), difficulty with catheterisation (OR: 16.7; 95%  
261 CI, 5.1–54.0), urethral strictures (OR: 2.3; 95% CI, 1.3–4.1), bladder wall erythema (OR: 5.8;  
262 95% CI, 4.0–8.3), and allergic reaction (OR: 2.7; 95% CI, 1.6–4.6) compared with BCG.  
263 However, significantly less urinary frequency (OR: 0.61; 95% CI, 0.49–0.75), nocturia (OR:  
264 0.79; 95% CI, 0.63–0.98), incontinence (OR: 0.22; 95% CI, 0.12–0.37), haematuria (OR: 0.56;  
265 95% CI, 0.42–0.74), fever (OR: 0.09; 95% CI, 0.04–0.10), fatigue (OR: 0.17; 95% CI, 0.11–  
266 0.28), and arthralgia (OR: 0.09; 95% CI, 0.03–0.31) were reported than for patients who  
267 received BCG.<sup>53</sup>

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

277

## 278 **[H1] Conductive hyperthermic chemotherapy**

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

286 Two conductive hyperthermic chemotherapy systems for bladder cancer have been reported,  
287 both of which use MMC: the Combat Bladder Recirculating System (BRS) and the Unithermia  
288 system. Minimal nursing 'hands-on' time is required once the system is set-up as a mid-  
289 treatment repeat instillation of MMC is not required compared to the RITE system allowing.  
290 This allows for a lower nurse to patient ratio when treatment is being administered. The  
291 Combat BRS system uses a 16 Fr three-way Foley catheter, which recirculates MMC in a  
292 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  $\pm 0.5$   
294  $^{\circ}\text{C}$ . 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.<sup>32,72,76</sup> 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  $46.5^{\circ}\text{C}$  to deliver it at  $44.5^{\circ}\text{C}$  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.<sup>33,76</sup> Results of a pharmacokinetics study suggested  
300 that peak plasma MMC concentration is achieved around 45 minutes after MMC instillation.  
301 <sup>77</sup>

302 Aqueous doxorubicin has been shown to efficacious for the treatment of NMIBC.<sup>78</sup> 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.<sup>79</sup>  
305 ThermoDox is a heat-activated liposomal encapsulation of doxorubicin that is a promising  
306 alternative to MMC. At  $40\text{-}45^{\circ}\text{C}$ ; the liposomes release doxorubicin directly at the heated  
307 source, which enables a targeted approach.<sup>80</sup> 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.<sup>80</sup> 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.<sup>81,82</sup>

314 Five studies have reported results for conductive hyperthermia,<sup>32 72 76 33 83</sup> 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<sup>32,72</sup> and  
320 three using the Unithermia system<sup>33,76,83</sup>, 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 ( $n=16$ )<sup>32</sup> and a complete response rate of 60-63% after 8 once weekly ablative intravesical  
325 treatments ( $n=39$ ).<sup>32,72</sup> 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.<sup>33,76,83</sup> These studies  
327 included one retrospective propensity score matched comparison<sup>83</sup>, which reported that BCG  
328 treated patients had a better RFS compared to conductive hyperthermia (89.5% versus  
329 70.1%,  $P = 0.054$ ).<sup>83</sup> 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).<sup>86</sup> Reliable adverse event data are available for the HIVEC system.



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

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

351 Prospective randomised data are eagerly awaited. HIVEC-I (EudraCT: 2013-002628-18)<sup>84</sup>  
352 and HIVEC-II (ISRCTN: 23639415)<sup>85</sup> are two multicentre, open-label, phase II RCTs recruiting  
353 patients from 12 Spanish and 13 UK centres respectively.. HIVEC-I will randomize 303  
354 patients with intermediate-risk disease to passive MMC, conductive hyperthermic MMC for  
355 30 mins, or conductive hyperthermic MMC for 60 minutes.<sup>84</sup> HIVEC-II will randomize 259  
356 patients with intermediate-risk disease to passive MMC or conductive hyperthermic MMC for  
357 60 mins.<sup>85</sup> Both studies have completed patient recruitment at the end of 2017 and results  
358 are eagerly awaited.

### 359 **[H1] EMDA MMC**

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

368 Intravesical EMDA MMC is administered using a battery-powered generator to deliver a  
369 controlled electric current of up to 30 mA.<sup>48</sup> The electrical current passes between the  
370 intravesical active electrode at the tip of a catheter to a dispersive ground electrode positioned  
371 on the lower abdomen (Figure 3). The specialized 16 Fr catheter is inserted and the bladder  
372 is washed with water, after which 40 mg MMC in 100 ml of water is instilled with the operating  
373 current maintained at 20 mA pulsed electrical current. Treatment time is 30 minutes per  
374 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.<sup>89</sup>

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<sup>48,90,91</sup> and a four studies in the adjuvant setting<sup>92-95</sup> (Table 6). Four studies reported  
382 outcomes for monotherapy EMDA MMC,<sup>48,90,91,94,95</sup> including one RCT in the neoadjuvant  
383 setting<sup>90</sup> and one in the adjuvant setting.<sup>94</sup>

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.<sup>92,93</sup> Di Stasi et al.<sup>93</sup> 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%,  $P = 0.0012$ ).<sup>93</sup> 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.<sup>92</sup> 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.<sup>94</sup> 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.<sup>90</sup> 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.<sup>90</sup> 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  $<0.0001$ ).<sup>90</sup> Colombo et al.<sup>48</sup> 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.<sup>48</sup>

413

## 414 [H2] Adverse events

415 Similar to hyperthermia delivery systems, 90% of patients complete adjuvant induction  
416 treatment of EMDA MMC (Table 7). In a RCT comparing EMDA MMC, passive MMC, and  
417 BCG, significantly more local and systemic adverse events occurred in patients who received  
418 BCG than those in the two MMC arms.<sup>94</sup> EMDA MMC had lower drug-related cystitis incidence  
419 (36% versus 67%, p=0.001), haematuria (22% versus 72%, p=0.001), frequency (19% versus  
420 58%, p=0.001), and fatigue (2.5% versus 44.4%, p=0.001) than BCG.<sup>94</sup> Pooled adverse  
421 events from 73 patients suggest that drug related cystitis and/or storage LUTS (23%), bladder  
422 spasm (19%), and haematuria (12%) were the most common adverse events and no urethral  
423 strictures were reported.<sup>91,94,95</sup> The most common reason for stopping EMDA MMC treatment  
424 was allergic reaction.<sup>93</sup> Compared with RITE plus MMC , EMDA MMC has an increased rate  
425 of suprapubic pain and dysuria, and patients who received RITE patients experienced less  
426 urinary frequency .<sup>48</sup> Anecdotally, subcutaneous burns have been reported to develop where  
427 the ground electrode pad is placed.

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

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

#### 438 **[H1] Comparison of cost between treatments**

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

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

451 The only cost-effectiveness analysis that has been performed was reported in the RCT  
452 comparing BCG plus EMDA MMC with BCG alone.<sup>93</sup> Based on a Markov model, sequential  
453 therapy was more costly than BCG therapy alone , but it was more efficacious with a 5-year  
454 increment cost-effectiveness ratio (ICER) of Can\$27,815 per life-year gained (US\$21,173,  
455 assuming Can\$1=US\$0.76).<sup>97</sup> This figure is below the maximum acceptable ICER of £20,000-  
456 £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.<sup>98,99</sup>

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.<sup>18</sup> 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).<sup>18</sup> The  
467 device can be removed 7 days later by grasping forceps and flexible cystoscopy.<sup>18</sup> In a phase  
468 1b study (NCT02722538),<sup>100</sup> 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.<sup>18</sup>

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%).<sup>19</sup> 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.<sup>19</sup> 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%).<sup>101</sup>

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

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

#### 508 **Key points**

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

524

#### 525 **Review criteria**

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

533

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538

539 **Author contributions**

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

542

543 **Competing interests statement**

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

547

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551

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%	<sup>47</sup>
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%	<sup>52</sup>

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%	<sup>53</sup>
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 plus 20 mg MMC in 50 ml saline over 60 mins	NA	Overall RFS: 29%	Overall: 62%	<sup>61</sup>
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	<sup>54</sup>
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 plus 40 mg MMC in 50 ml water	RFS: 57.1%	88%	<sup>55</sup>



Single-arm adjuvant or ablative RITE	2006- 2009	30: 14 ablative 16 adjuvant	High risk (previous chemotherapy 57%, 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%	<sup>62</sup>
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%	<sup>63</sup>
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%	<sup>56</sup>
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%	<sup>57</sup>
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%	<sup>58</sup>

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%	<sup>64</sup>
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 oncesweekly 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%	<sup>65</sup>
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%	<sup>59</sup>
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	<sup>66</sup>

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%	<sup>60</sup>
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	<sup>48</sup>
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%	<sup>49</sup>
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	<sup>50</sup>
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	<sup>44</sup>
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	<sup>51</sup>

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

558

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 spasms/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	<sup>47</sup>
Sooriakumaran et al., 2016	97	93	7	14	14	1	44	25	0	0	NR	NR	NR	<sup>52</sup>
Kiss B et al., 2015 <sup>61</sup>	21	62	52	24	0	38	52	24	10	10	NR	NR	NR	<sup>61</sup>
Maffezzini et al., 2014 <sup>55</sup>	42	88	0	62	0	29	71	12	0	0	29	NR	NR	<sup>55</sup>
Volpe et al., 2012	30	100	NR	27	7	3	23	30	0	13	NR	NR	7	<sup>62</sup>
Moskovitz et al., 2012	92	96	4	7	1	29	3	22	5	1	4	9	NR	<sup>63</sup>
Halachmi et al., 2011 <sup>57</sup>	56	91	NR	4	00	13	18	23	2	12.5	NR	NR	NR	<sup>57</sup>
Nativ et al., 2009 <sup>58</sup>	111	95	8	19	2	27	16	31	5	8	10	8	NR	<sup>58</sup>
Moskovitz et al., 2005	47	NR	4	17	00	66	6	17	6	4	NR	NR	NR	<sup>65</sup>
van der Heijden et al., 2004 <sup>59</sup>	90	100	NR	9	00	37	24	0	4	9	NR	NR	NR	<sup>59</sup>
Gofrit et al., 2004	52	96	NR	2	10	23	58	15	2	10	NR	NR	10	<sup>66</sup>
Colombo et al., 2003	42	69	NR	7	0	20	24	0	7	12	NR	NR	NR	<sup>60</sup>
Colombo et al., 1996	29	93	NR	NR	NR	NR	100	NR	0	NR	NR	72	NR	<sup>50</sup>
Colombo et al., 1995	44	NR	NR	NR	NR	NR	NR	NR	2	2	NR	NR	NR	<sup>44</sup>
Rigatti et al., 1991	12	NR	NR	NR	NR	25%	NR	42	0	NR	NR	NR	NR	<sup>51</sup>
<b>Total</b>	<b>813</b>	<b>92.0</b>	<b>98.3</b>	<b>17.2</b>	<b>4.8</b>	<b>29.5</b>	<b>32.0</b>	<b>20.3</b>	<b>3.6</b>	<b>5.7</b>	<b>12.6</b>	<b>23.9</b>	<b>8.5</b>	<b>NA</b>

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	<sup>32</sup>
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	<sup>72</sup>
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%	<sup>76</sup>
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	<sup>33</sup>

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%	<sup>83</sup>
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564 CH, conductive hyperthermia; CR, complete response; DFS, disease-free survival; RFS, recurrence-free survival; MMC, mitomycin C; NA, not applicable; RFS, recurrence  
565 free survival; TURBT, transurethral resection of the bladder tumour.

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

First author	Number of patients	Complete treatment (%)	Grade $\geq$ 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	<sup>32</sup>
Sousa et al., 2014	15	NR		20	13	27	33	27	0	7	0	7	<sup>72</sup>
<b>Total</b>	<b>55</b>	<b>98</b>	<b>5.5</b>	<b>21.8</b>	<b>20.0</b>	<b>27.3</b>	<b>38.2</b>	<b>30.9</b>	<b>1.8</b>	<b>3.6</b>	<b>5.5</b>	<b>3.6</b>	<b>NA</b>

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	<sup>76</sup>
Ekin et al., 2015	43	93	12	9	0	23	37	21	0	7	2	26	2	<sup>33</sup>
Ekin et al., 2015	40	95	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	<sup>83</sup>
<b>Total</b>	<b>117</b>	<b>94.0</b>	<b>11.7</b>	<b>9.3</b>	<b>3.9</b>	<b>23.3</b>	<b>37.2</b>	<b>22.1</b>	<b>0</b>	<b>6.5</b>	<b>2.6</b>	<b>20.8</b>	<b>1.3</b>	<b>NA</b>

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

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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%	<sup>92</sup>
RCT of TURBT versus TURBT plus immediate postoperative MMC (adjuvant) versus neoadjuvant EMDA MMC plus TURBT	1994- 2003	374: 124 TURBT 126 TURBT 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 weekly 40 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%	<sup>90</sup>
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)	<sup>93</sup>

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	<sup>94</sup>
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	<sup>48</sup>
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	<sup>95</sup>
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	<sup>91</sup>

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

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

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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	<sup>94</sup>
Riedi et al., 1998	22	86	NR	5	5	18	9	63	0	<sup>95</sup>
Brausi et al., 1998	15	93	NR	0	0	0	13	0	13	<sup>91</sup>
<b>Total</b>	<b>73</b>	<b>90.4%</b>	<b>8.3%</b>	<b>12.7%</b>	<b>11.0%</b>	<b>5.5%</b>	<b>23.3%</b>	<b>19.2%</b>	<b>5.5%</b>	<b>NA</b>

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

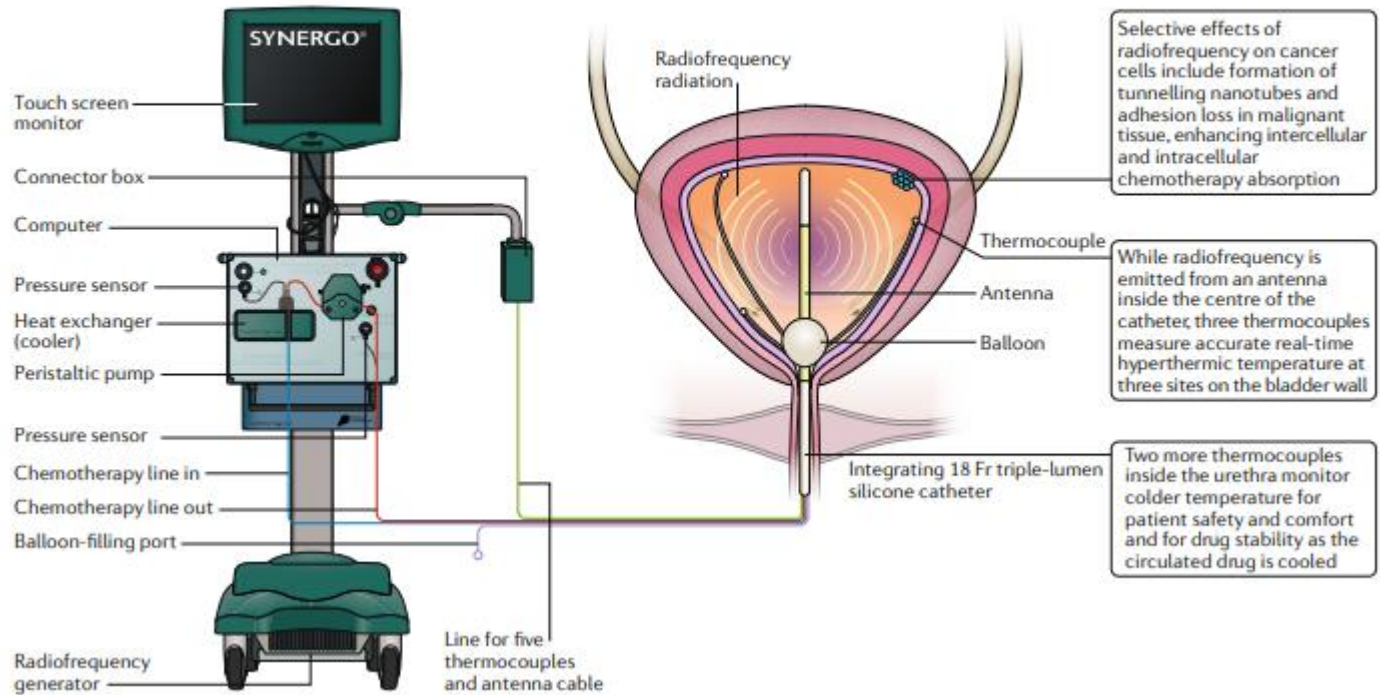
Factor	Synergo	HIVEC	Unithermia	EMDA
Estimated end-user cost (£) of disposables per treatment	650	195	150	260
Number of treatments	6 once weekly induction plus maintenance of 1 treatment every 6 weeks for year one (6 treatments) and 1 treatment every 8 weeks for year two (7 treatments)= 19 treatments total <sup>47</sup>  6 weekly induction plus 3 weekly at 3, 6, and 12 months, 15 treatments total <sup>31</sup>	6 weekly plus 6 monthly treatments, 12 treatments total <sup>32</sup>  6 weekly plus 9 monthly treatments, 15 treatments total	6 weekly plus 3 weekly instillations at 3 and 6 months, 12 treatments total <sup>33, 83</sup>	BCG and EMDA: 9 weekly treatments (2 BCG treatments plus 1 EMDA treatments repeated 3 times) plus 9 monthly (2 X EMDA plus 1 X BCG repeated 3 times), 9 EMDA plus 9 BCG total <sup>93</sup>  EMDA: 6 weekly plus 10 monthly EMDA, 16 treatments total <sup>94</sup>
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.

609 **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

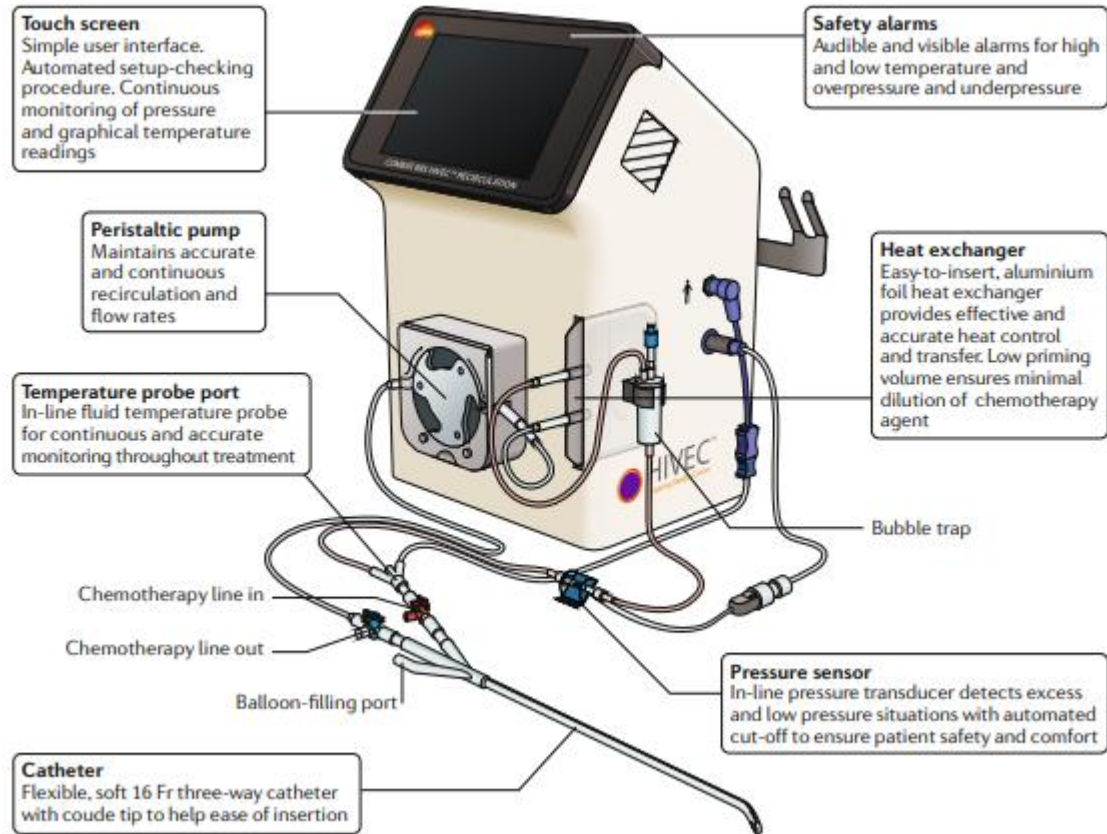
Synergism of radiofrequency radiation and chemotherapy, heated directly in bladder tissue while kept cold in bladder cavity → Radiofrequency-generated Foucault currents mobilize polarized chemotherapy molecules, resulting in an active diffusion → Tissue hyperthermia accelerates chemical reaction rate (through activation energy) and speeds up local physiological changes



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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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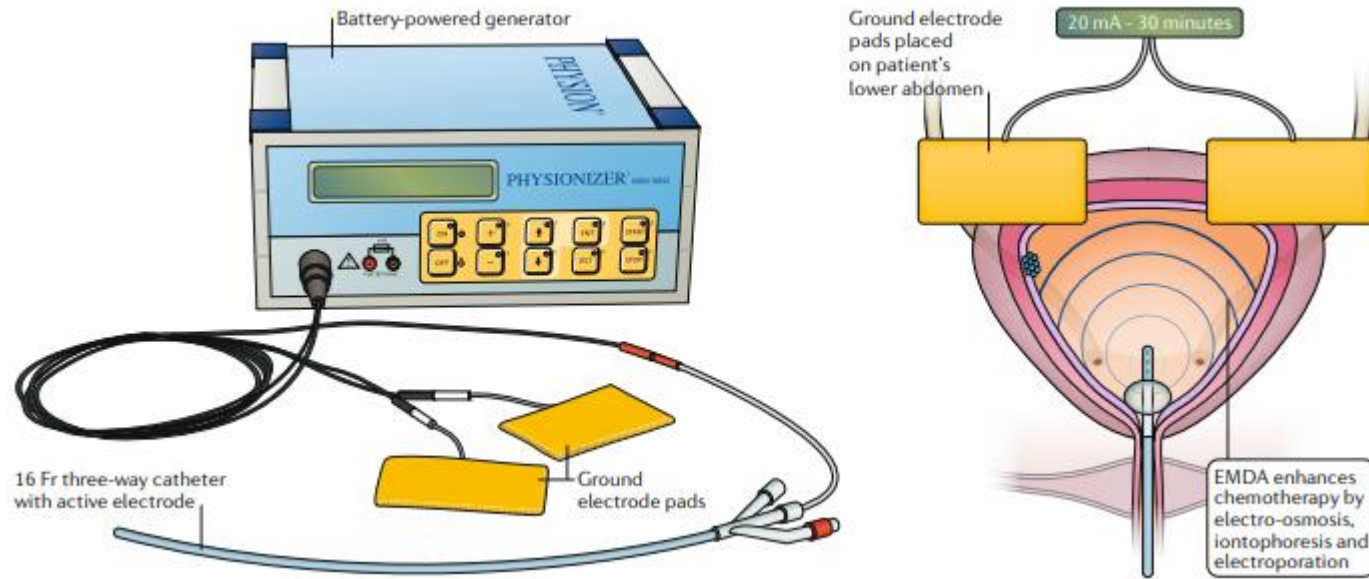


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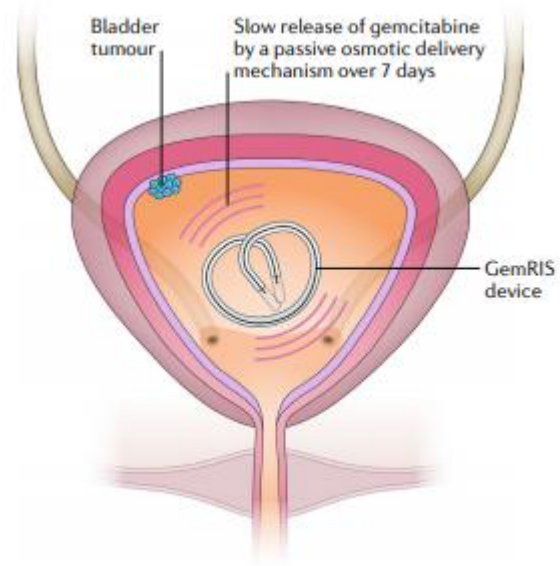
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623 Figure 3: Schematic diagram of the EMDA system. The EMDA system comprise of a battery-  
624 powered generator, a specialised triple lumen catheter with a lumen for the  
625 catheter tip balloon, inflow and outflow channel as well as an active electrode at the tip of the catheter. Two dispersive electrodes a positioned at the suprapubic area which  
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  
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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	<sup>60</sup>
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	<sup>53</sup>

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

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