

1 Radiofrequency-induced thermo-chemotherapy effect (RITE) versus a second
2 course of bacillus Calmette-Guérin (BCG) or institutional standard in patients
3 with recurrence of non-muscle invasive bladder cancer following induction or
4 maintenance BCG therapy (HYMN): A phase III, open-label, randomised
5 controlled trial

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58 **ABSTRACT**

59 **Background**

60 There is no effective intravesical second-line therapy for non-muscle invasive
61 bladder cancer (NMIBC) when bacillus Calmette-Guérin (BCG) fails.

62 **Objective**

63 To compare disease-free survival time (DFS) between radiofrequency-induced
64 thermo-chemotherapy effect (RITE) and institutional standard second-line therapy
65 (control) in NMIBC patients with recurrence following induction/ maintenance BCG.

66 **Design, settings, and participants**

67 Open-label, phase III randomised controlled trial accrued across 14 centres between
68 May 2010 and July 2013 [HYMN (ClinicalTrials.gov: NCT01094964)].

69 **Interventions**

70 Patients were randomly assigned (1:1) to RITE (60min, 40mg mitomycin-C, 42±2°C)
71 or control following stratification for CIS status (present/absent), therapy history
72 (failure of previous induction/ maintenance BCG) and treatment centre.

73 **Outcome measurements and statistical analysis**

74 Primary outcome measures were DFS and complete response (CR) at three months
75 for the CIS at randomisation subgroup. Analysis was by intention-to-treat.

76 **Results and limitations**

77 A total of 104 patients were randomised (48 RITE: 56 control). Median follow-up for
78 the 31 patients without a DFS event was 36 months. There was no significant
79 difference in DFS between treatment arms (HR 1.33, [95% CI 0.84-2.10], p=0.23) or
80 in three-month CR rate in CIS patients (n=71; RITE: 30% vs control: 47%, p=0.15).
81 There was no significant difference in DFS between treatment arms in non-CIS
82 patients (n=33; RITE: 53% vs control: 24% at 24 months, HR 0.50 [0.22-1.17],
83 p=0.11). DFS was significantly lower in RITE compared to control in CIS with/without
84 papillary patients (n=71; HR 2.06 [1.17-3.62], p=0.01; treatment-subgroup interaction
85 p=0.007. Disease progression was observed in 4 patients in each treatment arm.

86 Adverse events and health-related quality-of-life between treatment arms were
87 comparable.

88 **Conclusion**

89 DFS was similar between RITE and control. RITE may be a second line therapy for
90 non-CIS recurrence following BCG failure although confirmatory trials are needed.
91 RITE patients with CIS with/without papillary had lower DFS compared to control.
92 HYMN highlights the importance of the control arm when evaluating novel therapies.

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94 **Patient summary**

95 This study did not show a difference in bladder cancer outcomes between
96 microwave heated chemotherapy and standard of care treatment. Papillary bladder
97 lesions may benefit from microwave heated chemotherapy treatment, but more
98 research is needed. Both treatments are similarly well tolerated.

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100 Key words: bladder cancer, BCG failure, chemotherapy, device assisted therapy,
101 hyperthermia, mitomycin-C, radiofrequency, randomised controlled trial,
102 thermotherapy

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108 **1. INTRODUCTION**

109 Non-muscle invasive bladder cancer (NMIBC) represents 75% of bladder cancer and
110 adjuvant intravesical bacillus Calmette Guérin (BCG) is recommended for high risk
111 NMIBC following transurethral resection (TUR) of papillary urothelial carcinoma or as
112 ablative therapy for carcinoma *in situ* (CIS).

113 Despite maintenance BCG therapy, 55% of NMIBC patients develop recurrence and
114 20% progress to muscle invasive bladder cancer (MIBC) within 5 years [1].
115 Guidelines advocate early cystectomy or re-challenge with BCG following BCG
116 failure [2-4]. Although early cystectomy is the standard of care, it remains a morbid
117 procedure with a 90-day mortality of between 3.0-6.9% [5, 6]. Guidelines
118 recommending re-challenging with BCG accept its limited efficacy and there is
119 insufficient evidence to recommend the use of other intravesical agents [4, 7].
120 Radical radiotherapy is not effective for NMIBC [8].

121 Radiofrequency-induced thermo-chemotherapy effect (RITE) is a promising therapy
122 for NMIBC. RITE delivers hyperthermia to the bladder wall potentiating
123 chemotherapy cytotoxic effects and increases drug absorption by the formation of
124 tunnelling microtubules [9, 10] . A recent randomised controlled trial (RCT) of BCG
125 naïve NMIBC report a significantly higher 24-month RFS in RITE compared to BCG
126 treated patients (82% vs 65%, p=0.02) in per-protocol analysis (PPA) consistent with
127 previous studies [11, 12].

128 There has been no RCT comparing RITE to control in patients with recurrence of
129 NMIBC following failure of induction/ maintenance BCG. We report the results of
130 HYMN, a phase III RCT comparing RITE to control defined as a second course of
131 BCG or institutional standard in patients with NMIBC recurrence following induction
132 or maintenance BCG (ClinicalTrials.gov: NCT01094964, CRUK/09/012).

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138 **2. METHODS**

139 **2.1 Trial design**

140 HYMN is an open-label, two-arm, phase III RCT performed in accordance with the
141 Declaration of Helsinki. Fourteen institutions throughout the UK participated in the
142 trial (Supplementary Table 1). Appropriate ethical review board approved the trial
143 protocol (v4.0) at all recruiting sites (IRAS 10306).

144 **2.2 Patients**

145 Patients with recurrence of intermediate or high risk NMIBC according to European
146 Association of Urology (EAU) guidelines following induction/ maintenance BCG were
147 eligible [2]. All patients had complete TUR of papillary lesions and in pT1 disease
148 underwent re-resection to confirm the absence MIBC. Other inclusion criteria were
149 age ≥ 18 years, WHO performance status ≤ 4 and patients unfit or unwilling to have
150 radical cystectomy. All patients had imaging to exclude upper tract disease ≤ 12
151 months. Haematological and biochemical blood tests were within normal limits.

152 Key exclusion criteria included non-urothelial carcinoma, low grade NMIBC
153 recurrence, treatment with intravesical chemotherapy ≤ 6 months (single post-TUR
154 instillation allowed), prostatic urethra or upper tract disease, known mitomycin-C
155 allergy, active/ intractable urinary tract infection, urethral stricture, small bladder
156 capacity (< 250 ml), significant urinary incontinence or history of pelvic radiotherapy.

157 **2.3 Randomisation and masking**

158 Patients were randomised (1:1 ratio) using a random treatment allocation sequence
159 generated by the Cancer Research UK Clinical Trial Unit (CRCTU), University of
160 Birmingham, which was concealed from participants and accessed by telephone
161 using a central computerised randomisation service at CRCTU. Randomisation was
162 stratified by CIS status (present/absent), therapy history (failure of previous
163 induction/ maintenance BCG) and treatment centre. An independent Data Monitoring
164 Committee (DMC) was appointed to oversee the safety and monitor the interim
165 efficacy of treatment arms within the trial.

166 **2.4 Interventions**

167 Patients allocated to the experimental arm received six-weekly induction instillations
168 of RITE using the Synergo® SB-TS 101 System [13, 14]. Treatment comprise of two

169 30-minute cycles, each with 20mg MMC (50 ml sterile water) at $42\pm 2^{\circ}\text{C}$ (40mg MMC
170 in total) in accordance with the manufacturer's guidance [15]. Dose reduction was
171 not permitted. Patients disease-free three months after treatment commencement
172 would proceed to maintenance RITE (one instillation of RITE every six weeks for
173 year one and one instillation every eight weeks for year two).

174 Patients allocated to the control arm received either six consecutive weekly BCG
175 instillations (50ml normal saline) followed by maintenance therapy (three consecutive
176 weekly instillations at three, six, 12, 18 and 24 months) or institutional standard of
177 care defined at randomisation. All patients were followed up for a minimum of 24
178 months at three monthly intervals comprising of physical examination, cystoscopy
179 and urine cytology.

180 **2.5 Outcomes**

181 Co-primary outcome measures were disease-free survival time (DFS) for all patients
182 and 3-month complete response (CR) for patients with biopsy-proven CIS at
183 randomisation. DFS was determined as time from randomisation to earliest detection
184 of histologically confirmed recurrence, positive urinary cytology or death. Three-
185 month CR for patients with CIS was defined as absence of visible tumour at
186 cystoscopy, negative urinary cytology and no CIS on random bladder biopsy.

187 Secondary outcome measures include: progression-free survival time (PFS), overall
188 survival time (OS) and disease-specific survival time (DSS) in all patients;
189 recurrence-free survival time (RFS) in non-CIS patients and safety and tolerability of
190 RITE. Adverse events were recorded according to the NCI Common Toxicity Criteria
191 of Adverse Events v4.0. Health related quality of life (HRQoL) was assessed at trial
192 entry and three months intervals for 12 months using EQ-5D [16].

193 **2.6 Statistical analyses**

194 Statistical analyses were based on intention-to-treat (ITT). PPA was defined as
195 patients receiving ≥ 6 treatments. Kaplan-Meier method was used to assess time-to-
196 event outcomes. As the primary analysis, treatment arms were compared using log-
197 rank test with a univariable Cox regression model used to determine unadjusted
198 hazard ratios (HR). Secondary analysis used multivariable Cox regression model
199 with stratification factors (CIS status and therapy history) included as covariates to

200 give adjusted HRs and p-values as a sensitivity analysis. Pre-specified subgroup
201 analysis was used to assess treatment effects separately within each stratification
202 factor and they were compared using a treatment-subgroup interaction term
203 alongside their individual terms in a multivariable Cox regression model. CR rates
204 are compared using an odds ratio (OR) and Fishers Exact test for patients with CIS
205 at randomisation.

206 The original sample size calculations anticipated that 242 patients with 81 events per
207 arm would be required to detect an increase in DFS at 24 months from 45% to 60%
208 (HR of 0.64) and in an embedded subgroup analysis of CIS patients, at least 27
209 patients per arm would be required to detect an increase in three-month CR from
210 40% to 80% (both 80% power, 5% two-sided significance). Statistical analysis was
211 performed using Stata v14. Statistical significance was considered when $p < 0.05$. The
212 study conformed to CONSORT guidelines.

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225 3. RESULTS

226 3.1 Patients

227 The HYMN trial closed prematurely on February 2014 following a joint decision by
228 the independent DMC and trial steering committee (TSC) due to a higher than
229 expected CIS recurrence in RITE treated patients. A total of 104 patients (48 RITE
230 vs 56 control) were randomised between May 2010 and July 2013 (Figure 1). Follow-
231 up ended on July 2017.

232 Baseline patient characteristics were well balanced across treatment arms (Table 1).
233 There was a higher proportion of papillary disease with concurrent CIS randomised
234 to RITE compared to control (25% vs 18%, $p=0.38$). There was no difference in
235 patients who had random biopsies at 3 months between treatment arms. At trial
236 conception, it was estimated that 22% of patients would have CIS at baseline.
237 However, the actual proportion was 68% ($n=71$). High risk NMIBC was defined in
238 83% and 89% of the RITE and control arm respectively.

239 3.2 Efficacy

240 Disease-free survival analysis includes 73 events; 42 patients developed disease
241 recurrence, 15 had recurrent CIS, 5 had disease progression and 11 patients died.
242 Median follow-up time for the 31 patients without any of these DFS events was 36
243 months with only 4 patients less than 24 months follow-up. No significant overall
244 benefit was observed in DFS when comparing RITE to control (Figure 2a) with 24-
245 month DFS rate 35% versus 41% respectively (HR 1.33 [95% CI 0.84-2.10], $p=0.23$)
246 (adjusted $p=0.49$). In the pre-planned co-primary analysis, there was no significant
247 difference in the complete response rate of CIS at 3 months between RITE and
248 control arms (30% vs 47%, OR 0.43 [95% CI 0.18-1.28], $p=0.15$). Pre-planned
249 subgroup analysis showed that DFS of RITE treated patients were significantly lower
250 than control in patients with baseline CIS (HR 2.06 [95% CI 1.17-3.62], $p=0.01$;
251 Figure 2b). There was a non-significant higher DFS favouring RITE compared to
252 control in non-CIS patients at baseline (HR 0.50 [95% CI 0.22-1.17], $p=0.11$; Figure
253 2c). This treatment-subgroup interaction was statistically significant ($p=0.007$, Figure
254 3). DFS in non-CIS patients at 24-months for RITE and control patients were 53%
255 and 24% respectively.

256 The results for PPA were similar to ITT (Supplementary Figure 1). Subgroup analysis
257 of previous BCG showed no significant treatment-subgroup interaction (Figure 3).
258 Exploratory analysis of the effect of RITE on patients with CIS at baseline showed
259 that the detrimental effect on DFS was marked in those with concurrent papillary and
260 CIS disease (n=22) compared to those with CIS only (n=49) (Figure 3). There was
261 no evidence of a differential treatment effect in CIS only patients (HR 1.53 [95% CI
262 0.77-3.05], p=0.22). No difference between RITE and control was observed in PFS
263 (8 patients with progression, 24-month rates 83% vs 87%, p=0.16), OS (30 deaths,
264 24-month rates 85% vs 90%, p=0.18), and RFS (27 patients with disease recurrence
265 in the 55 with papillary disease, 24-month rates 23% vs 40%; p=0.98) but a
266 borderline difference in DSS (24-month rates 89% vs 96%; p=0.04) (Supplementary
267 Table 2).

268 **3.3 Safety**

269 41 RITE patients and 48 control patients were included in the PPA. Five RITE
270 patients did not complete ≥ 6 instillations due to adverse events: skin rash, urinary
271 urgency and nocturia, inability to catheterise (n=2), haematuria, and patient refusal of
272 treatment while five control arm patients were excluded due to the following adverse
273 events: urinary urgency (n=2), persistent dysuria, haematuria, and patient refusal of
274 treatment. Two patients in the RITE arm did not receive treatment: patient choice
275 (n=1) and ineligibility post-randomisation (n=1). Three patients in the control arm
276 were not treated: patient choice (n=2) and significant incontinence (n=2) after
277 randomisation.

278 One or more adverse events occurred in 84 (81%) patients (42 RITE patients vs 42
279 control patients). No difference in adverse events between each treatment modality
280 was observed (Table 2). Most adverse events were grade 1-2. There were two grade
281 4 toxicity in the control arm which was due to arthritis and the other BCG related
282 sepsis resulting in death. No difference in health-related quality of life was observed
283 between the two treatment arms although RITE patients rated their health status
284 higher than controls at three, six and nine months follow-up (Figure 4).

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288 4. DISCUSSION

289 The aim of the HYMN was to determine if RITE is superior to standard of care in
290 patients with recurrence of NMIBC following BCG. HYMN was a pragmatic study and
291 in the absence of standard of care for this patient cohort who refuse cystectomy, pre-
292 planned treatment plan for control was determined by the local institution. HYMN
293 remains the only RCT to test a novel therapy in this patient cohort. The trial showed
294 no difference in DFS between RITE and standard therapy in all patients and three-
295 month CR rate in CIS patients at baseline. Pre-planned subgroup analysis of DFS
296 showed RITE was beneficial in non-CIS patients (RITE 53% vs control 24% at 24-
297 months) although this was not statistically significant.

298 A post-hoc analysis shows a higher number of concurrent papillary and CIS tumours
299 in the RITE arm compared to control (25% versus 18%, $p=0.38$). The presence of
300 CIS with papillary disease is associated with an increased risk of disease recurrence
301 and progression and genomic studies suggest that these patients are genotypically
302 similar to MIBC [17, 18]. It is plausible that patients with concurrent papillary and CIS
303 have a significant risk of disease progression regardless of treatment modality.

304 The rationale for hyperthermia follows *in vitro* and clinical studies which showed that
305 increase in chemotherapy temperature can promote tissue permeation, promoting
306 better drug absorption and synergistically increased tumour cell apoptosis [9].
307 Previous RCT data suggest a benefit for RITE compared to BCG or MMC in BCG
308 naïve patients [11, 19]. In HYMN, we report that RITE treated non-CIS NMIBC
309 patients had a lower DFS compared to control although this was not significant. In a
310 predominantly non-CIS cohort (1.2% CIS), Colombo *et al.* reported that RITE had a
311 higher 24-month RFS compared to MMC alone (83% vs 43%, $p<0.001$) and a
312 durable response at 10-year RFS (53% vs 15%, $p<0.001$) [19, 20].

313 Arends *et al.* randomised 190 patients to either RITE or BCG, both with maintenance
314 therapy [11]. The proportion of patients with high risk disease was 31% (57/184) and
315 23% (42/184) of patients had CIS at randomisation. In ITT analysis, Arends *et al.*
316 reported a higher but non-significant 24-month RFS favouring the RITE compared to
317 BCG (78% vs 65%, $p=0.08$) in non-CIS disease. A PPA showed a significant benefit
318 favouring RITE compared to BCG (81% vs 65%, $p=0.02$) however outcome for CIS
319 patients were not reported [11]. The non-CIS RITE treated patients in HYMN hints

320 towards similar results although there were only 33 patients in this pre-planned
321 subgroup analysis.

322 An important finding in HYMN is the efficacy of the control arm. A single arm study of
323 Valrubicin in 90 cases of BCG-refractory CIS reported a 90-day CR rate of 21%
324 which was sufficient evidence for FDA approval [21]. A Food and Drug
325 Administration (FDA) public workshop and the International Bladder Cancer Group
326 (IBCG) recommended that a single arm study design is sufficient to provide evidence
327 of efficacy in the setting of recurrence following BCG therapy [22, 23]. Both the FDA-
328 AUA workshop and IBCG felt that a six-month CR rate of 40-50% and a RFS of ≥ 25 -
329 30% at 18-24 months in BCG refractory-CIS would be clinically meaningful [22, 23].
330 Both RITE and control arm in HYMN achieved a 24-month DFS of 35% and 41%
331 respectively, which was better than Valrubicin and above the recommended
332 threshold for clinically meaningful effect although patients in HYMN would have a
333 better prognosis as BCG relapsing and intolerant patients were included. We would
334 caution that a control arm remains important for the design of studies to assess
335 efficacy of novel agents in the setting of BCG failure NMIBC.

336 Study limitations include that HYMN closed early at interim analysis and did not
337 reach its recruitment target. Patients treated with RITE had 40 mg MMC which was
338 consistent with the dosage used in two previous RCTs [11, 19]. A single arm study of
339 RITE with 80mg MMC to treat CIS report a DFS of 86% with a mean follow-up of 26
340 months suggest that a higher MMC dose might be more effective [24]. Up to 23% of
341 patients in the control group received EMDA MMC which may be more effective than
342 challenging to BCG although efficacy between these two treatments are similar in
343 the randomised trial [25]. HYMN recruited a heterogenous group of BCG refractory,
344 resistance and intolerance as this trial commenced before the FDA-AUA
345 recommendations [23].

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351 **5. CONCLUSIONS**

352 DFS was similar between RITE and control treated patients. HYMN suggest the
353 potential for RITE as a second line therapy for non-CIS recurrence following BCG
354 although confirmatory trials are needed. RITE treated patients with CIS with/without
355 papillary had lower DFS compared to control. RITE is well tolerated compared to
356 control. HYMN highlights the importance of the control arm when evaluating novel
357 therapies.

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380 Development Ltd.

381 **Ethical approval of studies and informed consent**

382 The trial received ethical approval from the UK Multicentre Research Ethics
383 Committee and regulatory approval from the UK Medicines and Healthcare
384 Regulatory Agency in October 2009. In addition, each participating centre obtained
385 local institutional review board approval. Written consent was obtained from all study
386 participants.

387 **Declaration of intent and financial disclosures**

388 John D Kelly is a consultant for Combat Medical outside submitted work. Wei Shen
389 Tan has received travel support to attend conferences from Combat Medical and
390 Medical Enterprises Europe B.V. Jo Cresswell reported personal fees from
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392 Leyshon Griffiths reported personal fees from Prostrakan, Combat Medical and
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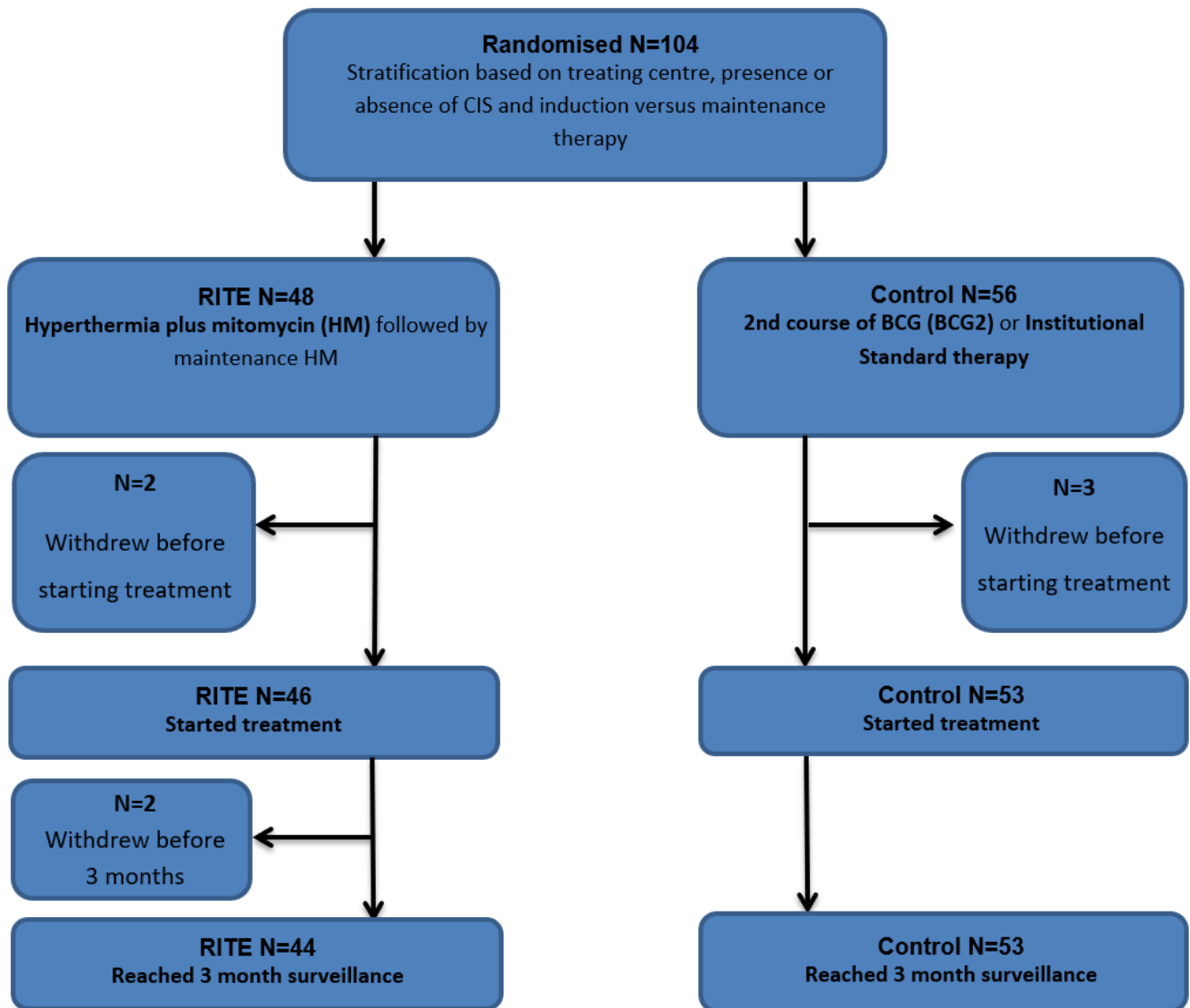
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435 Figure 1: CONSORT diagram for the HYMN trial

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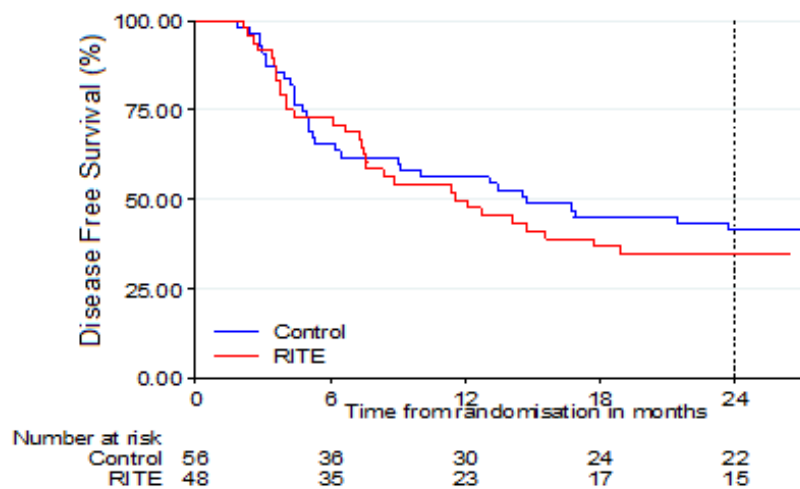
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443 Figure 2: Kaplan-Meier curves for disease-free survival time: (A) all randomised
 444 patients (n=104) [HR: 1.33, 95% CI: 0.84-2.10, p=0.23]; (B) Pre-planned subgroup
 445 analysis of all randomised patients with CIS at baseline (n=71) [HR:2.06, 95% CI:
 446 1.17-3.62, p=0.01]; (C) pre-planned subgroup analysis of all randomised patients
 447 without CIS at baseline (n=33) [HR: 0.50, 95% CI: 0.22-1.17, p=0.11].

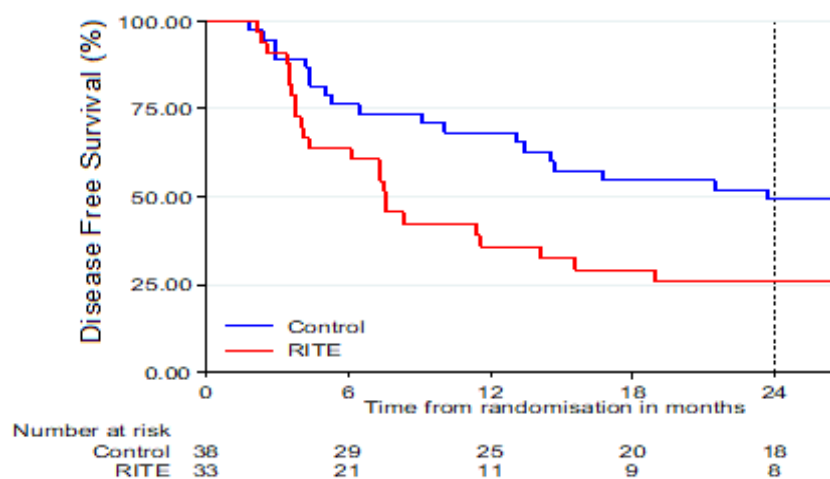
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449 (A)



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456 (B)



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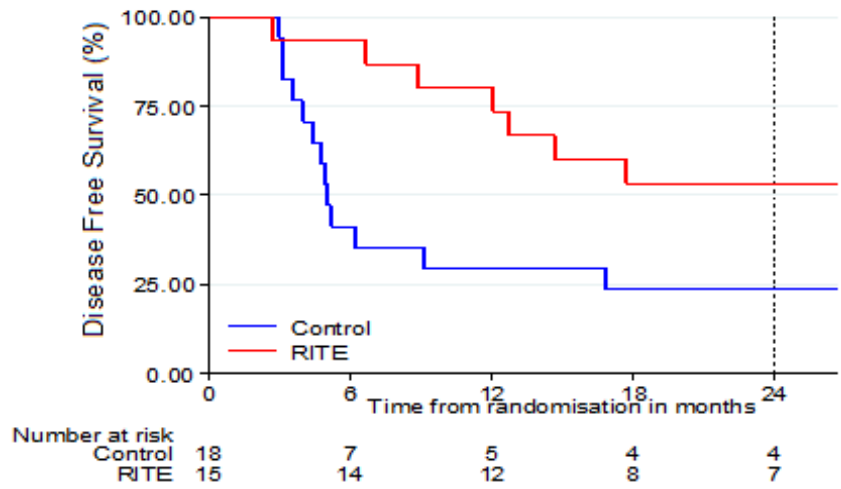
466 (C)

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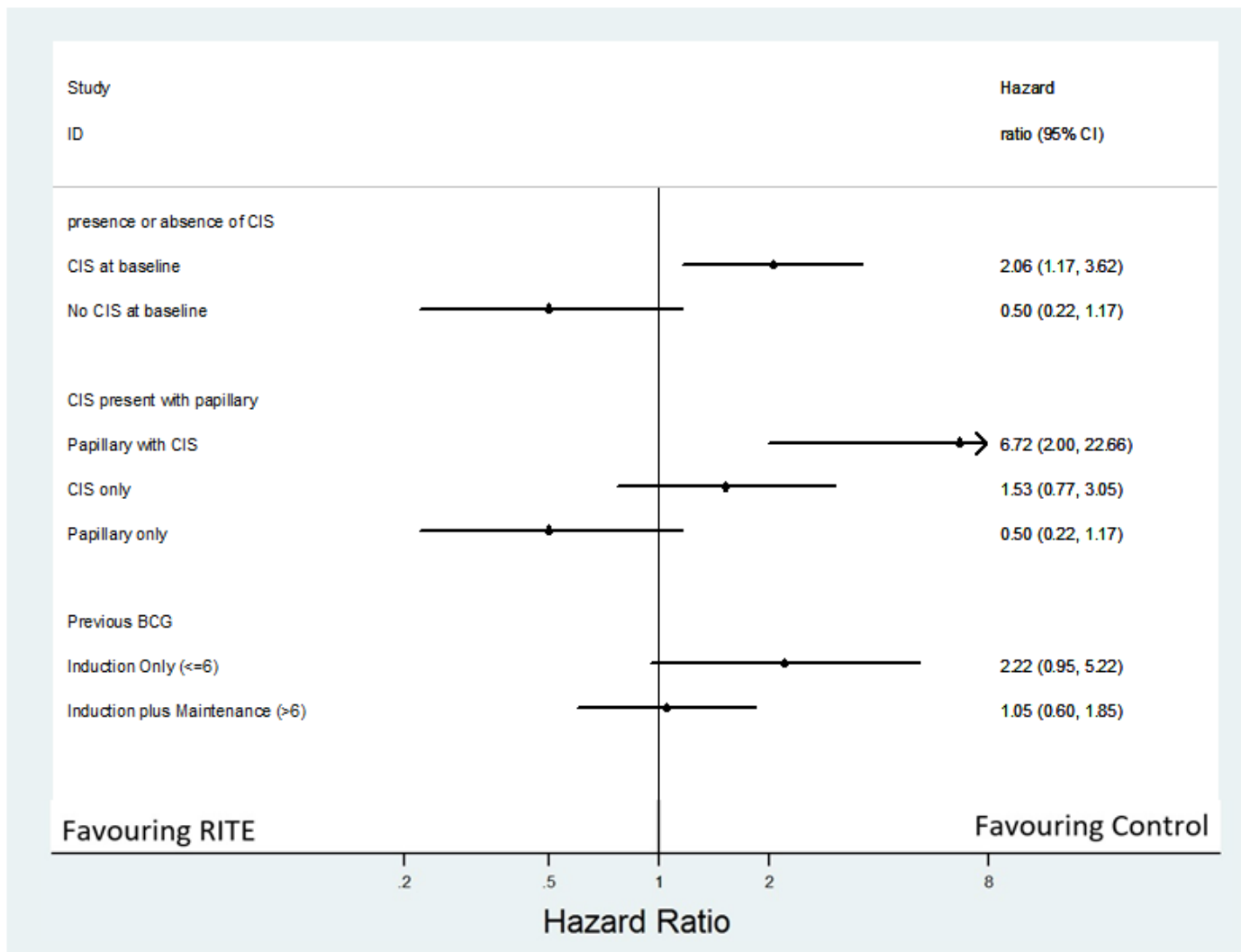
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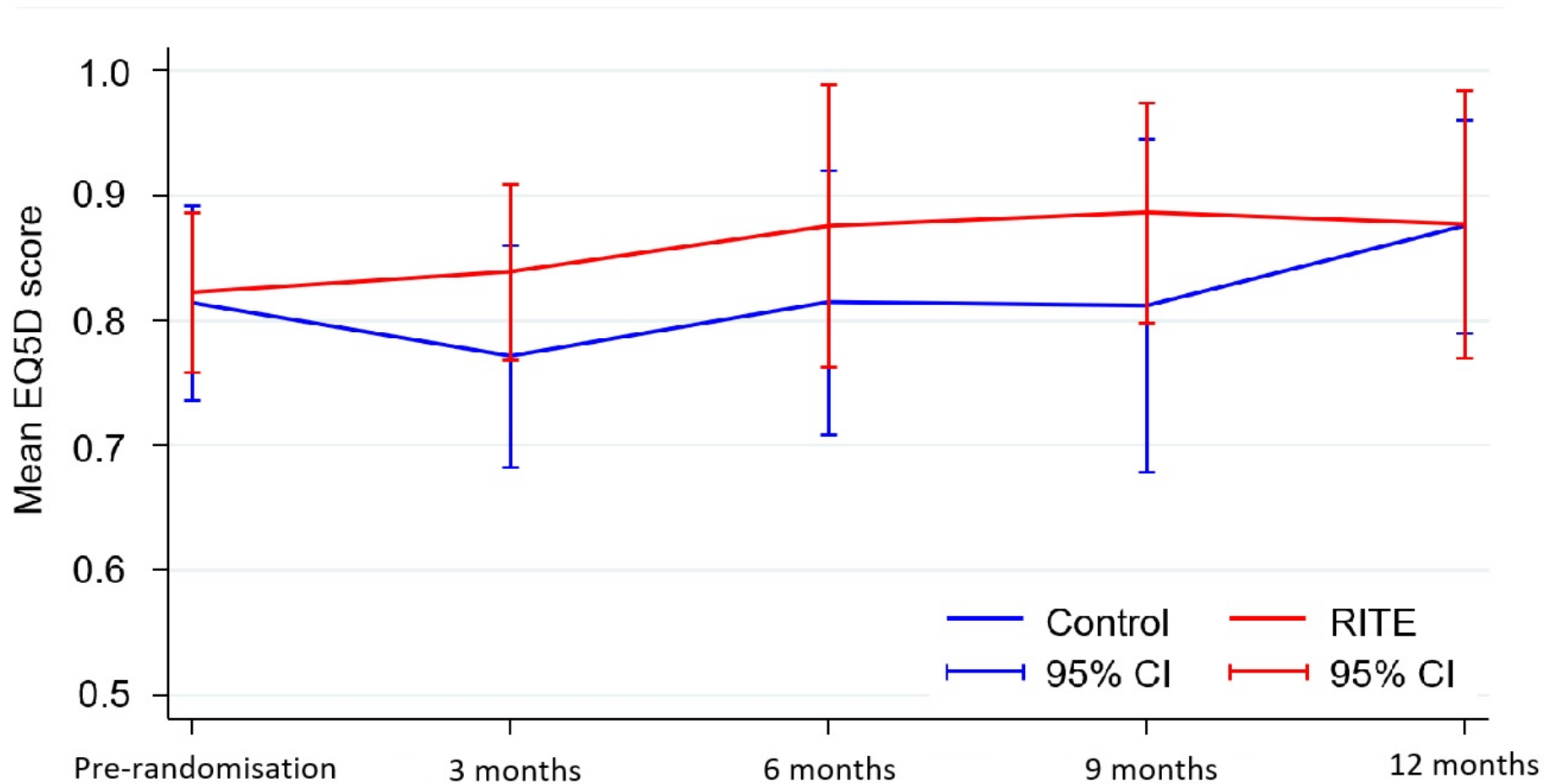
471 Figure 3: Forest plot showing hazard ratios and 95% confidence intervals for disease-free survival time for pre-planned subgroup
 472 analysis of stratification factors (CIS status and previous BCG) and extended exploratory analysis of CIS status

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487 Figure 4: Mean EQ-5D score for RITE and control at baseline, 3, 6, 9 and 12 months

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490 Table 1. Baseline characteristics of patients randomised

Characteristic	RITE (n=48)	Control (n=56)
Sex:		
Male	34 (71%)	44 (79%)
Age: Median (IQR)	77 (72-82)	76 (67-81)
Smoking status:		
Never	15 (31%)	16 (29%)
Previous	28 (58%)	39 (70%)
Current	5 (10%)	1 (1.8%)
Histology*:		
Papillary only	15 (31%)	18 (32%)
Ta G2	5	5
Ta G3	6	5
T1 G2	1	1
T1 G3	3	7
Papillary and CIS	12 (25%)	10 (18%)
Ta G1	0	1
Ta G2	3	0
Ta G3	7	3
T1 G3	2	6
CIS Only	21 (44%)	28 (50%)

Previous BCG*:		
Induction only (≤ 6 instillations)	18 (38%)	19 (34%)
Induction plus maintenance (> 6 instillations)	30 (63%)	37 (66%)
Institutional Standard:		
BCG alone		33 (59%)
MMC alone		10 (18%)
EMDA MMC		13 (23%)

491 * CIS status (present or absent) and previous BCG therapy (induction only or
 492 induction plus maintenance) used as stratification variables at randomisation

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508 Table 2: Reported adverse events stratified by treatment.

	All grades		Grades 3/4	
	RITE N=48	Control N=56	RITE N=48	Control N=56
Pain	46%	56%	4%	0%
Dysuria	54%	59%	0%	0%
Increased frequency	52%	54%	0%	2%
Increased urgency	42%	48%	0%	4%
Incontinence	23%	18%	0%	0%
Nocturia	33%	38%	0%	4%
Haematuria	48%	36%	2%	0%
Fatigue	33%	38%	4%	2%
Fever	13%	25%	0%	0%
UTI	27%	18%	0%	2%
Rash	15 %	25%	2%	4%
Stricture	6%	4%	0%	0%

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