Intravesical Chemohyperthermia vs. Bacillus Calmette-Guerin Instillation for Intermediate- and High-Risk Non-muscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis

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Background: The efficacy of intravesical chemotherapy maintenance for patients with non-muscle invasive bladder cancer (NMIBC) is inferior compared to intravesical bacillus Calmette–Guerin (BCG). How intravesical chemohyperthermia (CHT) compares with BCG is under investigation.

Objective: To compare the oncological outcomes and safety profile between intravesical CHT and BCG treatment for intermediate- and high-risk NMIBC.

Methods: We performed a systematic review and meta-analysis of clinical studies comparing CHT with BCG for intermediate- and high-risk NMIBC patients. A comprehensive literature search on OVID MEDLINE, EMBASE, and Cochrane Library was conducted. Risk of bias was assessed by the Cochrane RoB tool and ROBINS-I. Certainty of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.
INTRODUCTION

Bladder cancer is the 11th most common cancer worldwide, and more than 75% of the patients present with non-muscle invasive bladder cancer (NMIBC) (1, 2). Transurethral resection of bladder tumour (TURBT) is a potentially curative surgery, yet the oncological control of NMIBC is unsatisfactory with a one-year recurrence rate of up to 31%, and a five-year recurrence rate of up to 78% (3, 4).

NMIBC is classified into low-risk, intermediate-risk, and high-risk disease based on its clinical and pathological factors (5, 6). For intermediate- and high-risk NMIBC, intravesical Bacillus Calmette–Guerin (BCG) therapy has been shown to be effective in reducing disease recurrence and progression (7). On the other hand, intravesical BCG therapy is associated with local and systemic toxicities, and it may not be well-tolerated throughout the whole treatment course (8, 9). Moreover, BCG shortage is a significant global problem (10). There is an urgent need to seek for an alternative treatment that is at least equally effective, and with better tolerability and secured availability for patients with intermediate- and high-risk NMIBC (11).

Intravesical maintenance chemotherapy has long been investigated in patients with NMIBC. Although it was associated with a lower rate of adverse events, its treatment efficacy has been proven to be inferior to intravesical maintenance BCG therapy (12, 13). In recent years, there has been increasing use of adjuvant intravesical chemohyperthermia in NMIBC patients. By increasing the temperature of chemotherapy (Combat System) or the bladder wall (Synergo system) to 42–43°C degrees, may enhance its drug absorption and cytotoxic effects (14). Although intravesical CHT is a promising treatment, its distinction of treatment outcome comparing with BCG is not well-known. In this systematic review, we aim to investigate the treatment efficacy and adverse events of intravesical CHT vs. BCG in patients with intermediate- and high-risk NMIBC.

RESULTS

A total of 2,375 articles were identified and five studies were finally included. Among them, four randomised trials comprising 327 patients (CHT group: 156 patients; BCG group: 171 patients) were included in the meta-analysis. There were no significant differences in the 24–36 months recurrence rates (CHT: 29.5%, BCG: 37.4%; RR: 0.83, 95% CI 0.61–1.13; moderate certainty of evidence) and the 24–36 months progression rates (CHT: 4.4%, BCG: 7.6%, RR = 0.62, 95% CI 0.26–1.49; low certainty of evidence). There were also no significant differences in grade 1–2 adverse events (CHT group: 59.9%, BCG group 54.5%; RR = 1.10, 95% CI 0.93–1.30; moderate certainty of evidence) and grade 3 or above adverse events (CHT group: 23.2%, BCG group 22.5%; RR = 0.99, 95% CI 0.69–1.43; low certainty of evidence).

CONCLUSIONS

Intravesical CHT had equivalent oncological outcomes and similar safety profile when compared to BCG maintenance therapy for patients with intermediate- and high-risk NMIBC. CHT is a possible alternative treatment in the times of BCG shortage.

Keywords: bladder cancer, TURBT (trans-urethral resection of bladder tumour), BCG–Bacillus Calmette-Guérin vaccine, chemohyperthermia, meta-analysis

METHODS AND MATERIALS

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15). The study protocol was registered on the international prospective register of systematic reviews (PROSPERO) (Registration number: CRD42020223277).

LITERATURE SEARCH

We conducted a comprehensive literature search on OVID MEDLINE, EMBASE, and Cochrane Central Controlled Register of Trials (CENTRAL), using Medical Subject Headings (MeSH) terms and keywords related to “Bladder cancer,” “Bacillus Calmette-Guérin,” and “Chemohyperthermia.” The search was performed from database inception up to the 1st of September 2020. All full-text publications, conference abstracts and proceedings in English language were included. Reference lists of the included studies were sought for additional articles. The search strategy is presented in Supplementary Material.

SELECTION CRITERIA

Randomised controlled trials (RCTs) and observational studies comparing the use of CHT and BCG instillation in intermediate- or high-risk NMIBC patients post-TURBT were included. Only human studies were included and there was no limit to the type of CHT device used. Editorials, commentaries, reviews, case reports, case series and single arm studies were excluded. Studies comparing the use of CHT and normothermic chemotherapy were also excluded.

SCREENING AND DATA EXTRACTION

All identified articles were initially screened by two independent reviewers by title and abstract. Conflicts were resolved by a third senior author. Full texts of potentially eligible studies were then retrieved for further screening in the same manner.
Finally, a standardised and piloted data extraction form was devised to capture data such as baseline characteristics of studies, details of intervention and control, along with outcomes of interest. The corresponding authors of each study with missing data were contacted in order to retrieve any missing data.

Data Synthesis and Statistical Analysis
The primary outcomes of our study included recurrence and progression rates at 24–36 months. Secondary outcomes included recurrence-free survival (RFS), progression-free survival (PFS), grade 1–2 and grade 3 or above adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria (16). Meta-analyses were only performed when there were two or more RCTs reporting the same outcome under the same definition. Rates of recurrence, progression and AEs were analysed as dichotomous events using the Mantel-Haenszel method, and were reported as risk ratios (RR), 95% CIs and p-values. For RFS and PFS, hazard ratios (HR) and 95% Confidence Interval (95% CI) derived by the Cox Proportional hazards model were pooled using the inverse variance method, and were reported as HRs, 95% CIs and p-value. In studies where Hazard Ratios were not reported, HRs are estimated using validated methods outlined by Tierney et al. (17) as recommended by the Cochrane Collaboration (18). The random effects (RE) model was used to take into account substantial heterogeneity where identified, otherwise, the fixed effects (FE) model was used. Heterogeneity was assessed using the I^2 statistic, and substantial heterogeneity was defined as an I^2 value >50% or a Chi^2 p-value <0.10. Owing to the potential source of heterogeneity originating from the types of CHT used, subgroup differences were tested between the major types of CHT used, and was defined as a Chi^2 p-value <0.10. Planned sensitivity analyses were also performed on patients without BCG failure and without carcinoma in situ (CIS) diseases. All data-analyses were performed using Review Manager v.5.4. Results from non-randomised studies were summarised narratively. Risk of bias of RCTs was assessed using the Risk of Bias 2.0 tool as recommended by the Cochrane Collaboration (19, 20). Risk of bias in non-randomised studies were assessed using the non-randomised studies–of–interventions (ROBINS-I) tool (21).

Summary of findings for all outcomes, along with the certainty of evidence which was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (22) were tabulated using the GRADEpro tool (23).

RESULTS

Literature Search Results
The PRISMA flow diagram is shown in Figure 1. A total of 2,956 records were identified upon the literature search. No additional records were identified during screening of reference lists of included articles. 2,361 abstracts remained after removal of duplicates. A total of 2,277 articles were excluded upon initial screening, and 79 studies were further excluded upon full-text screening. Finally, four RCTs (24–27) were included for meta-analysis, and one observational retrospective study (28) was retrieved and included for qualitative synthesis. Two studies included both intermediate- and high-risk NMIBC patients (24, 25), and the other three studies included high-risk NMIBC patients only (26–28). All studies were non-inferiority trials and did not specifically focus on primary or recurrent cases. All five studies had similar follow-up durations of 24–36 months. The study information of the five studies is shown in Table 1. The risk of bias assessment and the GRADE summary of finding profiles are included in Supplementary Material.

Study Outcomes

Recurrence Rate at 24–36 Months
Four RCTs with 327 patients were included (24–27). There was no significant difference between the two groups (RR_FE 0.80, 95% CI 0.59–1.08; moderate certainty of evidence) (Figure 2). Upon subgroup analysis, no differences were found between the use of conductive hyperthermia and radiofrequency-induced thermochemotherapeutic effect (RITE). Sensitivity analysis after excluding BCG failure patients from the HYMN study shows CHT has a significantly lower recurrence rate when compared to BCG group (RR_FE: 0.64, 95% CI 0.42–0.98, p = 0.04) (Supplementary Material). Of note, in the RCT by Sousa et al. (26), the conductive CHT group had significantly lower rate of recurrence when compared to the BCG group (20.5% vs. 38.2%, p < 0.02). However, a retrospective matched cohort study by Ekin et al. (28) found a significantly higher recurrence rate in patients receiving conductive CHT compared to those who received BCG (35.9% vs. 20.5%, p < 0.05).

Progression Rate at 24–36 Months
Four RCTs with 327 patients were included (24–27). There was no significant difference between the two groups (RR_FE 0.60, 95% CI 0.26–1.41, p = 0.24; low certainty of evidence) (Figure 3). Upon subgroup analysis, no differences were found between the use of conductive hyperthermia and RITE was found upon subgroup analysis. When excluding patients with BCG failure, progression rate was also found to be similar in CHT patients when compared to BCG patients (RR_FE 0.38, 95% CI 0.12–1.22, p = 0.10). Of note, in the RCT performed by Sousa et al. (26), T1 progression and T2 progression were significantly reduced in the conductive system CHT group when compared to the BCG group (p < 0.05 and p < 0.01 respectively). However, in a retrospective matched cohort study performed by Ekin et al. (28) the use of conductive CHT was associated with significantly higher progression rate when compared to BCG (15.4% vs. 7.7%, p < 0.05).

Recurrence-Free Survival
Three RCTs were included in the meta-analysis (24, 25, 27). In terms of RFS, no significant difference was noted between the CHT group and the BCG group (HR_FE 0.81, 95% CI 0.42–1.56, p = 0.53; very low certainty of evidence) (Supplementary Material). However, there was significant heterogeneity amongst the included studies (I^2 = 68%, p = 0.04).
Our subgroup analysis suggested that this heterogeneity did not originate from the type of CHT systems used; no differences were found between the conductive CHT group and the SRITE group. When performing a sensitivity analysis to exclude patients with BCG failure (i.e., patients from the HYMN trial), RFS is found to be significantly better in CHT patients than BCG patients ($HR_{RE} 0.57$, 95% CI 0.33–0.98) with no significant heterogeneity ($I^2 = 0\%$, $p = 0.91$) (Supplementary Material), suggesting the potential source of heterogeneity to originate from BCG failure patients. Of note, in a retrospective study by Ekin et al. (28), it was found that the use of conductive CHT was associated with significantly worsened RFS when compared to BCG instillation ($HR 4.18$, 95% CI 1.37–12.71, $p = 0.012$). However, when performing sensitivity analysis by excluding the HYMN study, where only patients with BCG failures were considered, the remaining two studies show that CHT group has a better RFS when compared to the BCG group ($HR_{FE} 0.52$, 95% CI 0.29–0.93; Supplementary Figure 1). However, when excluding patients with CIS disease, the RFS is both groups remained similar ($HR_{FE} 0.72$, 95% CI 0.48–1.09) (Supplementary Material).

**Progression-Free Survival**

Two RCTs were included in the meta-analysis (24, 27). In terms of PFS, there was no significant difference between the CHT group and the BCG group ($HR_{RE} 0.92$, 95% CI 0.25–3.40; very low certainty of evidence) (Supplementary Material). However, there was significant heterogeneity amongst the included studies ($I^2 = 73\%$, $p = 0.06$). The heterogeneity might originate from the different types of CHT device being used as evident by the test for subgroup differences ($p = 0.06$), but this should be interpreted with caution due to the limited number of studies being included. Furthermore, the study by Tan et al. also included BCG failure and CIS patients, which may have lead to a significantly lower PFS rate. In the retrospective study by Ekin et al. (28), no significant difference was found between the CHT group and the BCG group ($HR 1.72$, 95% CI 0.28–10.36, $p = 0.550$).
| Study (year) | Country of study | Study design | Number of centres | Recruitment period | Duration of follow up (months) | Inclusion and exclusion criteria | Number of patients (Intervention/control) | Age (intervention/control) | Sex (M/F) | Device used | Regime for CHT | Regime for BCG |
|--------------|------------------|--------------|-------------------|-------------------|-------------------------------|--------------------------------|----------------------------------|--------------------------|-----------|-------------|----------------|----------------|
| Sousa 2020   | Spain            | RCT          | 2                 | Between March 2015 and June 2019 | Mean: 38 | 1. Histological confirmed previous UCC  
2. NMIBC following recurrence of G1-3 pTa or G1-2 pT1  
3. Tumour number ≤ 6 number of tumours  
4. Aged ≥ 18 years  
5. No solid tumour, muscle infiltrating aspect or CIS suspicious, positive cytology and recurrence of previous T1G3 or CIS tumours in the last 12 months | 16/17 | Mean ± SD: 71 ± 3.2/69 ± 2.7 | 27/6 | Combat BRS system | Weekly for 8 weeks, 80 mg MMC |
| Guerrero-Ramos 2020 | Spain | RCT | 1 | NR | Median: 24.8 | 1. NMIBC  
2. No CIS  
3. No intolerance or contraindication for receiving BCG or MMC | 24/24 | Entire group mean: 73 | 42/6 | Combat BRS system | Weekly for 6 weeks; follow by monthly for 6 months, 40 mg MMC |
| Ekin 2015 | Turkey | Retrospective cohort study | 2 | Between January 2004 and January 2014 | Median(IQR): 33(24–39) | 1. High-risk of NMIBC treated with intravesical C-HT or BCG instillation  
2. Performed second-TUR  
3. Not treated with reduced dose of BCG,  
4. No bladder diverticulum > 1 cm  
5. No histopathology non-urothelial carcinoma  
6. No concomitant urothelial carcinoma in the urethra or upper urinary tract  
7. No low bladder capacity (< 150 mL)  
8. No high post-voided residual urine (> 100 mL) | 39/39 | Mean ± SD (range): 68.05 ± 9.29 (47–84)/ 68.02 ± 8.42 (48–82) | 73/5 | Elmedical technologies BWT | Weekly for 6 weeks; Also 3 weekly instillations at month 3 and month 6. 40 mg MMC |

(Continued)
| Study (year) | Country of study | Study design | Number of centres | Recruitment period | Duration of follow up (months) | Inclusion and exclusion criteria | Number of patients (Intervention/control) | Age (Intervention/control) | Sex (M/F) | Device used | Regime for CHT | Regime for BCG |
|-------------|------------------|--------------|-------------------|-------------------|-------------------------------|---------------------------------|----------------------------------------|---------------------------|-----------|-------------|----------------|----------------|
| Arends 2016 | Israel Italy, the Netherlands Austria, France, Belgium | RCT 11 | Between 18 July 2002 and 25 December 2011 | Median(range): 25.6 (0.0–34.0) | 1. pT1 or grade3 UCC and/or CIS or multifocal (six or more) pTa lesions and/or multiple (three or more) recurrences of pTa lesions in the last 24 months 2. WHO performance status ≤2 3. Life expectancy >24 months 4. No histopathology non-urothelial carcinoma (basal cell carcinoma excluded) 5. No UCC involving the urethra or upper urinary tract 6. No previous history of UCC stage T2 or higher 7. No intravesical MMC treatments during the previous 12 months 8. No previous BCG therapy <48 mo 9. No previous pelvic radiotherapy, systemic chemotherapy or partial cystectomy 10. No bladder diverticulum > 1 cm, residual urine > 100 ml, bladder volume < 150 ml, urinary incontinence, urethral stricture impeding 20F catheterization 11. No persistent haematuria 12. No active intractable or uncontrollable UTI, active tuberculosis or BCG infection | 89/95 | Mean ± SD: 65.2 ± 10.67/67.4 ± 10.08 | 154/30 | Synergo system | Weekly for 6 weeks, followed by 6 maintenance sessions at 6-wk intervals during the rest of year 1. Two 30-min treatments with 20 mg MMC | Six weekly induction sessions and three weekly repeated maintenance sessions at months 3, 6, and 12 |
| Study (year) | Country of study | Study design | Number of centres | Recruitment period | Duration of follow up (months) | Inclusion and exclusion criteria | Number of patients (Intervention/control) | Age (intervention/control) | Sex (M/F) | Device used | Regime for CHT | Regime for BCG |
|--------------|------------------|--------------|-------------------|-------------------|-------------------------------|--------------------------------|----------------------------------------|--------------------------------------|-----------|-------------|----------------|----------------|
| Tan 2019     | UK               | RCT          | 14                | Between May 2010 and July 2013 | Median:36                    | 1. Recurrence of intermediate- or high-risk NMIBC following induction/maintenance BCG 2. Having complete TUR of papillary lesions 3. pT1 disease underwent re-resection to confirm the absence MIBC 4. Age ≥ 18 years 5. WHO performance status ≤ 4 6. Unfit or unwilling to have radical cystectomy 7. Imaging showed no upper tract disease ≤12 mo. 8. Haematological and biochemical blood tests were within normal limits 9. No non-urothelial carcinoma 10. No low-grade NMIBC recurrence | 48/56 | Median (IQR) 77 (72-82)/76 (67-81) | 78/26 | Synergo system | Weekly for 6 weeksPatients 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). Two 30-min cycles, each with 20 mg MMC | Six consecutive weekly instillations followed by maintenance therapy (three consecutive weekly instillations at 3, 6, 12, 18, and 24 mo) | |
### Adverse Events

Four RCTs with 368 patients were included (24–27). For Grade 1-2 AEs, there was no significant difference between the CHT group and the BCG group (RRFE 1.11, 95% CI 0.93–1.32, p = 0.26; moderate certainty of evidence), and no significant heterogeneity was detected ($I^2 = 0\%$, $p = 0.96$) (Figure 4). For grade 3 of above AEs, there was also no significant difference between the CHT group and the BCG group (RR 1.02FE, 95% CI 0.71–1.47, $p = 0.92$; low certainty of evidence), and no significant heterogeneity was detected ($I^2 = 0\%$, $p = 0.69$) (Figure 5).

### DISCUSSION

Intravesical BCG therapy is a standard treatment for patients with intermediate- and high-risk NMIBC following TURBT (5). However, it is not without limitations. First, more than half of the patients might develop local and systemic toxicities, such as bacterial/chemical cystitis, frequency, haematuria, allergic reactions and BCG sepsis (8, 9, 29). While a minimum duration of 1-year treatment course is recommended, about half of the patients would withdraw from treatment prior to completion of BCG therapy (30, 31). Second, the supply of BCG has been unsteady in the past decade. Globally, there were only a few manufacturers of BCG, and the production of BCG is generally limited by the slow growth of mycobacteria (10). Therefore, it is imperative for researchers to look for alternative treatments for patients with intermediate- and high-risk NMIBC.

Intravesical chemotherapy has been proven to be less effective than BCG (12, 13). However, the development of device-assisted technology could optimise the efficacy of chemotherapy and potentially maintaining its safety and tolerability. In particular, CHT has gained significant traction within the urological community leading to a steadily increasing use in the past decade. The cytotoxicity of chemotherapy can be accentuated when its temperature reaches 42 to 43 degrees (32). Several mechanisms of action of hyperthermia has been postulated to synergistically enhance the efficacy of intravesical chemotherapy. First, hyperthermia alone could cause the denaturation of cytoplasmic structures and enzymatic proteins, thus inducing cell death by apoptosis and necrosis (32–34). Second, temperature elevation could enhance the permeability of cell membrane and improve drug absorption (35, 36). Third, heat shock proteins could be released upon hyperthermia, thus stimulating an adaptive T cell response to induce both innate and adaptive immune system. Tumour chemosensitization may also be achieved via the heat shock proteins-mediated pathways (37, 38).

Delivery of hyperthermia can be achieved by two main methods, namely conductive hyperthermic chemotherapy (Combat system) and RITE (Synergo). For conductive hyperthermic chemotherapy, the chemotherapy solution was heated externally and recirculated to the bladder at a constant temperature. For RITE, microwave radiation was delivered to the bladder wall at a frequency of 915 MHz. Without the need of conductive delivery of energy, it has a potential benefit to penetrate low-conductive tissues (39).
In our study, we compared between intravesical CHT and BCG in patients with intermediate- and high-risk NMIBC. Our results showed that CHT could achieve an equivalent oncological outcome as BCG therapy in terms of recurrence and progression rates at 24–36 months. Our sensitivity analysis would suggest that efficacy was generally consistent across the two different types of CHT technologies, the Combat/Unithermia system and the Synergo system. One study population was, however, too small to allow statistically powered comparison between the CHT devices. Intravesical CHT is a reasonable treatment option for intermediate- and high-risk NMIBC given its similar efficacy to BCG. Although the use of CHT was associated with additional costs, a more steady supply can be assumed without the worry of BCG shortage. On the other hand, our meta-analysis showed that the rates of grade 1–2, and grade 3 or above AEs were similar between intravesical CHT and BCG. In other words, based on the current evidence, we cannot assume that CHT is safer or more tolerable than BCG therapy. A realistic expectation should be given when we counsel patients on the usage of CHT.

In many parts of the world, intravesical maintenance chemotherapy is the mainstay of treatment for intermediate-risk, and even high-risk NMIBC (40). A recent meta-analysis...
showed that intravesical CHT was associated with a lower recurrence rate when compared to normothermic chemotherapy. The HIVEC I and HIVEC II studies are both multicentre RCTs comparing between CHT and normothermic chemotherapy in patients with intermediate-risk NMIBC. Initial results on safety and tolerability were comparable between the two groups (41); the final oncological outcomes are eagerly awaited.

To our knowledge, this is the first meta-analysis comparing between CHT and BCG in patients with NMIBC. It is based on a comprehensive literature search including conference abstracts and proceedings, therefore publication bias is minimised. Only data from RCTs were meta-analysed, and the certainty of evidence was determined using the GRADE methodology. On the other hand, there are several limitations in our study. First, only four RCTs were included and the sample size is still relatively limited. More RCTs comparing intravesical CHT to BCG are warranted. Second, some of the included RCTs are still on-going, so the collected data may be premature and may not be reflective of the final results. Third, significant heterogeneity does exist in some of our analysis. This may be due to the differences in the underlying patient cohort characteristics; the results should be therefore interpreted with caution. Further sources of
heterogeneity may have been from the definition of high-risk bladder cancer, contributed by the recent change in guidelines as well as potentially different treatment regimens between studies. Finally, while carefully considered using sensitivity analyses, design studies incorporating CIS or papillary disease patients or BCG failure patients may be additional sources of heterogeneity. Nevertheless, our study did shed light on the utility of CHT in patients with intermediate- and high-risk NMIBC. Compared to BCG therapy, intravesical CHT could be an equally effective and tolerable treatment option. Although the utility of CHT implies additional cost, a more “comfortable” treatment regime for patients with a shorter overall treatment time may be preferred. Utility of CHT may also provide a solution to the problem of BCG shortage worldwide. The results have important implications in our clinical practise until higher level of evidence arises.

CONCLUSION

Our meta-analysis showed that intravesical CHT had equivalent oncological outcomes and similar safety profile when compared to BCG therapy for patients with intermediate- and high-risk NMIBC. In well-selected patients, i.e., those without BCG failure patients may be additional sources of heterogeneity. In well-selected patients, i.e., those without BCG failure patients may be additional sources of heterogeneity. Nevertheless, our study did shed light on the utility of CHT in patients with intermediate- and high-risk NMIBC. Compared to BCG therapy, intravesical CHT could be an equally effective and tolerable treatment option. Although the utility of CHT implies additional cost, a more “comfortable” treatment regime for patients with a shorter overall treatment time may be preferred. Utility of CHT may also provide a solution to the problem of BCG shortage worldwide. The results have important implications in our clinical practise until higher level of evidence arises.

REFERENCES

1. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. (2013) 63:234–41. doi: 10.1016/j.eururo.2012.07.033

2. Teoh JY, Huang J, Ko WY, Lok V, Choi P, Ng CF, et al. Global trends of bladder cancer incidence and mortality, and their associations with tobacco use and gross domestic product per capita. Eur Urol. (2020) 78:893–906. doi: 10.1016/j.eururo.2020.09.006

3. Sylvester RJ, van der Meiden AP, Oosterlinck W, Witjes JA, Bouffion C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. (2006) 49:466–5. doi: 10.1016/j.eururo.2005.12.031

4. Cambier S, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, et al. EORTC nomograms and risk groups for predicting recurrence, progression, and disease-specific and overall survival in non-muscle-invasive stage Ta-T1 urothelial bladder cancer patients treated with 1-3 years of maintenance bacillus calmette-guerin. Eur Urol. (2016) 69:60–9. doi: 10.1016/j.eururo.2015.06.045

5. Babjuk M, Bohle A, Burger M, Capoun O, Cohen D, Comperat EM, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. (2017) 71:447–61. doi: 10.1016/j.eururo.2016.05.041

6. Xylina E, Kent M, Kloth L, Pycha A, Compljo E, Svatek RS, et al. Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle-invasive urothelial carcinoma of the bladder. Br J Cancer. (2013) 109:1460–6. doi: 10.1038/bjc.2013.372

7. Oddens J, Brausi M, Sylvester R, Bono A, Van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol. (2013) 63:462–72. doi: 10.1016/j.eururo.2012.10.039

8. Brausi M, Oddens J, Sylvester R, Bono A, Van De Beek C, Van Andel G, et al. Side effects of bacillus calmette-guerin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. Eur Urol. (2014) 65:69–76. doi: 10.1016/j.eururo.2013.07.021

9. Ojea A, Nogueira JL, Solsona E, Flores N, Gomez JMF, Molina JR, et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus calmette-guerin (27 mg) versus very low-dose bacillus calmette-guerin (13.5 mg) versus Mitomycin C. Eur Urol. (2007) 52:1398–406. doi: 10.1016/j.eururo.2007.04.062

10. Bandari J, Maganty A, MacLeod LC, Davies BJ. Manufacturing and the Market: rationalizing the Shortage of Bacillus Calmette-Guerin. Eur Urol. (2018) 4:481–4. doi: 10.1016/j.euf.2018.06.018

11. Fankhauser CD, Teoh JY, Mostafid H. Treatment options and results of adjuvant treatment in nonmuscle-invasive bladder cancer (NMIBC) during the Bacillus Calmette-Guerin-shortage. Curr Opin Urol. (2020) 30:365–9.

12. Malmstrom PU, Sylvester RJ, Crawford DE, Friedrich M, Kroge S, Rintala E, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol. (2009) 56:247–56. doi: 10.1016/j.eururo.2009.04.038

13. Shang PF, Kwong J, Wang ZP, Tian J, Jiang L, Yang K, et al. Intravesical Bacillus Calmette-Guerin versus epirubicin for Ta and T1 bladder cancer. Cochrane Database Syst Rev. (2011) CD006885. doi: 10.1002/14651858.CD006885.pub2

14. Schaaf L, Schwab M, Uller C, Heine S, Muder TE, Schmid JO, et al. Hyperthermia synergizes with chemotherapy by inhibiting PARP1-dependent DNA replication arrest. Cancer Res. (2016) 76:2868–75. doi: 10.1158/0008-5472.CAN-15-2908

15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. (2009) 339:b2535. doi: 10.1136/bmj.b2535

16. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available online at: https://ctep.cancer.gov/
17. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Pragmatic methods for incorporating summary time-to-event data into meta-analysis. Trials. (2007) 8:16. doi: 10.1186/1745-6215-8-16
18. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. London: The Cochrane Collaboration (2008).
19. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. (2019) 366:l4898. doi: 10.1136/bmj.l4898
20. Nasser M. Cochrane handbook for systematic reviews of interventions. Am J Public Health. (2020) 110:753–4. doi: 10.2105/AJPH.2020.305609
21. Sterne JAC, Hernan MA, Reeves BC, Savovic J, Berkman ND, Visvanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Brit Med J. (2016) 355:j4919. doi: 10.1136/bmj.j4919
22. Schünemann H, Brozek J, Guyatt G, Oxman A. GRADE Handbook. Available online at: https://gdt.gradepro.org/app/handbook/handbook.html#h.ged5uqebmir9 (accessed August 8, 2021).
23. Debruyne FM, van der Meijden AP, Franssen MP. BCG-(RIVM) versus GRADE Handbook. (2019) 355:j4919. doi: 10.1136/bmj.j4919
24. Tan WS, Panchal A, Buckley L, Devill AL, Louhiere LS, Pope AM, et al. Radiofrequency-induced thermo-chemotherapy effect versus a second course of bacillus calmette-guerin or institutional standard in patients with recurrence of non-muscle-invasive bladder cancer following induction or maintenance bacillus calmette-guerin therapy (HYMN): a phase III, open-label, randomised controlled trial. Eur Urol. (2019) 75:63–71. doi: 10.1016/j.eururo.2018.09.005
25. Aréndts TJ, Nativ O, Maffezzini M, de Cobelli O, Canepa G, Verweij F, et al. Results of a Randomised Controlled Trial Comparing Intravesical Chemotherapy with Mitomycin C Versus Bacillus Calmette-Guerin for Adjuvant Treatment of Patients with Intermediate- and High-Risk Non-Muscle-Invasive Bladder Cancer. Eur Urol. (2016) 69:1046–52. doi: 10.1016/j.eururo.2016.01.006
26. Sousa A, Gonzalez-Valcarcel I, Mata JL, De La Morena JM, Martinez-Pineiro L. Chemoresection with hyperthermic intravesical instillation (HIVEC-R) vs standard treatment in patients with intermediate-high risk NMIBC: comparative, prospective, randomized, controlled study of efficacy and tolerability: preliminary results. J Urol. (2020) 203:e1123. doi: 10.1097/JU.0000000000001959.06
27. Guerrero-Ramos* F, González-Padilla Daniel A, González-Díaz A, Duarte-Ojeda José M, Miranda-Uterna N, Villacampa-Aubá F, et al. MP43-08 BCG vs chemohyperthermia with mitomycin c for high-risk non-muscle invasive bladder carcinoma: preliminary results of hivec-r randomized clinical trial. J Urol. (2019) 201:e620-e. doi: 10.1097/JU.0000056231.44325.78
28. Ekin RG, Akarlen K, Zorlu F, Tarhan H, Kucuk U, Yildirim Z, et al. Intravesical bacillus Calmette-Guerin versus chemohyperthermia for high-risk non-muscle-invasive bladder cancer. Can Urol Assoc J. (2015) 9:E278–83. doi: 10.5489/cuaj.2708
29. Cabas P, Rizzo M, Giuffre M, Antonello RM, Trombetta C, Luzzati R, et al. BCG infection (BCGitis) following intravesical instillation for bladder cancer and time interval between treatment and presentation: a systematic review. Urol Oncol. (2020) 39:85–92. doi: 10.1016/j.urolonc.2020.11.037
30. Serretta V, Scalici Gesolfo C, Alonge V, Cicero G, Moschini M, Colombro R. Does the compliance to intravesical BCG differ between common clinical practice and international multicentric trials? Urol Int. (2016) 96:20–4. doi: 10.1159/000430501
31. Alcorn J, Burton R, Topping A. Patterns of patient withdrawal from BCG treatment for bladder cancer: a retrospective time interval analysis. Int J Urol Nurs. (2019) 13:63–74. doi: 10.1111/jjun.12191
32. Westra A, Dewey WC. Variation in sensitivity to heat shock during the cell-cycle of chicken hamster cells in vitro. Int J Radiat Biol Relat Phys Chem Biol. (1971) 19:467–77. doi: 10.1080/0955300711458061
33. Mantio T, Gousetis G, Franco R, Botaitis S, Pappa A, Panayiotidis M. Effects of hyperthermia as a mitigation strategy in DNA damage-based cancer therapies. Semin Cancer Biol. (2016) 37–38:96–105. doi: 10.1016/j.semcancer.2016.03.004
34. Tan WS, Kelly JD. Intravesical device-assisted therapies for non-muscle-invasive bladder cancer. Nat Rev Urol. (2018) 15:667–85. doi: 10.1038/s41585-018-0092-z
35. Lefor AT, Makohon S, Ackerman NB. The effects of hyperthermia on vascular permeability in experimental liver metastasis. J Surg Oncol. (1985) 28:297–300. doi: 10.1002/jo.2930280412
36. Song CW. Effect of hyperthermia on vascular functions of normal tissues and experimental tumors; brief communication. J Natl Cancer Inst. (1978) 60:711–3. doi: 10.1093/jnci/60.3.711
37. Kampinga HH. Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. Int J Hyperthermia. (2006) 22:191–6. doi: 10.1080/02656730500332028
38. Milani V, Noesner E, Ghoze S, Kuppern M, Ahrens B, Scharner A, et al. Heat shock protein 70: role in antigen presentation and immune stimulation. Int J Hyperthermia. (2002) 18:563–73. doi: 10.1080/02656730210166140
39. Brace CL. Radiofrequency and microwave ablation of the liver, lung, kidney, and bone: what are the differences? Curr Prob Diagn Radiol. (2009) 38:135–43. doi: 10.1067/j.cprad.2007.10.001
40. Li K, Lin T, Chinese Bladder Cancer C, Xue W, Mu X, Xu E, et al. Current status of diagnosis and treatment of bladder cancer in China–analyses of Chinese Bladder Cancer Consortium database. Asian J Urol. (2015) 2:63–9. doi: 10.1016/j.jauj.2015.04.016
41. Tan WS, Palou J, Kelly J. 662–Safety and tolerability analysis of hyperthermic intravesical mitomycin to mitomycin alone in HIVEC I and HIVEC II: An interim analysis of 307 patients. Eur Urol Suppl. (2017) 16:e1150–1. doi: 10.1016/j.eururo.2016.06.005

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