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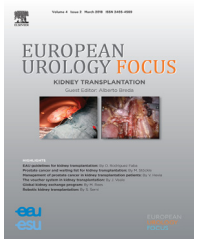

Review – Bladder Cancer

Intravesical Therapy in Patients with Intermediate-risk Non–muscle-invasive Bladder Cancer: A Systematic Review and Network Meta-analysis of Disease Recurrence

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Abstract

Context: Patients with intermediate-risk non–muscle-invasive bladder cancer (NMIBC) may pose a clinical dilemma without an agreed evidence-based decision tree for personalized treatment.
Objective: To perform a systematic review and network meta-analysis (NMA) to summarize available evidence on the oncologic outcomes of intravesical therapy in patients with intermediate-risk NMIBC.
Evidence acquisition: The MEDLINE, EMBASE, and ClinicalTrials.gov databases were searched in October 2020 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. Studies were deemed eligible if they reported on oncologic outcomes in patients with intermediate-risk NMIBC treated with transurethral resection of bladder tumor with and without intravesical chemotherapy or bacillus Calmette-Guérin (BCG) immunotherapy.
Evidence synthesis: Twelve studies were included in a qualitative synthesis (systematic review); three were deemed eligible for a quantitative synthesis (NMA). An NMA of five different regimens was conducted for the association of treatment with the 5-yr

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recurrence risk. Chemotherapy with maintenance was associated with a lower likelihood of 5-yr recurrence than chemotherapy without maintenance (odds ratio [OR] 0.51, 95% credible interval [CI] 0.26–1.03). Immunotherapy, regardless of whether a full- or reduced-dose regimen, was not associated with a significantly lower likelihood of 5-yr recurrence when compared with chemotherapy without maintenance (OR 0.90, 95% CI 0.39–2.11 vs OR 0.93, 95% CI 0.40–2.19). Analysis of the treatment ranking revealed that chemotherapy with maintenance had the lowest 5-yr recurrence risk (*P* score 0.9666).

Conclusions: Our analysis indicates that chemotherapy with a maintenance regimen confers a superior oncologic benefit in terms of 5-yr recurrence risk compared to chemotherapy without maintenance in patients with intermediate-risk NMIBC. Regardless of the dose regimen, immunotherapy with BCG does not appear to be superior to chemotherapy in patients with intermediate-risk NMIBC in term of disease recurrence. However, owing to the lack of comparative studies, there is an unmet need for well-designed, large-scale trials to validate our findings and generate robust evidence on disease recurrence and progression.

Patient summary: A maintenance schedule of chemotherapy reduces the rate of long-term recurrence of bladder cancer that has not invaded the bladder muscle. Chemotherapy inserted directly into the bladder and immunotherapy without maintenance schedules seem to have limited benefit in preventing cancer recurrence.

1. Introduction

Bladder cancer is the sixth most commonly diagnosed cancer worldwide [1,2]. Approximately 75% of bladder cancer patients present with non–muscle-invasive bladder cancer (NMIBC) [3]. NMIBC is a heterogeneous disease associated with a wide array of oncologic outcomes, which warrants an accurate and practical risk stratification strategy for treatment planning and patient counseling [4]. Several models, such as those of the European Organization for Research and Treatment of Cancer (EORTC) [5] and Club Urologico Espano de Tratamiento Oncologico [6], have been proposed for stratifying patients with NMIBC in terms of recurrence and progression risk. However, despite their ease of use, the predictive accuracy of these models is limited by intragroup heterogeneity among patients [7]. Moreover, the models do not take into account adverse pathologic features, such as lymphovascular invasion and variant histologies, that are associated with more aggressive disease and poor response to intravesical therapy [8–12]. Consequently, optimal decision-making remains challenging, especially for patients with intermediate-risk disease, the largest risk group among NMIBC patients.

Currently, adjuvant intravesical immunotherapy with bacillus Calmette-Guérin (BCG) or intravesical chemotherapy is the standard of care for patients with intermediate- and high-risk NMIBC [13]. Since treatment options and follow-up are dependent on risk stratification, patients with intermediate-risk NMIBC are vulnerable to inadequate therapy owing to the poorly defined and overlapping diagnostic criteria [13]. However, unnecessary adverse events and costs associated with treatment may outweigh the possible benefits for patients with intermediate-risk NMIBC. Consequently, patients with intermediate-risk NMIBC may pose a clinical dilemma without an agreed evidence-based decision tree for personalized treatment.

The primary aim of this systematic review and network meta-analysis (NMA) was to determine the oncologic outcomes of intravesical therapy among patients with intermediate-risk NMIBC. Such findings would help in decision-making, patient counseling, and trial design.

2. Evidence acquisition

2.1. Protocol

This systematic review and NMA were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for network meta-analysis [14]. The study protocol was registered a priori on the International Prospective Register of Systematic Reviews (PROSPERO; registration ID CRD42020212851).

2.2. Data sources and searches

The MEDLINE, EMBASE, and ClinicalTrials.gov databases were searched in October 2020 to identify studies reporting on the oncologic outcomes of intravesical therapy for patients with intermediate-risk NMIBC. A comprehensive systematic literature search was independently performed by two authors. Terms and keywords such as urinary bladder neoplasms, non–muscle-invasive bladder cancer, intermediate risk non–muscle-invasive bladder cancer, NMIBC, oncologic outcomes, local recurrence, disease-free survival, and overall survival were used to perform the search. The primary outcomes of interest were oncologic outcomes, including progression-free survival (PFS), recurrence-free survival (RFS), disease-free survival (DFS), and overall survival (OS).

After removing duplicates, two independent reviewers screened the titles and abstracts. Any citation that either reviewer thought should be included or for which suitability for inclusion was unclear was identified for full-text screening. Subsequently, full texts of eligible articles were reviewed for final inclusion and data extraction. Any discrepancy during the primary and secondary literature screenings were resolved by referring to the senior author.

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2.3. Eligibility criteria

We included randomized controlled trials (RCTs) that reported on oncologic outcomes of intravesical therapy for patients with intermediate-risk NMIBC. PICOS (population, intervention, control, outcomes, and study design) for this study was as follows: patients with intermediate-risk NMIBC according to the European Association of Urology (EAU) or the American Urological Association (AUA) guidelines, treated with transurethral resection of bladder tumor (TURBT) and intravesical chemotherapy or immunotherapy (BCG) compared to a control group including patients treated with TURBT alone or cohorts receiving single adjuvant therapy. The outcomes were oncologic outcomes, including PFS, RFS, DFS, and/or OS.

We excluded reviews, letters, editorials, animal studies, study protocols, case reports, meeting abstracts, replies from authors, brief correspondence, and articles not published in English. Furthermore, we excluded studies that did not provide data regarding the oncologic outcomes. References of all the papers included were scanned for additional studies of interest.

2.4. Data extraction

Data from each study were independently extracted by two reviewers. Extracted data included the following: study identifiers, study design, number of participants, number of participants within different NMIBC risk strata, oncologic outcomes, and demographic and clinical characteristics of the patients. Subsequently, the hazard ratio (HR) and 95% confidence interval for the oncologic outcomes were retrieved.

2.5. Risk-of-bias assessment

The risk of bias (RoB) was evaluated according to the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. This tool is based on seven domains that include bias due to confounding, participant selection, classification of interventions, deviations from the intended intervention, missing data, measurement of outcomes, and selection of the reported result (Supplementary Table 1). The RoB for each study was assessed independently by two authors. Disagreements were resolved via consultation with the coauthors.

2.6. Statistical analyses

NMA was used for simultaneous comparison of the 5-yr recurrence risk for multiple treatment strategies and pooling of direct and indirect evidence. For assessment of the 5-yr recurrence risk, arm-based analyses were performed to estimate the odds ratio (OR) of the 5-yr recurrence risk and 95% credible interval (CI) from the raw data presented in the manuscripts included [15]. The relative ranking of the different treatments for each outcome was estimated using the *P* score, which can be considered a frequentist analog to the surface under the cumulative ranking curves [16,17]. Network plots were used to illustrate the connectivity of the treatment networks in terms of 5-yr recurrence risk. R v1.14, framework 2.21 (R Foundation for Statistical Computing, Vienna, Austria) was used for the NMA.

3. Evidence synthesis

3.1. Description of the studies included

The literature search identified 522 unique references. Of these, 192 were excluded because of duplication and 255 because of unrelated outcomes during the screening process (Fig. 1). Of the 75 full-text articles assessed for eligibility, 63 were excluded based on the selection criteria.

Twelve studies were finally included in the qualitative synthesis (systematic review) [18–29]; three were deemed eligible for quantitative synthesis (NMA) [18,26,27]. Table 1 summarizes the characteristics of the studies.

We found significant heterogeneity across the studies in terms of treatment used for patients with intermediate-risk NMIBC. Ten studies reported data on different intravesical therapy regimens [18,19,22–29]. Among chemotherapeutics, epirubicin was used in four studies, mitomycin C (MMC) in three, and pirarubicin in one. Immunotherapy with BCG was used in four studies. Two studies reported outcomes for laser vaporization of bladder tumor (LVRBT) compared to TURBT [20,21].

3.2. Principal findings

3.2.1. Oncologic outcomes

In terms of oncologic outcomes, all 12 studies reported on the recurrence rate [18–29], eight reported data on the progression rate [18,19,23,24,26–29], and only two reported on survival outcomes such as OS and cancer-specific survival (CSS) [26,28]. Table 2 summarizes oncologic outcomes such as recurrence and progression rates among the studies.

3.2.1.1. Recurrence risk. All studies included reported the risk of recurrence for different treatment strategies for patients with intermediate-risk NMIBC (Table 2). Regarding intravesical chemotherapy, Naya et al [24] reported that among patients with intermediate-risk NMIBC, the 3-yr RFS rate was worse for those who received a single immediate installation of pirarubicin compared to those who received additional instillations of pirarubicin. Kelly et al [23] found that celecoxib added to a standard-of-care single intravesical MMC instillation within 24 h following TURBT did not improve 3-yr RFS.

Regarding intravesical immunotherapy with BCG, Gupta et al [22] reported no difference in recurrence rate between patients treated with monthly BCG for 12 doses and patients receiving BCG maintenance according to the SWOG protocol. Likewise, Oddens et al [25] reported that patients with intermediate-risk NMIBC treated with a full-dose schedule do not benefit from 1 yr of maintenance BCG therapy. Comparing the efficacy of maintenance with chemotherapy and BCG, Sylvester et al [28] reported statistically significant worse outcomes in terms of 9.2-yr recurrence and distant

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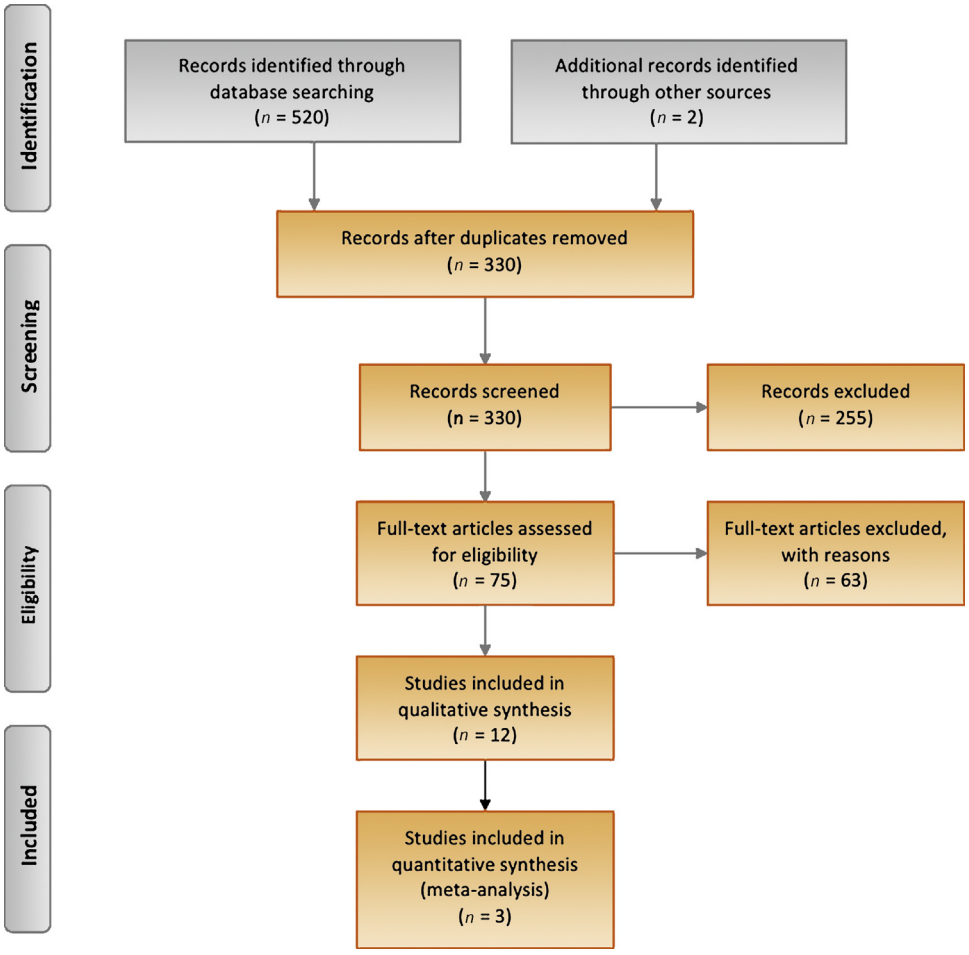

Fig. 1 – Flow diagram of the study selection procedure for the systematic review and network meta-analysis.

metastases rates for patients receiving epirubicin compared to those receiving BCG (both with 3-yr maintenance).

Two studies compared the effectiveness of LVRBT and TURBT followed by intravesical therapy. Xu et al [20] reported no significant difference in 2-yr recurrence rates between KTP laser and standard TURBT, both following pirarubicin instillations. Zhang et al [21] did not find differences in 1- and 3-yr recurrence rates between LVRBT with thulium laser and TURBT; in both groups, surgery was followed by epirubicin instillations.

In summary, according to the current literature, chemotherapy with maintenance seems to reduce the recurrence rate among patients with intermediate-risk NMIBC, while 1 yr of maintenance BCG therapy does not appear to affect recurrence outcomes in these patients. Different endoscopic procedures also do not demonstrate differences in recurrence risk among patients with intermediate-risk NMIBC.

3.2.1.2. Progression risk. Eight of the studies included reported data on the progression rate (Table 2). Sylvester et al [28] did not find a statistically significant difference in 9.2-yr progression rate between patients receiving epirubicin and those receiving BCG (both with 3-yr maintenance). Similarly, Ojea et al [26] did not find a difference in progression rates among patients with intermediate-risk NMIBC treated with MMC or full or low doses of BCG (27 mg and 14.5 mg). Kelly et al [23] found that celecoxib did not decrease the progression rate more than a single immediate intravesical MMC instillation alone in intermediate-risk NMIBC. The current data indicate that intravesical therapies do not differ in terms of the progression rate. However, these data need to be supported by well-designed and controlled large-scale trials.

3.2.1.3. Survival outcomes. Among survival outcomes, OS and CSS were reported in two studies of patients with intermediate-risk NMIBC treated with epirubicin, BCG, or MMC. Data from the EORTC trials [28] showed all-cause mortality of 38.8% among patients treated with epirubicin with 3-yr maintenance, compared to 30.3% among those treated with BCG 3-yr maintenance (HR 0.79, 95% CI 0.58–1.09; $p = 0.14$); cancer-specific mortality was 7.1% and 2.4%, respectively (HR 0.35, 95% CI 0.14–0.86; $p = 0.02$). Ojea et al [26] found cancer-specific mortality of 4.7%, 3%, and 3.6% among patients treated with MMC, BCG 27 mg, and BCG 14.5 mg, respectively, in a

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Table 1 – Characteristics of studies reporting oncologic outcomes for patients with intermediate-risk non–muscle invasive bladder cancer

Study	Country	Study design	Patients (IR/total)	IR patients in Tx arm 1/Tx arm 2	Treatment arm 1	Treatment arm 2	Definition of IR	Follow-up
Bosschieter 2017 [18]	Netherlands	RCT	413/2243	190/223	Immediate instillation of MMC after TURRT	Instillation of MMC delayed for 2 wk after TURBT	Primary, solitary pTa/pT1 G3 OR recurrent, solitary pTa/pT1 G1–3 tumors, no concomitant CIS	Median 32 mo (IQR 17–51)
Ojea 2017 [26]	Spain	RCT	430/430	BGC 27 mg: 142 BCG 13.5 mg: 139 MMC: 149	BCG 27 mg, BCG 13.5 mg	MMC 30 mg	TaG2 and T1G1–2, no concomitant CIS	MMC: 52.6 mo 27 mg BCG: 57.3 mo 13.5 mg BCG: 61.2 mo
Serretta 2010 [27]	Italy	RCT	482/482	237/245	5 weekly instillations of Epi (post TUR + immediate Epi)	5 weekly instillations + 10 monthly instillations of Epi (post TUR + immediate Epi)	EAU guidelines	Median 48 mo (range 3–78)
Elsawy 2018 [19]	Egypt	RCT	52/236	28/24	Intravesical Epi (post TURBT)	TURBT alone	Primary/ recurrent papillary bladder cancer, >1 cm	Mean 29 mo
Gupta 2020 [22]	India	RCT	14/78	7/7	Monthly BCG for 12 doses	BCG following the SWOG protocol	Multiple/ recurrent low-grade tumors	Duration 1 yr
Kelly 2018 [23]	UK	RCT	126/472	69/57	Twice daily celecoxib post TURBT + MMC (IR) or BCG (HiR)	Placebo post TURBT + MMC (IR) or BCG (HiR)	EAU guidelines	Median 44 mo (IQR 36–57)
Naya 2018 [24]	Japan	RCT	68/113	35/33	Single immediate post TURBT intravesical instillation of THP	Intravesical THP chemotherapy weekly for 8 wk	EAU guidelines	Median 36 mo
Oddens 2012 [25]	Netherlands	RCT	789/1355	1/3 dose, 1 yr: 192 FD, 1 yr: 191v 1/3 dose, 3 yr: 218 FD, 3 yr: 188	1/3 dose BCG + 1-yr maintenance post TUR	FD BCG + 1-yr maintenance post TUR 1/3 dose BCG + 3-yr maintenance post TUR FD BCG + 3-yr maintenance post TUR	Multiple T1, G1-2 tumors, <10 tumors, no concomitant CIS	Median 7.1 yr
Sylvester 2009 [28]	Europe (Belgium)	RCT	497/837	BCG: 161 BCG + INH: 166 Epi: 170	BCG alone or BCG plus INH	Epi	Single or multiple, primary or recurrent, T1, G1-2 tumors, no concomitant CIS	Median 9.2 yr
Turkeri 2010 [29]	Turkey	RCT	143/143	68/75	Single instillation of Epi post TURBT	Double instillations of Epi post TURBT	Primary and solitary or multiple (≤3) Ta (G2–3) or T1 (G1–2) tumors; no concomitant CIS	Duration 16.9 mo
Xu 2015 [20]	China	RCT	116/193	56/60	KTP laser + THP	TURBT + THP	EAU guidelines	NR
Zhang 2015 [21]	China	RCT	87/292	43/44	LVRBT + Epi	TURBT + Epi	EAU guidelines	Duration 36 mo

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; EAU = European Association of Urology; Epi = epirubicin; FD = full dose; G = grade; HiR = high risk; INH = isoniazid; IQR = interquartile range; IR = intermediate risk; KTP = potassium-titanyl-phosphate; LVRBT = laser vaporesection of bladder tumor; MMC = mitomycin C; RCT = randomized controlled trial; SWOG = Southwestern Oncology Group; THP = pirarubicin; TUR/TURBT = transurethral resection of bladder tumor; Tx = treatment.

study with median follow-up of approximately 5 yr. In fact, there are only limited data on survival outcomes for patients with intermediate-risk NMIBC. Nevertheless, BCG appears to have a marginal benefit compared to chemotherapy in terms of long-term OS and CSS.

3.3. *Network meta-analysis*

For quantitative synthesis in the NMA, therapy regimens from three studies were categorized into groups as follows: (1) chemotherapy as standard regimen ([total of

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Table 2 – Progression and recurrence rates for patients with intermediate-risk non–muscle invasive bladder cancer

Study	Progression	Recurrence
Bosschieter 2017 [18]	15 of 413 pts experienced DP	3-yr RR 20% for immediate MMC instillation vs 32% for delayed MMC installation
Ojea 2017 [26]	DP rate 9.4% for MMC, 9.9% for BCG 27 mg, and 12.9% for BCG 14.5 mg	RR 38.9% for MMC, 26.8% for BCG 27 mg, and 36% for BCG 13.5 mg
Serretta 2010 [27]	10 pts progressed to muscle-invasive disease (3 in 5 weekly Epi instillations arm vs 7 in extended Epi schedule arm)	3-yr RFR 54.4% for 5 weekly Epi instillations vs 62.1% for extended Epi schedule ($p = 0.11$) 3-yr RFS 62.7% for 5 weekly Epi instillations vs 69.5% for extended Epi schedule
Elsawy 2018 [19]	DP 1 event in intravesical Epi arm vs 0 events in TURBT alone arm	Recurrence: 4 events in intravesical Epi arm vs 4 events in TURBT alone arm
Gupta 2020 [22]	NR	Recurrence: 0/7 for monthly BCG for 12 doses vs 1/7 for BCG per the SWOG protocol ($p = 0.3$)
Kelly 2018 [23]	DP 3 pts (4.3%) treated with TURBT + MMC (IR) or BCG (HiR) + celecoxib vs 1 pt (1.7%) treated with TURBT + MMC (IR) or BCG (HiR) + placebo ($p = 0.6$).	3-yr RFR 52% for TURBT + MMC (IR) or BCG (HiR) + celecoxib vs 50% for TURBT + MMC (IR) or BCG (HiR) + placebo (HR 0.90, log-rank $p = 0.7$).
Naya 2018 [24]	DP not noted during this period in any patient	3-yr RFS 63.4% for single immediate THP installation vs 86.1% for additional THP installations (log-rank test, $p < 0.01$)
Oddens 2012 [25]	NR	DFI for 1/3 BCG dose: 106 events/192 pts for 1-yr maintenance vs 97 events/218 pts for 3-yr maintenance (HR 1.35, 95% CI 1.03–1.79) DFI for full BCG dose: 72 events/191 pts for 1-yr maintenance vs 81 events/188 pts for 3-yr maintenance (HR 0.88, 95% CI 0.64–1.21)
Sylvester 2009 [28]	9.2-yr DP 7.1% for Epi vs 4.0% for BCG (HR 0.56, 95% CI 0.26–1.23; $p = 0.14$) DP or DM 13.5% for Epi vs 5.2% for BCG (HR 0.39, 95% CI 0.21–0.73; $p = 0.002$)	9.2-yr RR 58.8% for epirubicin vs 40.1% for BCG (HR 0.59, 95% CI 0.45–0.76; $p < 0.001$) DM 8.8% for epirubicin arm vs 3.7% for BCG (HR 0.42, 95% CI 0.20–0.90; $p = 0.027$)
Turkeri 2010 [29]	Grade and stage progression: 1.5% for single instillation vs 4% for double instillation ($p = 0.165$)	RR 14.7% for single instillation vs 21.3% for double instillation ($p = 0.305$)
Xu 2015 [20]	NR	2-yr RR 26.8% for laser + THP vs 30% for TURBT + THP
Zhang 2015 [21]	NR	1-yr RR 54.5% for TURBT + Epi vs 51.2% for LVRBT + Epi (HR 0.935, 95% CI 0.62–1.42; $p = 0.752$) 3-yr RR 68.2% for TURBT + Epi vs 65.1% for LVRBT + Epi (HR 0.933, 95% CI 0.59–1.47; $p = 0.762$)

BCG = bacillus Calmette-Guérin; CI = confidence interval; DFI = disease-free interval; DM = distant metastasis; DP = disease progression; Epi = epirubicin; HiR = high risk; HR = hazard ratio; IR = intermediate risk; LVRBT = laser vaporesection of bladder tumor; MMC = mitomycin C; NR = not reported; THP = pirarubicin; TURBT = transurethral resection of bladder tumor; pt = patient; RFR = recurrence-free rate; RFS = recurrence-free survival; RR = recurrence rate.

6 instillations of epirubicin: immediate epirubicin after TURBT + 5 weekly instillations] or [total of 9 installations with MMC 40 mg: immediate within 24 h after TURBT instillation + 3 weekly instillations + 5 monthly instillations]); (2) chemotherapy as a delayed regimen (total of 9 installations with MMC 40 mg: instillation starting 2 wk after TURBT + 3 weekly instillations + 5 monthly instillations); (3) chemotherapy as an extended regimen ([total of 16 instillations of epirubicin: immediate epirubicin after TURBT + 5 weekly instillations + 10 monthly instillations] OR [MMC 30 mg given once a week for 6 wk followed by another 6 instillations given once every 2 wk during 12 wk]; (4) immunotherapy at full dose (BCG 27 mg given once a week for 6 wk followed by another 6 instillations given once every 2 wk during 12 wk); and (5) immunotherapy at a reduced dose (BCG 13.5 mg given once a week for 6 wk followed by another 6 instillations given once every 2 wk during 12 wk). The networks of eligible comparisons are graphically represented in a network plot of the association of treatment regimen with 5-yr recurrence risk in Figure 2. Network plots show interconnections between different therapy regimens (represented by a node). Connections between different therapy regimens are represented by links; numbers indicate the number of studies.

An NMA of the five intravesical therapy regimens listed above was conducted with regard to the 5-yr recurrence risk in intermediate-risk NMIBC (Fig. 3). Chemotherapy in the extended regimen was associated with a lower likelihood of 5-yr recurrence compared to chemotherapy in the standard regimen (OR 0.51, 95% CI 0.26–1.03). By contrast, a delayed

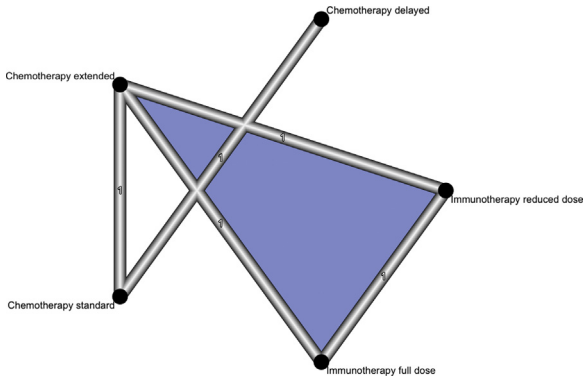

Fig. 2 – Network plot showing the association of treatment with the 5-yr recurrence risk in intermediate-risk non–muscle-invasive bladder cancer. The plot shows interconnections between different therapy regimens (represented by a node). Connections between different therapy regimens are represented through links, and the numbers indicate the number of studies.

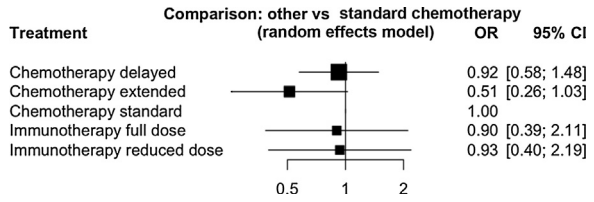

Fig. 3 – Forest plot showing the association of treatment with the 5-yr recurrence risk in intermediate-risk non–muscle-invasive bladder cancer. OR = odds ratio; CI = confidence interval.

chemotherapy regimen was not associated with a significantly lower likelihood of 5-yr recurrence compared to standard chemotherapy (OR 0.92, 95% CI 0.58–1.48). Similarly, compared to a standard chemotherapy regimen, immunotherapy, regardless of whether at a full or reduced dose, was not associated with a significantly lower likelihood of 5-yr recurrence (OR 0.90, 95% CI 0.39–2.11, and OR 0.93, 95% CI 0.40–2.19, respectively). According to the analysis of treatment ranking, it is highly likely that chemotherapy in the extended regimen has the lowest rate of the 5-yr recurrence (*P* score 0.9666). The treatment ranking of other therapies is presented in Supplementary Table 2.

3.4. Discussion

We performed a systematic review of the oncologic outcomes of intravesical therapy for patients with intermediate-risk NMIBC. We also performed an NMA to indirectly compare the association of different intravesical therapy regimens with the 5-yr recurrence risk. This approach led to several interesting findings.

First, according to our results, chemotherapy in the extended regimen (with maintenance) was associated with the lowest likelihood of 5-yr recurrence for patients with intermediate-risk NMIBC. Therefore, immediate intravesical chemotherapy instillation after TURBT and then five or six weekly instillations followed by prolonged monthly instillations or instillations given once every 2 wk for a few months is the regimen that provides the best long-term oncologic outcomes in terms of recurrence in intermediate-risk NMIBC. This supports the AUA guidelines recommending 6 wk of induction intravesical chemotherapy with maintenance for an unspecified duration in intermediate-risk NMIBC [30]. At the same time, some of the studies included reported intravesical chemotherapy with maintenance for up to 12 wk that is not the regimen recommended by the current guidelines. This therapy might be used according to historic recommendations before the current treatment strategies. Nevertheless, our analysis does not reflect the impact of intravesical therapy on progression risk, which may also pose a challenge in identifying the optimal treatment options for intermediate-risk NMIBC.

Second, we found that chemotherapy delayed for 2 wk after TURBT was not significantly associated with a lower likelihood of 5-yr recurrence when compared to standard chemotherapy in intermediate-risk NMIBC. The EAU guidelines indicate that repeat chemotherapy instillations improve RFS for patients with intermediate-risk NMIBC regardless of a previous single instillation immediately after TURBT [13]. Sylvester et al [31] reported that a single instillation of chemotherapy immediately after TURBT compared to TURBT alone reduces the risk of recurrence in NMIBC, except for patients at high risk of recurrence because of its lack of efficacy in this subgroup. In their meta-analysis, Sylvester et al also provide evidence that the use of postoperative irrigation also reduces recurrences, which can be explained by a role in preventing implantation of circulating tumor cells at the site of resection. Unfortunately, data on postoperative irrigation use in the studies included in our NMA are lacking. Moreover, no study has reported results for combination therapy, although it was previously shown that combination therapy might provide prophylactic advantage in terms of recurrence when compared to BCG therapy alone for patients with intermediate- and high-risk NMIBC [32].

Interestingly, immunotherapy with BCG, regardless of the doses used, was not associated with a significantly lower likelihood of 5-yr recurrence compared to chemotherapy for patients with intermediate-risk NMIBC in our analysis. Hence, it seems that BCG instillations do not provide long-term benefits over chemotherapy in intermediate-risk NMIBC. This is particularly important because of the current worldwide shortage of BCG [33]. In contrast to our results, a previous meta-analysis found that 27 mg BCG was more effective than 13.5 mg BCG in reducing tumor recurrences (risk ratio 0.66, 95% CI 0.49–0.89; $p = 0.006$) [34]. Astram et al included both intermediate- and high-risk NMIBC without subgroup analysis in their meta-analysis, while our NMA included only patients with intermediate-risk NMIBC. However, it should be stressed that the article included in our NMA did not use the maintenance schedule of BCG therapy, which was shown to be more effective in preventing recurrence. For example, Han et al [35] recommended adjuvant intravesical BCG with maintenance therapy for patients with papillary carcinoma. Chemotherapy or BCG plus chemotherapy was not better than BCG alone in preventing tumor recurrence [35]. Supporting these results, another meta-analysis showed that maintenance BCG was superior to MMC in preventing disease recurrence [36]. The discrepancy in these results can probably be attributed to the inclusion of all NMIBC patients regardless of risk group. Nevertheless, as both the EAU and AUA guidelines recommend 1-yr BCG maintenance in intermediate-risk NMIBC [13,30], most of the studies included highlight the poor compliance with NMIBC guidelines worldwide [37].

Another challenge in interpreting the results of the studies included is the lack of data on some relevant clinicopathologic features. The studies included did not take into account adverse pathologic features such as tumor extent and variant histology, which are associated with worse oncologic outcomes and suboptimal response to intravesical therapies [12,38–40]. The introduction of immune checkpoint inhibition (CPI) and its combinations might provide a further understanding of the role of intravesical therapy in intermediate-risk NMIBC. A few ongoing trials are evaluating the role of intravesical CPI in intermediate-

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risk NMIBC: the phase 1/2 PemBla trial is comparing the safety, tolerability, and efficacy of intravesical or intravenous pembrolizumab (NCT03167151). In addition, in the current era of personalized medicine, molecular biomarkers are promising tools for predicting patient response to intravesical chemotherapy and immunotherapy [41]. However, none of the studies included provided data on biomarkers expression or their predictive role. We believe that tissue-based and urine-based molecular biomarkers hold promise for changing the management of intermediate-risk NMIBC.

The main strength of our systematic review and NMA is that, to the best of our knowledge, it is the first to evaluate oncologic outcomes of intravesical therapy for patients with intermediate-risk NMIBC. Nevertheless, there are several limitations. The main limitation is the significant heterogeneity across the studies in terms of different treatment regimens and definitions of outcomes (endpoints). Hence, an NMA was feasible only among three studies comparing different intravesical therapy strategies and only for the 5-yr recurrence risk. However, the long-term survival differences may be biased by the treatment received after recurrence. Second, the small sample size in most of the studies included may have limited the power of the studies to reveal clinically significant findings. Third, the heterogeneity in risk stratification definition underlines the necessity for standardized criteria to facilitate accurate decision-making. Fourth, inconsistencies in the intervention regimens and evaluation of the curative effect in the trials included might affect the generalizability of our results for patients with intermediate-risk NMIBC because of different treatment regimens and a heterogeneous case mix. Moreover, the articles included on celecoxib and comparison of laser and standard TURBT techniques might provide mixed and unclear messages to readers. These treatments are not widely used and current guidelines do not recommend them. However, patients in these studies underwent intravesical instillation in addition to celecoxib received during single intravesical MMC instillation following TURBT. Likewise, laser therapy was followed by intravesical instillation. We included these studies in the qualitative evidence synthesis because they matched our inclusion criteria (articles on patients with intermediate-risk NMIBC treated with TURBT and/or intravesical therapy). Nevertheless, we did not include them in the quantitative analysis for the reasons mentioned above. Although indirect treatment comparisons have been used and validated to compare outcomes from RCTs, this approach falls short of a head-to-head treatment comparison. Thus, direct and well-designed comparative trials are required to validate the findings of our study.

4. Conclusions

Our analysis indicates that intravesical chemotherapy with a maintenance regimen confers a superior oncologic benefit in terms of the 5-yr recurrence risk compared to chemotherapy without maintenance for patients with intermediate-risk NMIBC. Use of a single immediate intravesical instillation of chemotherapy did not result in a clear reduction in the recurrence rate. Regardless of dose regimens, intravesical BCG immunotherapy does not appear to be superior to chemotherapy for patients with intermediate-risk NMIBC. However, owing to the lack of comparative studies, there is an unmet need for well-designed, large-scale trials to validate our findings and generate robust evidence on disease recurrence and progression.

Author contributions: Ekaterina Laukhtina 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.

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Acquisition of data: Al-Ani, Ali.
Analysis and interpretation of data: Laukhtina, Abufaraj.
Drafting of the manuscript: Laukhtina, Abufaraj.
Critical revision of the manuscript for important intellectual content: Mori, Moschini, Quhal, Motlagh, Pradere, Schuettfort, Mostafaei, Katayama, Grossmann, Soria.
Statistical analysis: Laukhtina, Mori.
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Supervision: Shariat, Abufaraj, Enikeev, Fajkovic.
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Appendix A. Supplementary data

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