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Platinum Priority – Bladder Cancer

Editorial by J. Alfred Witjes on pp. 72–73 of this issue

Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guérin or Institutional Standard in Patients with Recurrence of Non–muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial

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Abstract

Background: There is no effective intravesical second-line therapy for non–muscle-invasive bladder cancer (NMIBC) when bacillus Calmette-Guérin (BCG) fails.
Objective: To compare disease-free survival time (DFS) between radiofrequency-induced thermo-chemotherapy effect (RITE) and institutional standard second-line therapy (control) in NMIBC patients with recurrence following induction/maintenance BCG.
Design, settings, and participants: Open-label, phase III randomised controlled trial accrued across 14 centres between May 2010 and July 2013 (HYMN [ClinicalTrials.gov: NCT01094964]).
Intervention: Patients were randomly assigned (1:1) to RITE (60 min, 40 mg mitomycin-C, 42 ± 2 °C) or control following stratification for carcinoma in situ (CIS) status (present/absent), therapy history (failure of previous induction/maintenance BCG), and treatment centre.

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Outcome measurements and statistical analysis: Primary outcome measures were DFS and complete response (CR) at 3 mo for the CIS at randomisation subgroup. Analysis was based on intention-to-treat.
Results and limitations: A total of 104 patients were randomised (48 RITE: 56 control). Median follow-up for the 31 patients without a DFS event was 36 mo. There was no significant difference in DFS between treatment arms (hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.84–2.10, $p = 0.23$) or in 3-mo CR rate in CIS patients ($n = 71$; RITE: 30% vs control: 47%, $p = 0.15$). There was no significant difference in DFS between treatment arms in non-CIS patients ($n = 33$; RITE: 53% vs control: 24% at 24 mo, HR 0.50, 95% CI 0.22–1.17, $p = 0.11$). DFS was significantly lower in RITE than in control in CIS with/without papillary patients ($n = 71$; HR 2.06, 95% CI 1.17–3.62, $p = 0.01$; treatment-subgroup interaction $p = 0.007$). Disease progression was observed in four patients in each treatment arm. Adverse events and health-related quality of life between treatment arms were comparable.
Conclusions: DFS was similar between RITE and control. RITE may be a second-line therapy for non-CIS recurrence following BCG failure; however, confirmatory trials are needed. RITE patients with CIS with/without papillary had lower DFS than control. HYMN highlights the importance of the control arm when evaluating novel therapies.
Patient summary: This study did not show a difference in bladder cancer outcomes between microwave-heated chemotherapy and standard of care treatment. Papillary bladder lesions may benefit from microwave-heated chemotherapy treatment; however, more research is needed. Both treatments are similarly well tolerated.

1. Introduction

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

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

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

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

2. Materials and methods

2.1. Trial design

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

2.2. Patients

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

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

2.3. Randomisation and masking

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

2.4. Interventions

Patients allocated to the experimental arm received 6-weekly induction instillations of RITE using the Synergo SB-TS 101 System [13,14]. Treatment comprised two 30-min cycles, each with 20 mg MMC (50 ml sterile water) at 42 ± 2 °C (40 mg MMC in total), in accordance with the manufacturer's guidance [15]. Dose reduction was not permitted. Patients who were disease-free 3 mo after treatment commencement would proceed to maintenance RITE (one instillation of RITE every 6 wk for 1st yr and one instillation every 8 wk for 2nd yr).

Patients allocated to the control arm received either six consecutive weekly BCG instillations (50 ml normal saline) followed by maintenance therapy (three consecutive weekly instillations at 3, 6, 12, 18, and 24 mo) or institutional standard of care defined at randomisation. All patients were followed-up for a minimum of 24 mo at 3-mo intervals comprising physical examination, cystoscopy, and urine cytology.

2.5. Outcomes

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

Secondary outcome measures were: progression-free survival time (PFS), overall survival time (OS), and disease-specific survival time (DSS) in all patients; RFS time in non-CIS patients; and safety and tolerability of RITE. Adverse events were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Health-related quality of life (HRQoL) was assessed at trial entry and at 3-mo intervals for 12 mo using EQ-5D [16].

2.6. Statistical analyses

Statistical analyses were based on intention-to-treat (ITT). PPA was defined as patients receiving equal to or more than six treatments. Kaplan-Meier method was used to assess time-to-event outcomes. For primary analysis, treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HRs). Secondary analysis used multivariable Cox regression model with stratification factors (CIS status and therapy history) included as covariates to give adjusted HRs and *p* values as a sensitivity analysis. Pre-specified subgroup analysis was used to assess treatment effects separately within each stratification factor, and they were compared using a treatment-subgroup interaction term alongside their individual terms in a multivariable Cox regression model. CR rates were

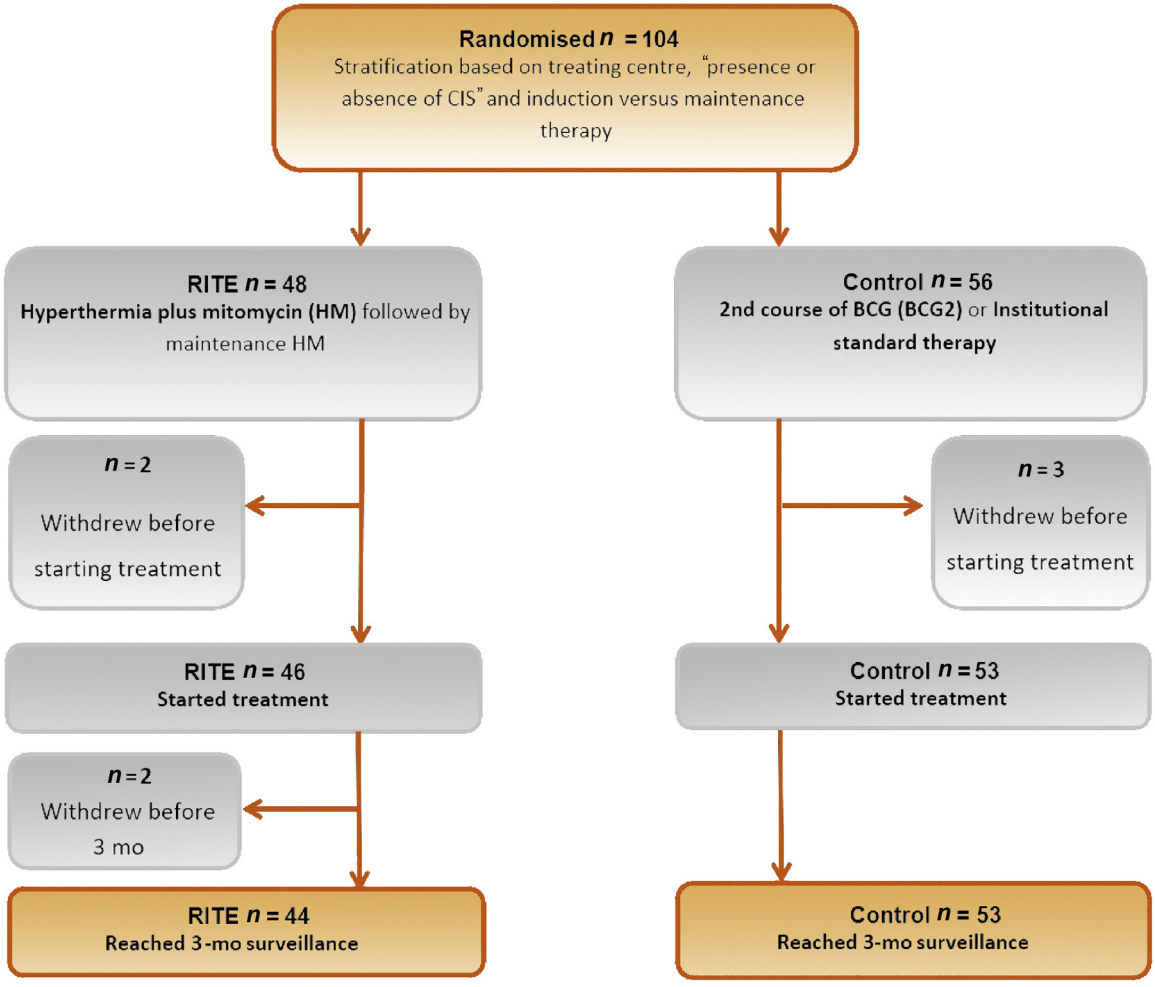

Fig. 1 – CONSORT diagram for the HYMN trial.
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; RITE = radiofrequency-induced thermo-chemotherapy effect.

compared using an odds ratio (OR) and Fisher's exact test for patients with CIS at randomisation.

The original sample size calculations anticipated that 242 patients with 81 events per arm would be required to detect an increase in DFS at 24 mo from 45% to 60% (HR 0.64), and in an embedded subgroup analysis of CIS patients, at least 27 patients per arm would be required to detect an increase in 3-mo CR from 40% to 80% (both 80% power, 5% two-sided significance). Statistical analysis was performed using Stata version 14. Statistical significance was considered when p value was <0.05. The study conferred to CONSORT guidelines.

3. Results

3.1. Patients

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

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

Table 1 – Baseline characteristics of patients randomised

Characteristic	RITE ($n = 48$)	Control ($n = 56$)
Sex, *n* (%)		
Male	34 (71)	44 (79)
Age, median (IQR)	77 (72–82)	76 (67–81)
Smoking status, *n* (%)		
Never	15 (31)	16 (29)
Previous	28 (58)	39 (70)
Current	5 (10)	1 (1.8)
Histology[a], *n* (%)		
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[a], *n* (%)		
Induction only (≤6 instillations)	18 (38)	19 (34)
Induction plus maintenance (>6 instillations)	30 (63)	37 (66)
Institutional standard, *n* (%)		
BCG alone		33 (59)
MMC alone		10 (18)
EMDA MMC		13 (23)

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; EMDA = electromotive drug administration; IQR = interquartile range; MMC = mitomycin C; RITE = radiofrequency-induced thermochemotherapy effect.

[a] CIS status (present or absent) and previous BCG therapy (induction only or induction plus maintenance) used as stratification variables at randomisation.

3.2. Efficacy

DFS analysis includes 73 events; 42 patients developed disease recurrence, 15 had recurrent CIS, five had disease progression, and 11 died. Median follow-up time for the 31 patients without any of these DFS events was 36 mo, with only four patients with less than 24 mo of follow-up. No significant overall benefit was observed in DFS when comparing RITE with control (Fig. 2A), with 24-mo DFS rate 35% versus 41%, respectively (HR 1.33, 95% confidence interval [CI] 0.84–2.10], $p = 0.23$; adjusted $p = 0.49$). In the pre-planned co-primary analysis, there was no significant difference in the CR rate of CIS at 3 mo between RITE and control arms (30% vs 47%, OR 0.43, 95% CI 0.18–1.28, $p = 0.15$). Pre-planned subgroup analysis showed that DFS of RITE-treated patients was significantly lower than that of control in patients with baseline CIS (HR 2.06, 95% CI 1.17–3.62, $p = 0.01$; Fig. 2B). There was a nonsignificant higher DFS favouring RITE than control in non-CIS patients at baseline (HR 0.50, 95% CI 0.22–1.17, $p = 0.11$; Fig. 2 C). This treatment-subgroup interaction was statistically significant ($p = 0.007$; Fig. 3). DFS in non-CIS patients at 24 mo for RITE and control patients were 53% and 24%, respectively.

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

3.3. Safety

In total, 41 RITE and 48 control patients were included in the PPA. Five RITE patients did not complete six or more than six instillations due to adverse events, such as skin rash, urinary urgency and nocturia, inability to catheterise ($n = 2$), haematuria, and patient refusal of treatment, whereas five control arm patients were excluded due to adverse events, such as urinary urgency ($n = 2$), persistent dysuria, haematuria, and patient refusal of treatment. Two patients in the RITE arm did not receive treatment: patient choice ($n = 1$) and ineligibility post-randomisation ($n = 1$). Three patients in the control arm were not treated: patient choice ($n = 2$) and significant incontinence ($n = 2$) after randomisation.

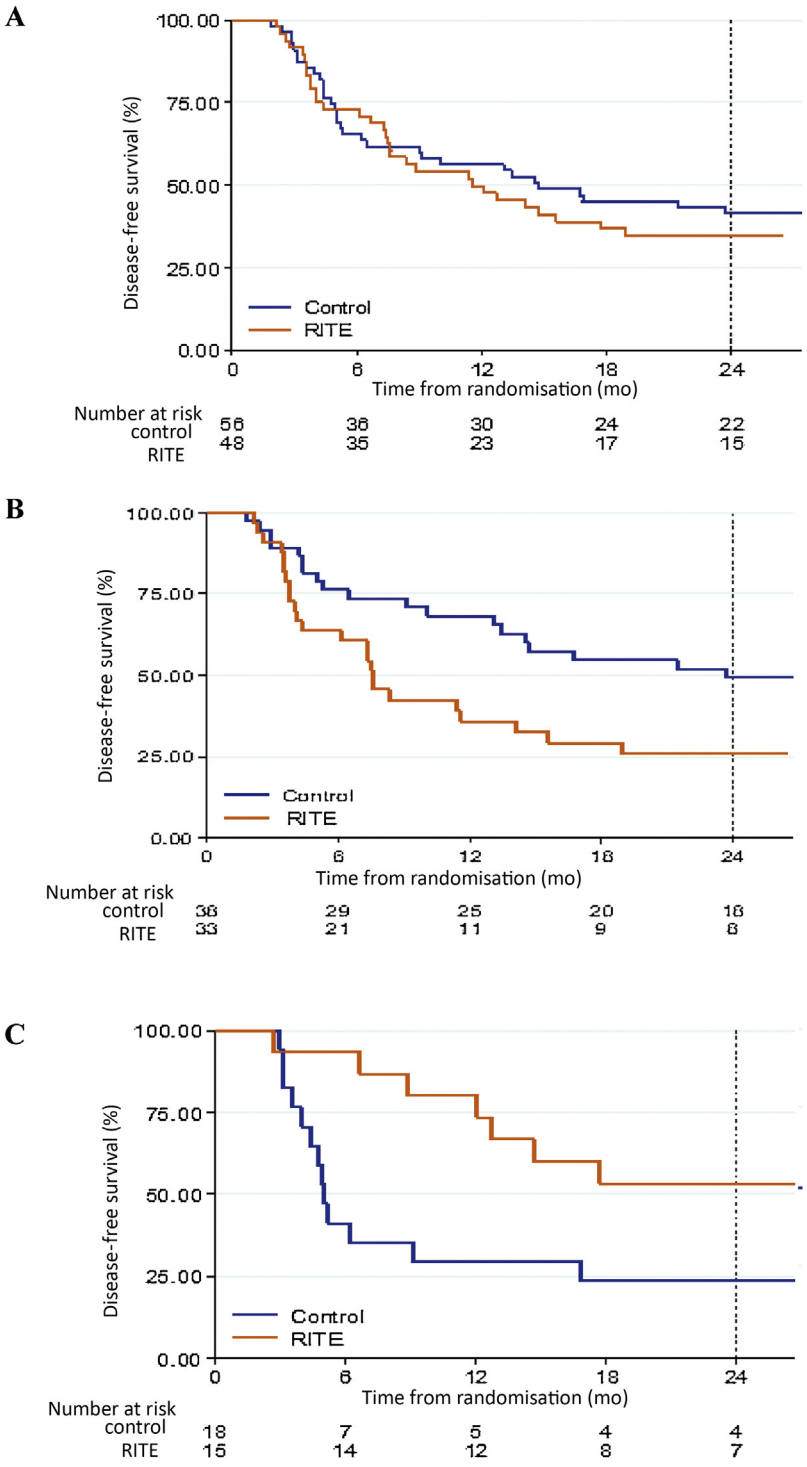

Fig. 2 – Kaplan-Meier curves for disease-free survival time: (A) All randomised patients (n = 104; hazard ratio [HR]: 1.33, 95% confidence interval [CI]: 0.84–2.10, p = 0.23); (B) Pre-planned subgroup analysis of all randomised patients with carcinoma in situ (CIS) at baseline (n = 71; HR: 2.06, 95% CI: 1.17–3.62, p = 0.01); (C) Pre-planned subgroup analysis of all randomised patients without CIS at baseline (n = 33; HR: 0.50, 95% CI: 0.22–1.17, p = 0.11). RITE = radiofrequency-induced thermo-chemotherapy effect.

One or more adverse events occurred in 84 (81%) patients (42 RITE patients vs 42 control patients). No difference in adverse events between each treatment modality was observed (Table 2). Most adverse events were grade 1–2. There were two grade ≥4 toxicities in the control arm, which was due to arthritis, and the other BCG-related sepsis resulting in death. No difference in HRQoL was observed between the two treatment arms, although RITE patients rated their health status higher than controls at 3, 6, and 9 mo of follow-up (Fig. 4).

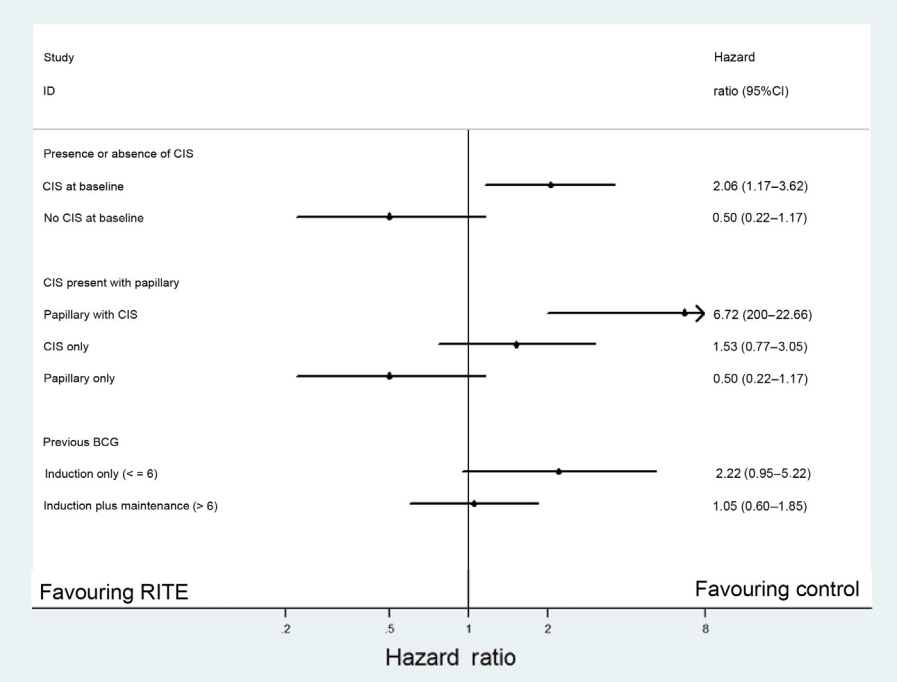

Fig. 3 – Forest plot showing hazard ratios and 95% confidence intervals for disease-free survival time for pre-planned subgroup analysis of stratification factors (carcinoma in situ [CIS] status and previous bacillus Calmette-Guérin) and extended exploratory analysis of CIS status. BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; RITE = radiofrequency-induced thermo-chemotherapy effect.

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

RITE = radiofrequency-induced thermo-chemotherapy effect; UTI = urinary tract infection.
Note: other adverse events reported in <10% of patients (RITE vs control) include stricture (6% vs 2%), nausea (8% vs 9%), vomiting (4% vs 4%), myelosuppression (4% vs 0%), skin problems (0% vs 7%), renal problems (4% vs 7%), flu symptoms (0% vs 7%), respiratory problems (8% vs 2%), gastro problems (6% vs 0%), headache (2% vs 4%), weight loss (2% vs 2%), and wound infection (2% vs 2%).

4. Discussion

The aim of the HYMN was to determine if RITE is superior to standard of care in patients with recurrence of NMIBC following BCG. HYMN was a pragmatic study, and in the absence of standard of care for this patient cohort who refused cystectomy, pre-planned treatment plan for control was determined by the local institution. HYMN remains the only RCT to test a novel therapy in this patient cohort. The trial showed no difference in DFS between RITE and standard therapy in all patients and 3-month CR rate in CIS patients at baseline. Pre-planned subgroup analysis of DFS showed that RITE was beneficial in non-CIS patients (RITE 53% vs control 24% at 24 mo); however, this was not statistically significant.

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

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

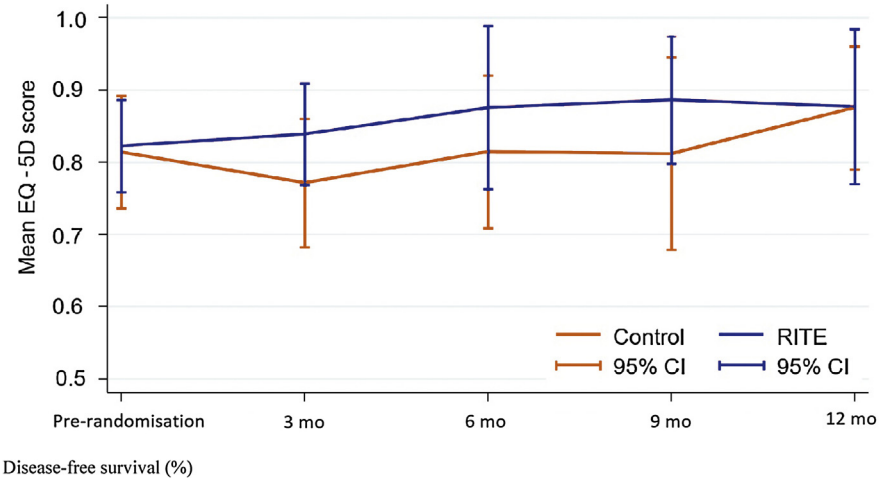

Fig. 4 – Mean EQ-5D score for radiofrequency-induced thermo-chemotherapy effect and control at baseline, 3, 6, 9, and 12 mo. CI = confidence interval; RITE = radiofrequency-induced thermo-chemotherapy effect.

Arends et al. [11] randomised 190 patients to either RITE or BCG, both with maintenance therapy. The proportion of patients with high-risk disease was 31% (57/184), and 23% (42/184) patients had CIS at randomisation. In ITT analysis, Arends et al. [11] reported a higher but nonsignificant 24-mo RFS favouring the RITE compared with BCG (78% vs 65%, $p = 0.08$) in non-CIS disease. A PPA showed a significant benefit favouring RITE compared with BCG (81% vs 65%, $p = 0.02$); however, outcome for CIS patients were not reported [11]. The non-CIS RITE-treated patients in HYMN hints towards similar results, although there were only 33 patients in this pre-planned subgroup analysis.

An important finding in HYMN is the efficacy of the control arm. A single-arm study of valrubicin in 90 cases of BCG-refractory CIS reported a 90-d CR rate of 21%, which was sufficient evidence for Food and Drug Administration FDA approval [21]. An FDA public workshop and the International Bladder Cancer Group (IBCG) recommended that a single-arm study design is sufficient to provide evidence of efficacy in the setting of recurrence following BCG therapy [22,23]. Both the FDA-American Urological Association (AUA) workshop and IBCG felt that a 6-mo CR rate of 40–50% and RFS of $\geq$25–30% at 18–24 mo in BCG refractory-CIS would be clinically meaningful [22,23]. Both RITE and control arm in HYMN achieved a 24-mo DFS of 35% and 41%, respectively, which was better than valrubicin and above the recommended threshold for clinically meaningful effect although patients in HYMN would have a better prognosis as BCG relapsing and intolerant patients were included. We would caution that a control arm remains important for the design of studies to assess the efficacy of novel agents in the setting of BCG failure NMIBC.

Study limitations include that HYMN closed early at interim analysis and did not reach its recruitment target. Patients treated with RITE had 40 mg MMC, which was consistent with the dosage used in two previous RCTs [11,19]. A single-arm study of RITE with 80 mg MMC to treat CIS reporting a DFS of 86% with a mean follow-up of 26 mo suggests that a higher MMC dose might be more effective [24]. Up to 23% patients in the control group received MMC via electromotive drug administration, which may be more effective than challenging to BCG; however, efficacy between these two treatments is similar in the randomised trial [25]. HYMN recruited a heterogenous group of BCG refectory, resistance, and intolerance as this trial commenced before the FDA-AUA recommendations [23].

5. Conclusions

DFS was similar between RITE- and control-treated patients. HYMN suggests the potential for RITE as a second-line therapy for non-CIS recurrence following BCG; however, confirmatory trials are needed. RITE-treated patients with CIS with/without papillary had lower DFS than control. RITE is well tolerated compared with control. HYMN highlights the importance of the control arm when evaluating novel therapies.

Author contributions: John D. Kelly had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kelly, Billingham, Mostafid, Griffiths.
Acquisition of data: Kelly, Feneley, Cresswell, Issa, Mostafid, Madaan, Bhatt, McGrath, Sangar, Griffiths, Page, Hodgson, Datta.
Analysis and interpretation of data: Tan, Panchal, Kelly, Billingham, Buckley.
Drafting of the manuscript: Tan, Kelly, Billingham.
Critical revision of the manuscript for important intellectual content: Tan, Panchal, Buckley, Devall, Loubière, Pope, Feneley, Cresswell, Issa, Mostafid, Madaan, Bhatt, McGrath, Sangar, Griffiths, Page, Hodgson, Datta, Billingham, Kelly.
Statistical analysis: Panchal, Buckley, Billingham.
Obtaining funding: Kelly, Billingham.
Administrative, technical, or material support: Devall, Loubière, Pope.
Supervision: Kelly, Billingham.
Other: None.

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(eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: John D Kelly is a consultant for Combat Medical outside submitted work. Wei Shen Tan has received travel support from Combat Medical and Medical Enterprises Europe B.V. Jo Cresswell reported personal fees from honorarium from ProStraken for a teaching course outside the submitted work. T.R. Leyshon Griffiths reported personal fees from Prostrakan, Combat Medical and Ipsen outside the submitted work. Lucinda Billingham reported personal fees from Astra Zeneca, Eli Lilly, Celgene, Pfizer and Roche outside the submitted work. All other authors report nothing to disclose.

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Ethical approval of studies and informed consent: The trial received ethical approval from the UK Multicentre Research Ethics Committee and regulatory approval from the UK Medicines and Healthcare Regulatory Agency in October 2009. In addition, each participating centre obtained local institutional review board approval. Written consent was obtained from all study participants.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.005.

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