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Adjuvant Intravesical Chemohyperthermia Versus Passive Chemotherapy in Patients with Intermediate-risk Non–muscle-invasive Bladder Cancer (HIVEC-II): A Phase 2, Open-label, Randomised Controlled Trial

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Abstract

Background: Adjuvant intravesical chemotherapy following tumour resection is recommended for intermediate-risk non–muscle-invasive bladder cancer (NMIBC).
Objective: To assess the efficacy and safety of adjuvant intravesical chemohyperthermia (CHT) for intermediate-risk NMIBC.
Design, setting, and participants: HIVEC-II is an open-label, phase 2 randomised controlled trial of CHT versus chemotherapy alone in patients with intermediate-risk NMIBC recruited at 15 centres between May 2014 and December 2017 (ISRCTN 23639415). Randomisation was stratified by treating hospital.
Interventions: Patients were randomly assigned (1:1) to adjuvant CHT with mitomycin C at 43°C or to room-temperature mitomycin C (control). Both treatment arms received six weekly instillations of 40 mg of mitomycin C lasting for 60 min.
Outcome measurements and statistical analysis: The primary endpoint was 24-mo disease-free survival as determined via cystoscopy and urinary cytology. Analysis was by intention to treat.

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Mitomycin C
Non–muscle-invasive bladder cancer
Randomised control trial

Results: A total of 259 patients (131 CHT vs 128 control) were randomised. At 24 mo, 42 patients (32%) in the CHT group and 49 (38%) in the control group had experienced recurrence. Disease-free survival at 24 mo was 61% (95% confidence interval [CI] 51–69%) in the CHT arm and 60% (95% CI 50–68%) in the control arm (hazard ratio [HR] 0.92, 95% CI 0.62–1.37; log-rank $p = 0.8$). Progression-free survival was higher in the control arm (HR 3.44, 95% CI 1.09–10.82; log-rank $p = 0.02$) on intention-to-treat analysis but was not significantly higher on per-protocol analysis (HR 2.87, 95% CI 0.83–9.98; log-rank $p = 0.06$). Overall survival was similar (HR 2.55, 95% CI 0.77–8.40; log-rank $p = 0.09$). Patients undergoing CHT were less likely to complete their treatment (n =75, 59% vs n = 111, 89%). Adverse events were reported by 164 patients (87 CHT vs 77 control). Major (grade III) adverse events were rare (13 CHT vs 7 control).

Conclusions: CHT cannot be recommended over chemotherapy alone for intermediate-risk NMIBC. Adverse events following CHT were of low grade and short-lived, although patients were less likely to complete their treatment.

Patient summary: The HIVEC-II trial investigated the role of heated chemotherapy instillations in the bladder for treatment of intermediate-risk non–muscle-invasive bladder cancer. We found no cancer control benefit from heated chemotherapy instillations over room-temperature chemotherapy. Adverse events following heated chemotherapy were low grade and short-lived, although these patients were less likely to complete their treatment.

1. Introduction

More than 570 000 new bladder cancer cases are diagnosed yearly, making bladder cancer the 12th most common cancer worldwide, and ranks 14th for cancer mortality [1]. The majority of bladder cancers comprise non–muscle-invasive bladder cancer (NMIBC), which has a high recurrence rate but low mortality, resulting in a high worldwide prevalence of 1.3 million cases (5-yr prevalence) and an age-standardised incidence of between <3/100 000 and >30/100 000 cases [2].

NMIBC is classified as low-, intermediate-, high-, or very high-risk disease [3]. Patients with intermediate-risk (IR) disease represent a heterogeneous cohort and include cases that do not fulfil the criteria for low- or high-risk disease [4]. Efforts to reduce disease recurrence and progression in IR NMIBC have led to the recommendation of adjuvant intravesical chemotherapy or immunotherapy following transurethral resection of bladder tumour (TURBT) [5]. It has been reported that adjuvant six weekly instillations of mitomycin C (MMC) reduces the absolute risk of recurrence by 8.2% (95% confidence interval [CI] 3.8–12.5%) and is a treatment option according to the European Association of Urology (EAU) guidelines [3,6]. In the USA, intravesical bacillus Calmette-Guérin (BCG) is often used for patients with IR NMIBC, however in the era of BCG shortages, identification of alternative therapies remains essential [4,5].

Data for checkpoint inhibitors in BCG-unresponsive NMIBC are promising, although 13% of patients suffered grade III–IV toxicity, which is rare following intravesical treatments [7]. Hence, the risk/benefit ratio for checkpoint inhibitors in patients with IR NMIBC is unfavourable and an unmet need to identify effective nontoxic treatments for this patient cohort remains.

In vitro and in vivo studies have shown that hyperthermia is effective in synergistically augmenting the efficacy of chemotherapy [8]. Previous chemohyperthermia (CHT) delivery systems use radiofrequency-induced hyperthermia, which is effective in IR and high-risk papillary NMIBC [9–11]. However, this approach has not been widely adopted because of the higher cost and patient tolerability during treatment. Alternative systems delivering CHT via convection hyperthermia are attractive and such systems are currently widely used throughout Europe, particularly in the UK, Spain, and Germany, based on retrospective published data [12,13].

HIVEC-II is a multicentre randomised controlled trial (RCT) comparing hyperthermia plus MMC to MMC alone in patients with IR NMIBC (ISRCTN 23639415). We report the efficacy and safety of CHT with a conductive hyperthermia delivery system in this patient cohort.

2. Patients and methods

2.1. Trial design

HIVEC-II is an open-label, two-arm, phase 2 RCT performed in accordance with the Declaration of Helsinki. Fifteen UK institutions participated in the trial. Appropriate ethics review boards approved the trial protocol (version 7.0) at all recruiting sites (approval reference: 13/LO/1434). The study was registered on ISRCTN (ISRCTN 23639415) and was sponsored by Queen Mary University, London. The Barts Cancer Institute Centre for Experimental Cancer Medicine (BCI CECM) clinical trials team had overall responsibility for trial management.

2.2. Patients

All patients fulfilled the EAU criteria for IR NMIBC defined according to the European Organization for Research and Treatment of Cancer risk tables (recurrence scores of 1–9) [14]. Patients with carcinoma in situ (CIS) and/or evidence of Grade 3 (G3) disease were excluded. Patients had either new or recurrent grade 1 (G1) or 2 (G2) disease and stage pTa or pT1 urothelial carcinoma. Eligible patients underwent complete TURBT of all papillary lesions before adjuvant treatment. Patients with

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pT1 disease who fulfilled the inclusion criteria had confirmation of muscle at histology; if present, repeat resection was not mandated. Full inclusion and exclusion criteria are reported in the Supplementary material.

2.3. Randomisation and blinding

Patients were randomised by computer within 10 wk of tumour board meeting using a 1:1 allocation ratio and a stratified block randomisation size of 4. Randomisation was stratified by treating hospital. The random treatment allocation sequence was generated by the BCI CECM using the top-down method. Participants and investigators were not blinded to treatment allocation. To oversee the safety and monitor the interim efficacy of the treatment arms, a data monitoring committee was appointed.

2.4. Interventions

Patients randomised to the experimental arm received six once-weekly instillations of MMC with CHT using a Combat bladder recirculating system (Combat Medical, St. Albans, UK), a hyperthermia system that delivers chemotherapy via a catheter [8]. The system monitors the temperature of circulating chemotherapy delivered via a 16 Fr Foley catheter within a closed circuit. Each instillation comprised 40 mg of MMC dissolved in 40 ml of sterile water and each treatment lasted for a minimum of 1 h (maximum of 2 h). The temperature of the drug solution was maintained at 43 ± 1°C and was regulated using an aluminium heat exchanger in accordance with the manufacturer's operational guidelines.

Patients randomised to the control arm received six once-weekly instillations of 40 mg MMC in 40 ml of sterile water for a minimum of 1 h. No dose reductions or modifications were permitted, and patients were recommended to restrict their fluid intake before treatment to minimise any drug-diluting effect.

Patients who could not tolerate treatment were permitted to delay subsequent instillation by 1 wk. Patients were withdrawn from the study if there were two consecutive treatment delays, with subsequent treatment administered at the discretion of the treating clinician. Concomitant medication deemed necessary by the treating clinician was allowed except for corticosteroids and other chemotherapy. Patients were followed with cystoscopy surveillance and urinary cytology every 3 mo for the first 12 mo and then at 18 and 24 mo.

2.5. Outcomes

The primary outcome measure was disease-free survival (DFS), defined as days between the date of randomisation and the earliest date of identification of recurrent disease (including disease progression) or death from any cause. Disease recurrence was defined as the presence of urothelial carcinoma histologically or positive urinary cytology. For patients with no recorded event, DFS was censored at the date of last follow-up when patients were alive and disease-free.

Secondary outcome measures included: recurrence rate at 3 mo, recurrence-free survival (RFS), progression-free survival (PFS), disease-specific survival (DSS), overall survival (OS), and treatment safety and tolerability. PFS was defined as days between the date of randomisation and the earliest date of identification of disease progression or date of death from any cause. Progression was defined as tumour stage ≥pT2 at TURBT. Safety and tolerability were assessed at each point of clinical contact using the National Cancer Institute Common Terminology Criteria for Adverse Events v4·03.

2.6. Statistical analyses

Analyses of safety and tolerability measures, including baseline characteristics, were based on all patients who were randomised and received at least one instillation of treatment. Analyses of efficacy outcome measures were based on the intention-to-treat principle, unless otherwise stated. Per-protocol treatment was defined as completion of all planned (six) intravesical instillations. DFS, RFS, PFS, DSS, and OS for both treatment arms were determined using the Kaplan-Meier method, from which 24-mo event rates were calculated. Hazard ratios (HRs) and 95% confidence intervals (CIs) for these endpoints were determined using Cox proportional hazards models adjusted for treating hospital, and p values were determined using the log-rank test with stratification by treating hospital. The safety and tolerability of the treatments were assessed using descriptive statistics, and incidence rates for adverse events (AEs) were reported.

The original sample size calculations suggested that 191 patients (95 control, 96 CHT) with 71 DFS events would be required. This assumed a 24-mo DFS rate of 63% for the control arm and 79% for the CHT arm (absolute difference of 16%) at a two-sided significance level of 5% and 80% power. An interim analysis was performed and identified a lower than estimated recurrence rate. Hence, in order to achieve 71 events, the sample size was increased to 259 patients (129 control, 130 CHT). This assumed a 24-mo DFS rate of 73% for the control arm and 85.2% for the CHT arm (absolute difference of 12.2%) at a two-sided significance level of 5% and 80% power.

Sample size calculations were performed using the Lakatos and Edward log-rank test procedure within the PASS statistical software package (NCSS, Kaysville, UT, USA) [15,16]. Statistical analyses were performed using STATA v16.1 (StataCorp, College Station, TX, USA). The statistical significance threshold was set at 0.05. The study complied with CONSORT guidelines.

3. Results

3.1. Patients

Between May 8, 2014 and December 21, 2017, 259 patients with IR NMIBC from 15 UK sites were randomised, of whom 252 were ultimately treated (CHT 127 and control 125; Fig. 1). It was subsequently found that one randomised patient was ineligible. Patient baseline characteristics are reported in Table 1. The median patient age was 70 yr (range 19–88) and 178 patients (71%) were male. In the overall cohort, 135 patients (54%) had a primary cancer diagnosis, 242 (96%) had pTa disease, and 213 (85%) had G2 disease. During the study, 101 DFS events were observed (49 CHT, 52 control). A total of 42 patients (32%) in the CHT arm and 49 (38%) in the control arm experienced disease recurrence by 24 mo.

3.2. Efficacy

The median follow-up in the absence of disease recurrence or death (n = 158) was 24 mo (95% CI 24–25). At 24-mo follow-up, the DFS rate was 61% (95% CI 51–69%) in the CHT arm and 60% (95% CI 50–68%) in the control arm (HR 0.92, 95% CI 0.62–1.37; log-rank p = 0.8; Fig. 2). Exploratory analyses with stratification by NMIBC risk factors such as recurrent disease, tumour grade, tumour multiplicity, and tumour size also revealed similar efficacy between the treatment arms (Fig. 3).

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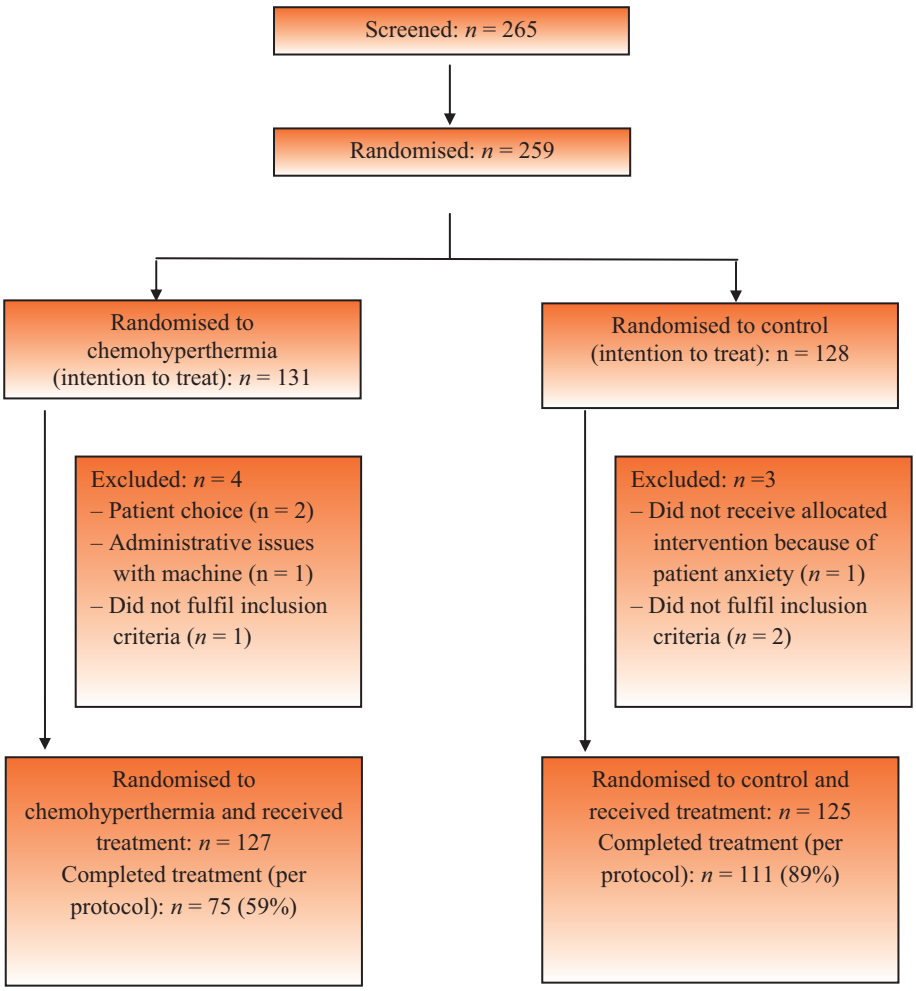

Fig. 1 – CONSORT diagram for the HIVEC-II trial.

On per-protocol analysis, the 24-mo DFS rate was better in the CHT arm (65%, 95% CI 52–75%) than in the control arm (59%, 95% CI 48–68%), although the difference did not reach statistical significance (HR 0.75, 95% CI 0.46–1.22; log-rank p = 0.4; Supplementary Fig. 1). A total of seven patients (5 control, 2 CHT) developed CIS at 3–9 mo during follow-up, of whom six had a history of G2 pTa disease and one patient had G2 pT1.

Following adjuvant treatment, ten patients (8%) in the CHT arm and 15 (12%) in the control arm experienced disease recurrence at 3 mo (adds ratio 0.61, 95% CI 0.26–1.43; p = 0.3). The 3-mo DFS rate was 99% (95% CI 94–100%) for the CHT arm and 98% (95% CI 94–100%) for the control arm. A total of four patients, all with initial G2 pTa histology, who were treated with CHT experienced disease progression. A further eight patients in the CHT arm and four in the control arm died during follow-up without disease progression. Patients treated with CHT were significantly more likely to experience disease progression in comparison to the control treatment (HR 3.44, 95% CI 1.09–10.8; log-rank p = 0.02; Fig. 4). However, on per-protocol analysis, PFS was similar between the treatment arms (HR 2.87, 95% CI 0.83–9.98; log-rank p = 0.06; Supplementary Fig. 2). One patient who was treated with CHT developed metastatic disease. An exploratory sensitivity analysis for which T1 tumours were excluded suggested similar outcomes. OS was comparable between the treatment arms (HR 2.55, 95% CI 0.77–8.40; log-rank p = 0.09).

3.3. *AEs and treatment tolerability*

Patients treated with CHT were less likely to complete their treatment according to the protocol when compared to the control group (75 [59%] CHT, 111 [89%] control). The most common reasons for not completing all planned instillations in the CHT arm included equipment issues (n = 19), bladder spasm/urgency (n = 10), and allergic reaction/rash (n = 9). In the control arm, reasons for noncompliance with the treatment protocol included: allergic reaction/ rash (n = 5), other non–treatment-related causes (n = 3), and bladder spasm/urgency (n = 2; Supplementary Table 1). A total of 632 AEs were observed, 341 in the CHT arm and 291 in the control arm, of which 212 and 145, respectively were treatment-related. Eighty-seven patients in the CHT arm and 77 patients in the control arm experienced at least one AE. Major (grade ≥III) AEs were rare, with just 20

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Table 1 – Baseline characteristics of patients who were randomised and received at least one instillation of treatment

Parameter	Control (n = 125)	Chemohyperthermia (n = 127)
Male, n (%)	81 (65)	97 (76)
Median age, yr (interquartile range)	69 (62–75)	70 (62–76)
Ethnicity, n (%)		
White	124 (99)	118 (93)
Black	1 (1)	2 (2)
Asian	0	5 (4)
Other	0	2 (2)
Diagnosis type, n (%)		
New diagnosis	67 (54)	68 (54)
Recurrence	57 (46)	59 (46)
Not applicable[a]	1 (1)	0
Tumour stage, n (%)		
Ta	119 (95)	123 (97)
T1	5 (4)	4 (3)
Not applicable[a]	1 (1)	0
Tumour grade, n (%)		
Grade 1	23 (18)	15 (12)
Grade 2	101 (81)	112 (88)
Not applicable[a]	1 (1)	0
Number of tumours, n (%)		
≤2 tumours	74 (59)	85 (67)
>2 tumours	51 (41)	42 (33)
Tumour size, n (%)		
≤3 cm	76 (61)	84 (66)
>3 cm	46 (37)	40 (31)
Unknown	3 (2)	3 (2)

[a] One patient was randomised despite being ineligible for study inclusion. As a result, this patient had values of "Not applicable" for diagnosis type, tumour stage, and tumour grade.

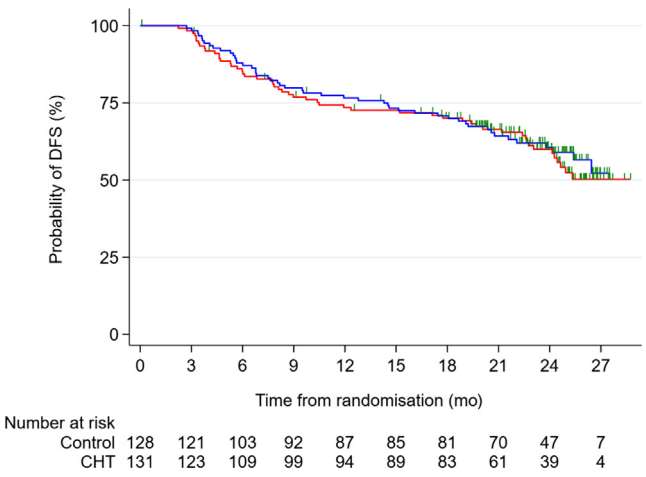

Fig. 2 – Kaplan-Meier curves for disease-free survival (DFS) in the intention-to-treat analysis for the control (red line) and chemohyperthermia (CHT; blue line) groups (hazard ratio 0.92, 95% confidence interval 0.62–1.37; log-rank p = 0.8). "|" indicates one hash mark at each censoring time, regardless of the number censored at that time. Analysis was performed using the Cox proportional hazards model and log-rank test, both adjusted for treating hospital.

instances reported (13 CHT, 7 control) involving 16 patients (11 CHT, 5 control). There were no grade IV or V treatment-related AEs.

The most common treatment-related AEs included urinary tract pain (27 CHT, 22 control), urinary frequency (22 CHT, 15 control), haematuria (25 CHT, 5 control), urinary urgency (16 CHT, 11 control), and rash (12 CHT, 13 control; Table 2). Two patients in the CHT arm reported a serious AE: one was an anaphylactic reaction (not treatment-related) and the other was haematuria (treatment-related).

4. Discussion

The HIVEC-II trial was designed to test the hypothesis that CHT is superior to and resulted in better DFS than with standard MMC in patients with IR NMIBC. We report no significant difference in DFS between the arms. We also observed that progression was more common among patients treated with CHT in comparison to patients undergoing the control treatment.

HIVEC-II is the first published RCT to use conductive hyperthermia for bladder cancer. There are reports that the alternative radiofrequency-induced thermotherapy effect (RITE), which uses radiofrequency to heat the bladder wall lining, is effective [10,11]. In an RCT of 83 patients with IR and high-risk NMIBC, RITE resulted in a significantly higher RFS (60% vs 20%; $p < 0.001$) in comparison to MMC at median follow-up of 91 mo [11]. Another RCT of 190 BCG-naïve patients with IR or high-risk NMIBC reported that patients with papillary-only disease treated with RITE had significantly better RFS compared to those treated with BCG (81.8% vs 64.8%; $p = 0.02$) following per-protocol analysis [10]. However, in the BCG failure setting, the HYMN trial closed early at interim analysis as RITE-treated patients with CIS with/without papillary disease had a lower DFS rate in comparison to the control group [9].

At the outset of the HIVEC-II trial, the role of hyperthermia was supported by in vitro studies suggesting synergy and non-RCTs indicating improvements in oncological outcomes [8]. In vitro studies revealed that hyperthermia promotes cancer cell death by denaturing cytoplasmic structures and proteins, enhancing cell membrane permeability, and activating heat shock proteins, which stimulates an adaptive T-cell response [17–20]. RCTs showed that RITE use as discussed above was efficacious [10,11]. A further rationale for this trial was that conductive hyperthermia for delivery of intraperitoneal chemotherapy is the standard of care for selected patients with colorectal cancer and peritoneal metastasis in combination with cytoreductive surgery [21,22].

The results from HIVEC-II do not support the use of CHT for IR NMIBC. The 2-yr DFS rates were similar between the CHT and control arms (61% vs 60%) and although the trial was powered to detect an absolute difference in 24-mo DFS rate of 12.2%, it is unlikely that a larger sample size would alter our conclusions. We recommend that patients with IR NMIBC who experience disease recurrence following MMC should receive maintenance BCG for a minimum of 1 yr [4,23].

Repeated periods of BCG shortage over the past 5 yr have led clinicians to seek alternative treatments, particularly in Europe. In some institutions, CHT use has become the standard of care either as monotherapy or in combination with BCG therapy [13,24]. Pooled data from meta-analysis suggest that CHT has similar efficacy to BCG [25]. However,

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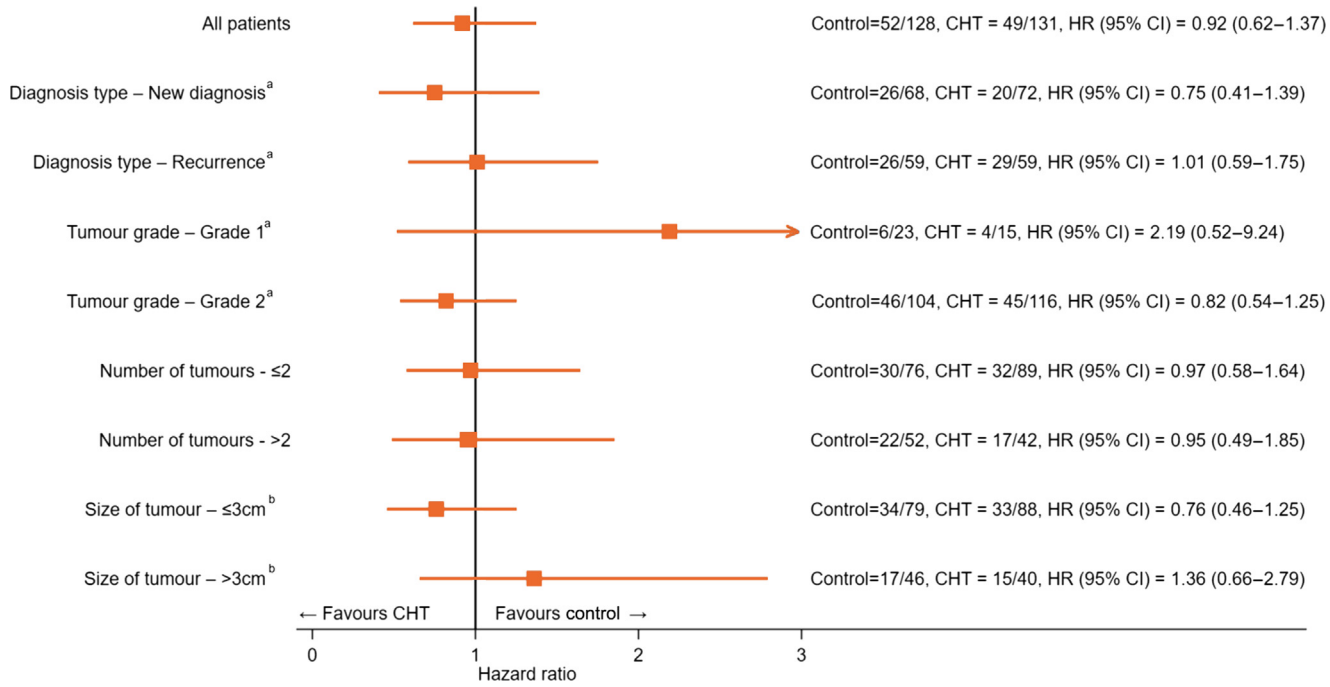

Fig. 3 – Forest plot reporting hazard ratios (HRs) and 95% confidence intervals (CIs) for disease-free survival according to intermediate-risk non–muscle-invasive bladder cancer risk factors in the intention-to-treat analysis. The solid black line represents a HR of 1. Analyses were performed using Cox proportional hazards models adjusted for treating hospital. CHT = chemohyperthermia. [a]One patient was randomised despite being ineligible for study inclusion and was therefore excluded from the analyses denoted with this annotation in the forest plot. [b]Six patients had an unknown tumour size that could not be estimated and were therefore excluded from the analyses denoted with this annotation in the forest plot.

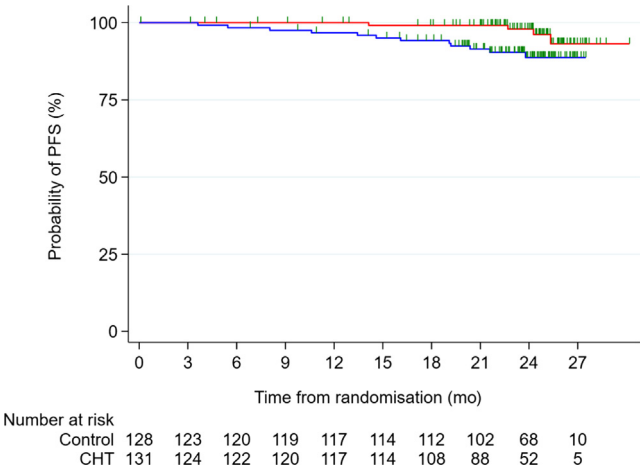

Fig. 4 – Kaplan-Meier curves for progression-free survival (PFS) in the intention-to-treat analysis for the control (red line) and chemohyperthermia (CHT; blue line) groups (hazard ratio 3.44, 95% confidence interval 1.09–10.82; log-rank $p = 0.02$). "|" indicates one hash mark at each censoring time, regardless of the number censored at that time. Analysis was performed using the Cox proportional hazards model and log-rank test, both adjusted for treating hospital.

Table 2 – Treatment-related adverse events reported for at least 3% of patients who were randomised and received at least one instillation of treatment[a]

Adverse event	All grades		Major adverse event (grade III)	
	Control (*n*)	CHT (*n*)	Control (*n*)	CHT (*n*)
Urinary tract pain	22	27	0	1
Urinary frequency	15	22	0	0
Haematuria	5	25	0	1
Urinary urgency	11	16	0	0
Rash	13	12	1	0
Pain	6	10	0	0
Urinary tract infection	8	6	0	0
Fatigue	4	7	0	0
Nocturia	4	5	0	0
Urinary incontinence	2	5	0	0

CHT = chemohyperthermia.
[a] No grade ≥IV treatment-related adverse events were observed. The worst toxicity for each patient for each adverse event term has been included in this summary table.

our current results suggest that CHT has comparable efficacy to passive MMC, which is considered to be less effective than BCG [26,27].

Our results have several caveats. HIVEC-II was powered as a superiority trial to detect an absolute difference in 24-mo DFS of 12.2% favouring CHT. Hence, a difference smaller than this may exist between the treatment arms, although we would argue that any benefit from CHT would be marginal. Our cohort comprised patients with IR NMIBC according to a previous version of the EAU guidelines that included G2 pT1 disease [14]. However, this only accounted for nine patients (4%) and the majority of the cohort had new or recurrent G1–2 pTa NMIBC. While the MMC dose was similar for the two groups (40 mg of MMC in 40 ml

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of water, 1 mg/ ml), the drug concentration differed because of the requirement to prime the tubing of the Combat system, which requires 60 ml. CHT treatment tolerability may be better than reported (59% vs 89%) owing to equipment-related issues (n = 19), although this would not have an impact on the primary endpoint of the trial. Finally, we did not capture the use of perioperative chemotherapy after TURBT.

5. Conclusions

In the HIVEC-II trial, patients with IR NMIBC treated with six weekly intravesical CHT with MMC did not derive an oncological benefit in comparison to room-temperature MMC. CHT cannot be recommended over chemotherapy alone for IR NMIBC. AEs were common in both arms but were short-lived and mild. Patients receiving CHT were less likely to complete their treatment.

Author contributions: Wei Shen Tan 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.
Acquisition of data: Tan, Prendergast, Ackerman, Yogeswaran, Cresswell, Mariappan, Phull, Hunter-Campbell, Lazarowicz, Mishra, Rane, Davies, Warburton, Cooke, Mostafid, Wilby, Mills, Issa, Kelly.
Analysis and interpretation of data: Tan, Prendergast, Ackerman, Yogeswaran, Cresswell, Mariappan, Phull, Hunter-Campbell, Lazarowicz, Mishra, Rane, Davies, Warburton, Cooke, Mostafid, Wilby, Mills, Issa, Kelly.
Drafting of the manuscript: Tan, Kelly
Critical revision of the manuscript for important intellectual content: Tan, Prendergast, Ackerman, Yogeswaran, Cresswell, Mariappan, Phull, Hunter-Campbell, Lazarowicz, Mishra, Rane, Davies, Warburton, Cooke, Mostafid, Wilby, Mills, Issa, Kelly.
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