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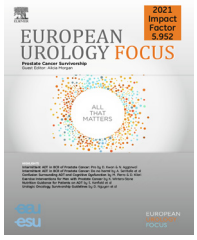

Review – Bladder Cancer

A Systematic Review and Meta-analysis of Chemoablation for Non–muscle-invasive Bladder Cancer

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Abstract

Context: The ablative effect of intravesical therapy is known for decades. However, the clinical feasibility and efficacy of chemoablation for non–muscle-invasive bladder cancer (NMIBC) have not become accepted.

Objective: To assess the treatment outcomes of chemoablation for NMIBC and to compare its safety with that of the standard treatment, transurethral resection of bladder tumors (TURBT) followed by intravesical therapy.

Evidence acquisition: Multiple databases were queried in July 2022 for studies investigating the complete response (CR) rates and adverse events in NMIBC patients treated with chemoablation using mitomycin C (MMC), gemcitabine, epirubicin, or bacillus Calmette-Guérin.

Evidence synthesis: Overall, 23 studies comprising 1199 patients were eligible for this meta-analysis. Among these studies, 20 assessed the efficacy of chemoablation and three compared the treatment outcomes of MMC chemoablation versus standard treatment. Among patients treated with weekly administration of any agent, the pooled CR rates at initial assessment were 50.9% (95% confidence interval [CI]: 45.9–55.9) for the marker

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Epirubicin
Bacillus Calmette-Guérin

lesion and 47.5% (95% CI: 36.5–58.7) for well-selected NMIBC (ie, small tumors and/or a small number of tumors). Novel regimens for chemoablation such as MMC-gel (70.6%, 95% CI: 60.1–79.3) and an intensive MMC regimen (64.7%, 95% CI: 56.2–72.3) provided better CR rates in well-selected NMIBC patients. Comparable CR rates were noted irrespective of tumor multiplicity, whereas tumor size <5 mm was associated with a higher CR rate than tumor size ≥5 mm (odds ratio: 0.36, 95% CI: 0.17–0.79). The novel intensive MMC regimen resulted in lower rates of dysuria and urinary frequency than standard treatment.
Conclusions: Despite the lack of long-term outcomes, chemoablation appears to be a promising treatment option for well-selected NMIBC patients and can potentially help avoid unnecessary TURBT, specifically in some elderly patients with intermediate-risk NMIBC. Further well-designed studies with larger cohorts are necessary to address the differential tolerability and long-term anticancer efficacy of this resurging approach.
Patient summary: Bladder instillation therapy has a potential ablative effect for well-selected non–muscle-invasive bladder cancer. This can lead to the omission of an unnecessary surgical treatment.
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1. Introduction

Non–muscle-invasive bladder cancer (NMIBC) is a heterogeneous disease with highly variable clinical behavior [1–6]. Intravesical therapy with transurethral resection of bladder tumors (TURBT) is the standard treatment for NMIBC, however with a high probability of recurrence [1,7]. According to the risk classification, immediate single instillation of chemotherapy such as mitomycin C (MMC), epirubicin (EPI), or pirarubicin and/or maintenance of MMC or bacillus Calmette-Guérin (BCG) are recommended by the European Association of Urology (EAU) guidelines [1]. Despite adequate therapy, approximately 30–50% of patients will eventually experience disease recurrence within 1 yr; therefore, NMIBC patients often undergo repeated TURBT [1], which is a driver of high treatment costs associated with bladder cancer as well as morbidity in this generally elderly population [8,9]. Indeed, TURBT is an invasive procedure and carries an increased risk of unplanned hospital admission as well as mortality risk [10–12].

The ablative effect of intravesical therapy was demonstrated by marker lesion studies several decades ago [13]. This has generated the hypothesis that neoadjuvant intravesical therapy might improve the quality of TURBT, leading to decreased recurrence rates or even allowing omission of TURBT in patients with small and only few tumors. Recently, the interest in chemoablation has been revoked, with several studies demonstrating the efficacy and feasibility of chemoablation with MMC versus standard treatment (TURBT followed by intravesical treatment) in a well-selected group of NMIBC patients [14–16]. There is, however, no robust evidence to support the clinical utility of chemoablation for NMIBC [17]. Therefore, we aimed to assess the efficacy of chemoablation as well as the differential efficacy of chemoablation stratified by tumor characteristics, and to compare the treatment outcomes of chemoablation versus the current standard treatment (ie, TURBT ± postoperative intravesical treatment) in NMIBC patients.

2. Evidence acquisition

The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD 42022348199).

2.1. Search strategy

This systematic review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Meta-analyses of Observational Studies in Epidemiology Statement (Supplementary Table 1) [18]. In November 2022, we performed a literature search on PubMed, Web of Science, and Scopus databases to identify studies investigating the treatment outcomes of chemoablation for NMIBC. The keywords used in our initial search strategy were (bladder) OR (urothelial) AND (tumor) OR (cancer) OR (carcinoma) AND (chemoablation) OR (chemoresection) OR (intravesical) OR (instillation). Adding the keyword (neoadjuvant), we performed additional literature search (Fig. 1 and Supplementary material). Furthermore, we also reviewed abstracts presented at recent major conferences such as the American Urological Association and the EAU meetings to include unpublished studies and avoid publication bias. The primary outcomes of interest were complete response (CR) rates at initial assessment and differential CR rates stratified by tumor characteristics. The safety of chemoablation was also compared with the current standard treatment (TURBT followed by intravesical treatment). Two investigators conducted initial screening based on titles and abstracts to identify eligible studies. Potentially relevant studies were subjected to a full-text review. In addition, manual searches of reference lists of relevant articles were also performed to identify additional studies. Disagreements were resolved by consensus with coauthors.

2.2. Inclusion and exclusion criteria

Studies were included if these evaluated NMIBC patients (patients), who were treated with chemoablation using MMC, gemcitabine (GEM), EPI, and BCG (interventions), compared with those treated with TURBT and postoperative intravesical therapy (comparisons) to assess the differential CR rates and the safety of chemoablation for NMIBC (outcome), in nonrandomized, observational, randomized, or cohort studies (study design). Studies lacking original patient data, reviews, letters, editorial comments, replies from authors, case reports, and articles not written in English were excluded. References of all included publications were scanned for additional studies of interest.

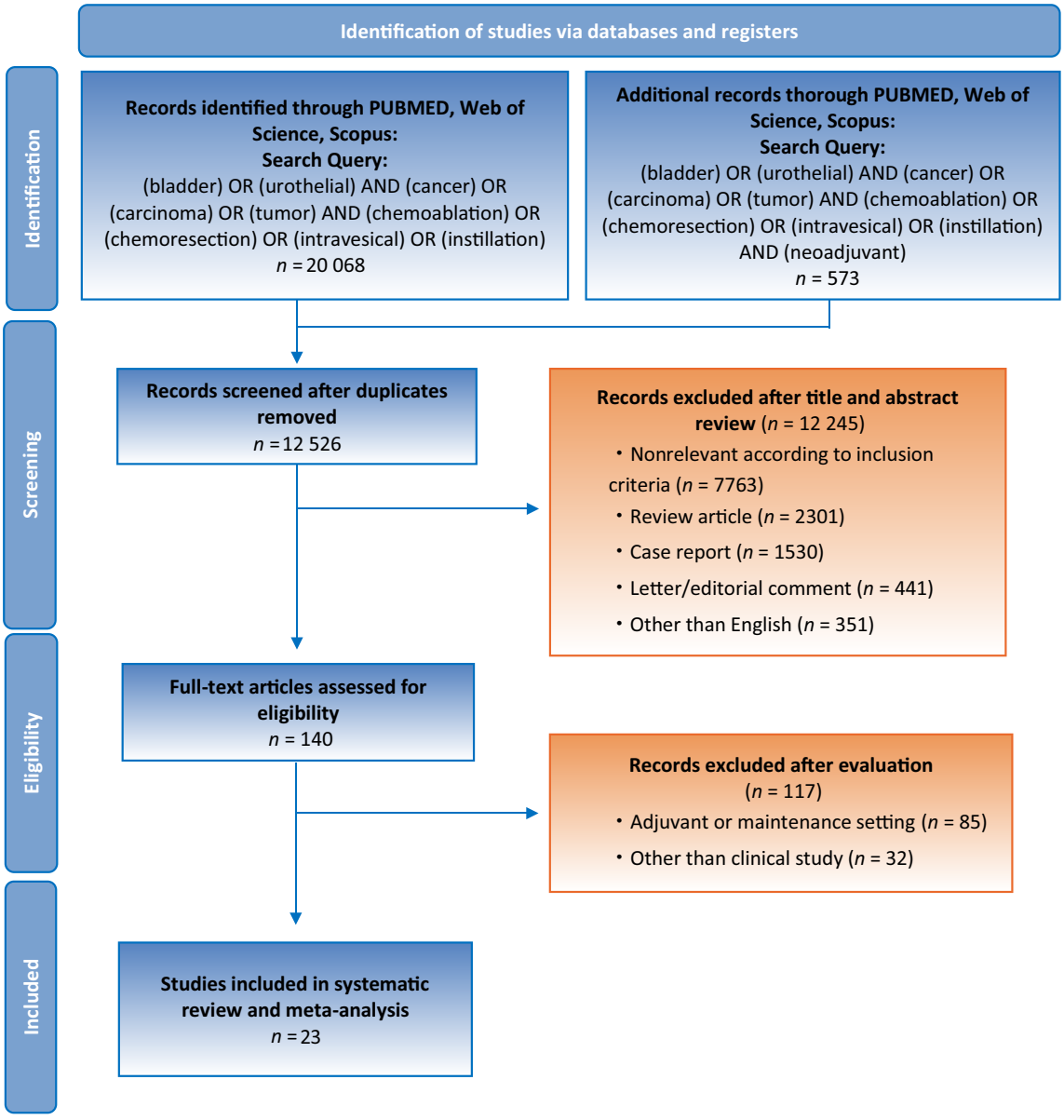


Fig. 1 – The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart, detailing the article selection process.

2.3. *Data extraction*

Two authors independently extracted the data such as the first author's name, country, publication year, recruitment periods, number of patients, inclusion criteria, age, sex, number of tumors, tumor size, grade, prior/present pathologic T stage, primary or recurrent tumors, history of previous bladder instillation therapy, follow-up period, number of any and severe adverse events (AEs; Common Terminology Criteria for Adverse Events [CTCAE] grade 3–5), other treatment-related AEs, CR rates, and long-term recurrence rates if available. In cases of suspected duplicate cohorts from the same author or institution, the higher-quality or the most recent data were used in the analyses. All discrepancies were resolved by consensus with coauthors.

2.4. *Risk of bias assessment*

The assessment of study quality and risk of bias was performed following the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool and the risk of bias (RoB version2), referring to the *Cochrane Handbook for Systematic Reviews of Interventions* [18]. Each bias domain and the overall risk of bias were judged as a "low," "moderate," "serious," or "critical" risk of bias. The presence of confounders was determined by consensus and review of

the literature. The ROBINS-I and risk-of-bias assessment of each study were conducted independently by two authors (Supplementary Fig. 1 and Supplementary Table 2).

2.5. Statistical analyses

Forest plots were used to analyze and summarize the pooled CR rates and odds ratio (OR) with a 95% confidence interval (CI) to describe the association between tumor demographics and CR rates. When analyzing the association between tumor demographics and CR rates, we only included studies published in the past 5 yr to avoid temporal biases. The ORs were also utilized to describe the differences in the rates of AEs between chemoablation and conventional management. A pooled analysis of CR rates was performed using generalized linear mixed models (GLMMs), which have been recommended in meta-analyses as a one-step approach to fully accounting for within-study variances [19,20]. Heterogeneity among the outcomes of included studies in this meta-analysis was assessed using Cochrane's Q test and I^2 statistics [21,22]. When significant heterogeneity ($p < 0.05$ in Cochrane Q test and a ratio of >50% in I^2 statistics) was observed, we investigated the cause of heterogeneity, and a random-effect model was applied [23,24]. A fixed-effect model was utilized to calculate the pooled CR rates and ORs for non-heterogeneous results [22]. Funnel plots were used to assess the publication bias (Supplementary Fig. 2–4). All analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), and the statistical significance level was set at $p < 0.05$. We used "metaprop" in the "meta" package to calculate the pooled CR rates using a GLMM.

3. Evidence synthesis

3.1. Study selection and characteristics

Our initial search identified 20 068 records and the additional search identified 573 records. After removing duplicates, 12 526 records remained for screening the titles and abstracts (Fig. 1). After screening, a full-text review was performed for 140 articles. Finally, we identified 23 studies eligible for the meta-analysis according to the inclusion criteria [13–16,25–44]. Of these, 20 studies comprising 901 patients [13,25–42,44] and three comparative studies comprising 298 patients assessed MMC chemoablation versus current standard treatment [14–16,43]. The demographics of each included study are summarized in Tables 1 and 2, and Supplementary Table 3.

3.2. Efficacy of chemoablation for NMIBC

3.2.1. Meta analysis of CR rates at initial assessment

3.2.1.1. Study characteristics. A total of 23 studies were included in the analysis. As shown in Tables 1 and 2, the most frequently used agent for chemoablation was MMC (61%), followed by GEM (22%). Among the studies of MMC, eight studies applied a weekly instillation regimen and/or device-assisted regimen (ie, electromotive drug administration [EMDA] or hyperthermic intravesical chemotherapy [HIVEC]) [13,25,26,30,37,41,42,44], and one study applied single-dose MMC with EMDA [31]. As a novel intravesical treatment procedure/regimen, two studies assessed the efficacy of MMC-containing reverse thermal gel (MMC-gel) [29,34], and three studies assessed the efficacy of the intensive MMC regimen such as three instillations per week for 2 wk [14,16,30]. The timing of initial cystoscopic and/or histologic assessment ranged from 1 to 8 wk; 19 studies (83%) performed initial assessment within 4 wk after the final instillation of intravesical therapy.

3.2.1.2. Weekly instillation. Eleven studies comprising 385 patients provided data on CR rates at initial assessment for the marker lesion, defined as one marker tumor that remained unresected at TURBT for the chemoablative efficacy evaluation. Among all agents, the pooled CR rate was 50.9% (95% CI: 45.9–55.9; Fig. 2A). There was no statistical difference between different agents ($p = 0.19$). We did not find significant heterogeneity in this analysis.

Ten studies comprising 275 patients provided data on CR rates at initial assessment for bladder tumors in selected NMIBC patients with small tumors and/or a small number of tumors depending on their criteria in the studies. The pooled CR rate was 47.5% (95% CI: 36.5–58.7; Fig. 2B), including both MMC and GEM. The Cochrane's Q ($p < 0.001$) and I^2 ($I^2 = 68\%$) tests revealed significant heterogeneity. There was no difference in CR rates between MMC and GEM, as well as between MMC and device-assisted MMC ($p = 0.3$ and 0.5, respectively; Supplementary Fig. 5).

3.2.1.3. Novel intravesical treatment regimens. Three studies comprising 133 patients and two comprising 85 patients provided data on CR rates at initial assessment in selected NMIBC patients treated with an intensive MMC regimen and MMC-gel. The pooled CR rate of the intensive MMC regimen was 64.7% (95% CI: 56.2–72.3) and that of MMC-gel was 70.6% (95% CI: 60.1–79.3; Fig. 2C). There was no difference between the intensive MMC regimen and MMC-gel in terms of CR rates ($p = 0.4$). We did not find significant heterogeneity in both analyses.

3.2.2. Short-term oncologic outcomes

Excluding the marker lesion study, several studies showed short-term oncologic outcomes for NMIBC patients who achieved a CR at the initial assessment. For weekly instillation, Brausi et al [26] compared the efficacy of eight weekly MMC versus MMC with EMDA and reported that, among 11 patients who achieved a CR at the initial assessment, five (45%) experienced disease recurrence. The disease-free intervals were 10.5 mo in the MMC group and 14.5 mo in the MMC with EMDA group [26]. Maffezzini et al [36] assessed the efficacy of four weekly GEM instillations and demonstrated a median recurrence-free interval of 9.1 mo in the entire cohort. Within the first 12 mo after treatment, seven of 13 patients who achieved a CR experienced disease recurrence, with a 56% recurrence-free probability at the end of the 1st year [36].

For novel intravesical treatment regimens, Chevli et al [29] assessed the efficacy of MMC-gel for intermediate-risk Ta low-grade NMIBC and showed a CR rate of 40% 9 mo after the initiation of treatment, and the probability of durable response 9 mo after the CR after treatment initiation was 72.5% (95% CI: 54.4–84.3).

Table 1 – Demographics of included studies assessing the efficacy of chemoablation for bladder tumors

Authors	Country	Year	Recruitment	Regimen	Number of pts.	Inclusion criteria	Evaluable tumors	Treatment completion, *n* (%)	Definition of CR	CR at initial assessment, *n* (%)	Timing of initial assessment (wk) [a]
Mitomycin											
Prout [13]	USA	1982	1979–1981	MMC 40 mg × 8 weekly	28	Recurrent tumor	Marker lesion	25 (89)	No macroscopic tumors Negative urine cytology	14/28 (50)	4
Maffezzini [37]	Italy	1996	1991–1994	MMC 40 mg × 4 weekly	42	Recurrent tumor with no previous intravesical therapy	Number: <3 Diameter:<1.5 cm	All	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	29/42 (69)	1
Colombo [42]	Italy	1996	1989–1993	1. MMC 40 mg in 50 ml with hyperthermia 2. MMC 40 mg × 4 weekly	52	Ta/T1 any grade	Marker lesion	All	No macroscopic tumors Negative in bladder biopsy	1. 19/29 (66) 2. 5/23 (22)	1–2
Bono [25] [b]	EORTC (multicenter)	1996	1986–1989	MMC 30 mg in 50 ml × 8 weekly	108	Primary or recurrent multiple Ta/T1 tumors	Marker lesion (diameter: <1 cm)	99 (92)	No macroscopic tumors Negative in bladder biopsy	48/96 (50)	2
Brausi [26]	Italy	1998	1993–1995	1. MMC 40 mg × 8 weekly 2. MMC/EMDA × 8 weekly	27	Primary or recurrent multiple Ta/T1 tumors	Marker lesion (diameter: <1.5 cm)	All	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	1. 5/12 (42) 2. 6/15 (40)	2
Colombo [41]	Italy	2001	1996–1998	1. MMC 40 mg in 50 ml 2. MMC 40 mg in 50 ml with hyperthermia 3. MMC 40 mg in 50 ml with EMDA × 4 weekly	80	Recurrent single LG tumors	Number: single Diameter: <2.0 cm	All	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	1. 10/36 (28) 2. 19/29 (66) 3. 6/15 (40)	1–2
Sousa [44]	Spain	2014	2010–2011	MMC 80 mg in 50 ml with hyperthermia × 8 weekly	15	Intermediate/high-risk NMIBC	No limit	All	Total absence of UC (pT0)	8/15 (53)	1–2
Decaestecker [31]	Belgium	2018	2012–2015	MMC 60 mg with EMDA, single dose	32	Primary or recurrent, single or multiple, small (<2 cm) papillary tumors	Number: no limit Diameter: <2.0 cm	All	No macroscopic tumors	8/32 10/36 (all sessions)	2–4
Colombo [30]	Italy	2012	2010–2011	1. MMC 40 mg × 6 weekly 2. MMC 40 mg × 3/wk × 2	1. 27 2. 27	Recurrent single tumors	Number: single Diameter: <1.5 cm	1. All 2. 25 (93)	No macroscopic tumors Negative in bladder biopsy	1. 12 (44) 2. 19 (70)	1–2

(continued on next page)

Table 1 (*continued*)

Authors	Country	Year	Recruitment	Regimen	Number of pts.	Inclusion criteria	Evaluable tumors	Treatment completion, *n* (%)	Definition of CR	CR at initial assessment, *n* (%)	Timing of initial assessment (wk) [a]
Lenis [34]	Israel	2017	NA	MMC gel (VesiGel): 1. VesiGel 40 mg at 64 ml gel (*n* = 20) 2. VesiGel 80 mg at 64 ml gel (*n* = 22) 3. MMC 40 mg in 40 ml (*n* = 23) × 6 weekly	64	LG NMIBC eligible for TURBT	Number: <3: 49/>3: 15 Diameter: <1 cm: 48/>1 cm: 16	All	No macroscopic tumors Negative in bladder biopsy	1. 9 (45) 2. 19 (86) 3. 16 (70)	2–4
Chevli [29]	USA	2022	2018–2020	MMC gel (UGN-102) × 6 weekly	63	LG NMIBC (Ta) Intermediate risk [c]	Number: single/multiple: 11/50 Diameter: <3/>3 cm: 44/17	67 (90)	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	41 (65)	4–6
BCG											
Mack [35]	Belgium	2001	1996–1998	BCG 30 mg × 6 weekly	44	Primary or recurrent, multiple Ta/T1 LG tumors	Number: <10 lesions Diameter: <2.0 cm	39 (89)	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	27 (61)	2
Van der Meijden [40]	NA	1996	NA	MMC × 4 weekly + BCG × 6 weekly	35	NA	Marker lesion	All	No macroscopic tumors Negative in bladder biopsy	19 (54)	2
Gemcitabine											
Gontero [33]	Italy	2004	2002–2003	GEM 2000 mg in 50 ml × 6 weekly	39	Recurrent multiple (no more than 7) Ta/T1 LG tumors Intermediate risk [c]	Marker lesion (diameter: 0.5–1.0 cm)	All	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	22 (56)	2
Serretta [39]	Italy	2005	NA	1. GEM 500 mg (*n* = 9) 2. GEM 1000 mg (*n* = 9) 3. GEM 2000 mg (*n* = 9) in 50 ml × 6 weekly	27	Recurrent multiple Ta/T1 LG tumors	Marker lesion (solitary with 1.0–1.5 cm or 2–3 tumors with 0.5–1.0 cm)	All	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	1. 1 (11) 2. 2 (22) 3. 3 (33)	2–3
Campodonico [28]/ Maffezzini [36]	Italy	2005/ 2007	2003–2004	GEM 2000 mg in 50 ml × 4 weekly	26 (28)	Recurrent single or multiple Ta/T1 LG tumors	Number: <3 lesions Diameter: <1.5 cm	20 (77)	No macroscopic tumors Negative in bladder biopsy	10 (50)	2
Gardmark [32]	Sweden	2005	2002–2004	GEM 2000 mg in 100 ml: 1. Single dose 2. 2/wk × 3 3. 1/wk × 6	30	Recurrent multiple Ta LG tumors	Marker lesion (diameter: 0.5–1.0cm)	All	No macroscopic tumors	All: 9/29 (31) 1. 1/11 2. 4/10 3. 4/9	3
Brausi [27]	Italy	2011	NA	GEM 2000 mg in 50 ml × 6 weekly	14	Primary single tumor	Diameter: <2.0 cm	All	No macroscopic tumors	2 (14)	2

Table 1 (*continued*)

Authors	Country	Year	Recruitment	Regimen	Number of pts.	Inclusion criteria	Evaluable tumors	Treatment completion, *n* (%)	Definition of CR	CR at initial assessment, *n* (%)	Timing of initial assessment (wk) [a]
									Negative in bladder biopsy Negative urine cytology		
Epirubicin											
Popert [38]	UK	1994	NA	EPI single dose: 1. 50 mg in 50 ml saline (n = 40) 2. 100 mg in 50 ml saline (n = 41)	81	Recurrent tumor with no previous intravesical therapy	Marker lesion (diameter: 0.5 cm)	All	No macroscopic tumors Negative in bladder biopsy	37 (46)	8
Bono [25] [b]	EORTC (multicenter)	1996	1986–1989	EPI 50 mg in 50 ml × 8 weekly	40	Primary or recurrent multiple Ta/T1	Marker lesion (diameter: <1 cm)	39 (98)	No macroscopic tumors Negative in bladder biopsy	20/36 (56)	2

BCG = bacillus Calmette-Guérin; CR = complete response; EMDA = electromotive drug administration; EORTC = European Organization for Research and Treatment of Cancer; EPI = epirubicin; GEM = gemcitabine; LG = low grade; MMC = mitomycin C; NA = not applicable; NMIBC = non–muscle-invasive bladder cancer; pts. = patients; TURBT = transurethral resection of a bladder tumor; UC = urothelial carcinoma.

[a] Timing of initial assessment was defined as weeks after the completion of intravesical therapy.

[b] Described in separating the two arms.

[c] Intermediate-risk disease was defined as having one or two of the following: presence of multiple tumors, solitary (tumor >3 cm and/or recurrence—one occurrence of LG NMIBC within 1 yr of the current diagnosis).

3.2.3. *Oncologic outcomes of chemoablation versus standard treatment*

As shown in Table 2, three studies compared the treatment outcomes of chemoablation versus current standard treatment for recurrent tumors. Two studies reported the differential CR rates between the two treatments [15,16]. In the CALIBER trial, which compared the efficacy of chemoablation with four weekly MMC instillations versus TURBT ± immediate single-dose MMC, the CR rates at the initial assessment at 3 mo were 37.0% (95% CI: 24.3–51.3) with chemoablation and 80.8% (95% CI: 60.6–93.4) with standard treatment [15]. However, there were no differences between chemoablation (82.7%) and standard treatment (75.4%, p = 0.09) in the 12-mo recurrence-free rate, while among the patients with residual disease at initial assessment, this rate was significantly lower in the standard treatment group (40%) than in the chemoablation group (84%, p = 0.01) [15]. A prospective study conducted by Racioppi et al [16] comparing the efficacy of intensive MMC chemoablation with three instillations per week for 2 wk versus TURBT + adjuvant six weekly MMC instillations showed similar CR rates at the initial assessment at 3 mo (72% vs 79%) as well as at 39 mo (62% vs 70%, p = 0.38). Most recently, long-term follow-up results from the DaBlaCa study showed that the 24-mo recurrence-free survival was comparable between chemoablation (43%, 95% CI: 30–56) and standard treatment (36%, 95% CI: 24–50, p = 0.15) [43].

3.2.4. *Meta analysis of risk of non-CR at initial assessment stratified by tumor demographics*

Five studies published in the past 5 yr provided data on the differential non-CR rates stratified by the tumor demographics [14,16,29,31,34]. As shown in Figure 3, tumor size of <5 mm was associated with better CR rates than tumor size of ≥5 mm (pooled OR: 0.36, 95% CI: 0.17–0.79); however, this association disappeared when stratified by tumor size of 10 mm (pooled OR: 0.93, 95% CI: 0.34–2.50). We did not find any association of non-CR rates with tumor multiplicity (pooled OR: 0.77, 95% CI: 0.28–2.15). We did not find significant heterogeneity in all analyses.

3.3. *Safety of novel intravesical treatment regimens*

3.3.1. *AEs of MMC-gel*

A single-arm phase 2 study conducted by Chevli et al [29] showed the detailed AE profiles of the application of MMC-gel. The rates of any and severe (CTCAE grade 3–5) AEs were 90% and 7.9%, respectively, while treatment-related AEs were noted in 63% of participants. The most frequent treatment-related AE was dysuria (41%), followed by frequency (21%), hematuria (16%), and cystitis (14%).

3.3.2. *AEs of weekly MMC versus intensive MMC regimen*

Only the phase 2 randomized controlled trial (RCT) conducted by Colombo et al [30] compared the safety of the intensive MMC regimen (three instillations per week for 2 wk) versus six weekly MMC instillations before TURBT. The authors revealed no differences in the rates of urinary frequency (p = 0.85), cystitis (p = 0.52), incontinence (p = 0.33), hematuria (p = 0.22), and lower urinary tract pain (p = 0.65) between the two different instillation regimens.

Table 2 – Demographics of included comparative studies assessing chemoablation with mitomycin versus standard treatment

Study name/first author	Country	Year	Recruitment	Setting	Intervention	Control	Number of pts.			Inclusion criteria	Evaluable tumors	Definition of CR	CR, *n* (%)		Timing of initial assessment (mo) [a]
							Total	Intervention	Control				Intervention	Control	
Weekly MMC regimen															
CALIBER/ Mostafid [15]	UK	2020	2015–2017	RCT	MMC 40 mg × 4 weekly	TURBT ± immediate single MMC	84	54	28	Recurrent single or multiple tumors with previous low-risk NMIBC EORTC recurrence risk score <6	Number: no limit Diameter: no limit	No macroscopic tumors Negative in bladder biopsy	20 (37)	21 (81)	3
Intensive MMC regimen															
DaBlaCa-13/ Lindgren [14,43]	Denmark	2020/ 2022	2018–2021	RCT	MMC 40 mg 3/wk × 2	TURBT+ adjuvant MMC or BCG × 6 weekly	120	59	61	Recurrent multiple tumors with previous Ta BCa EORTC intermediate/ high risk [a]	Number: no limit Diameter: <2.0 cm	No macroscopic tumors	33 (57)	NA	1–2
Racioppi [16]	Italy	2019	2007–2013	Prospective	MMC 40 mg 3/wk × 2	TURBT + immediate and adjuvant MMC × 6 weekly	94	47	47	Recurrent single or multiple tumors with previous EORTC low-/ intermediate-risk NMIBC	Number: NA Diameter: <2.0 cm	No macroscopic tumors Negative in bladder biopsy Negative urine cytology	34 (72) 31 (66) 30 (64) 30 (64) 29 (62)	37 (79) 34 (72) 34 (72) 33 (70) 33 (70)	3 9 15 21 27

BCa = bladder cancer; BCG = bacillus Calmette-Guérin; CR = complete response; EORTC = European Organization for Research and Treatment of Cancer; MMC = mitomycin C; NA = not applicable; NMIBC = non–muscle-invasive bladder cancer; pts. = patients; RCT = randomized controlled trial; TURBT = transurethral resection of a bladder tumor.

[a] Timing of Initial assessment was defined as months after the completion of intravesical therapy.

(A) Weekly administration for marker lesion

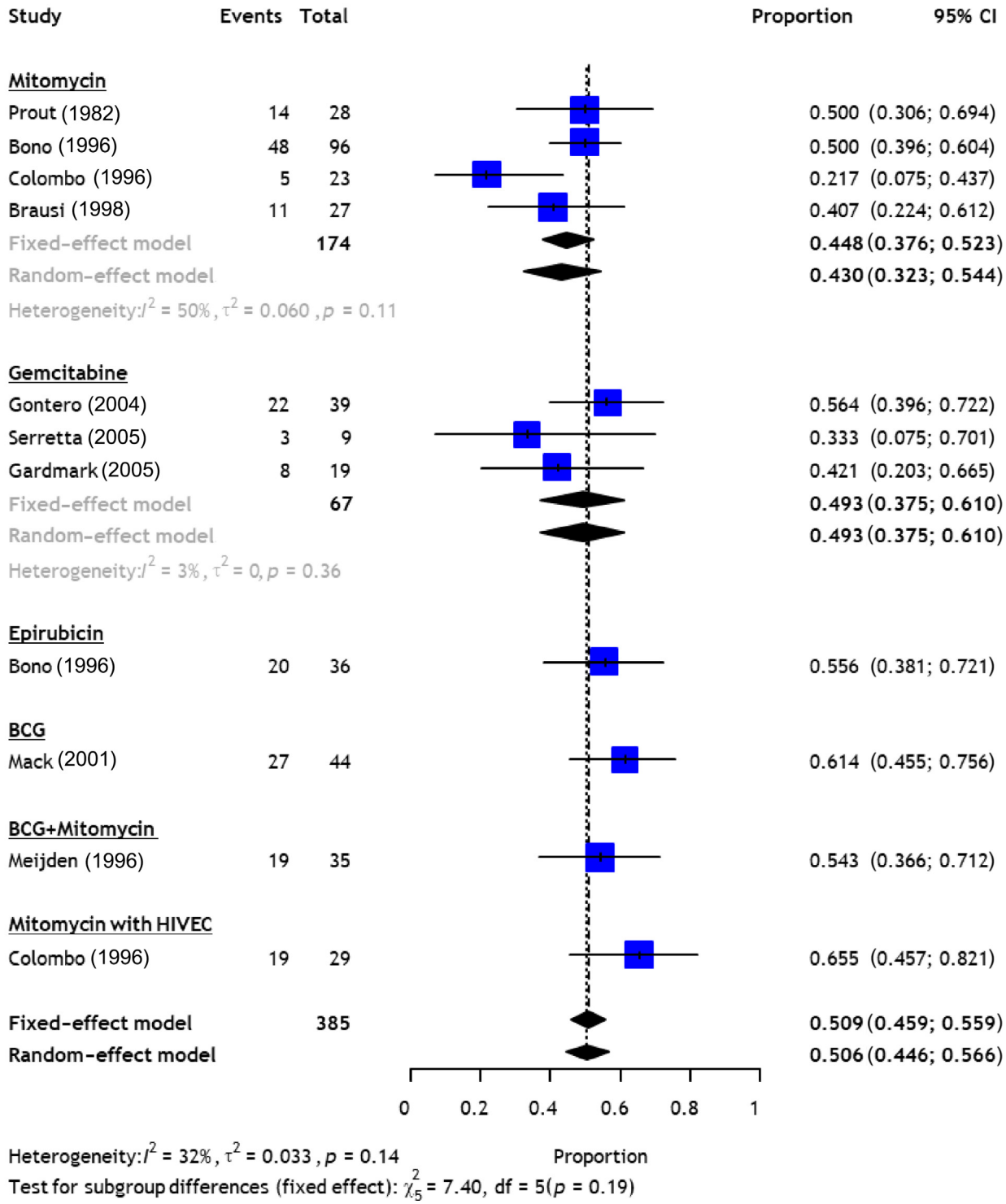


Fig. 2 – Forest plots showing pooled CR rates of chemoablation for NMIBC at initial assessment: (A) weekly administration for marker lesion, (B) weekly administration for selected NMIBC, and (C) novel intravesical treatment regimens for selected NMIBC. BCG = bacillus Calmette-Guérin; CI = confidence interval; CR = complete response; df = degree of freedom; EMDA = electromotive drug administration; HIVEC = hyperthermic intravesical chemotherapy; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer.

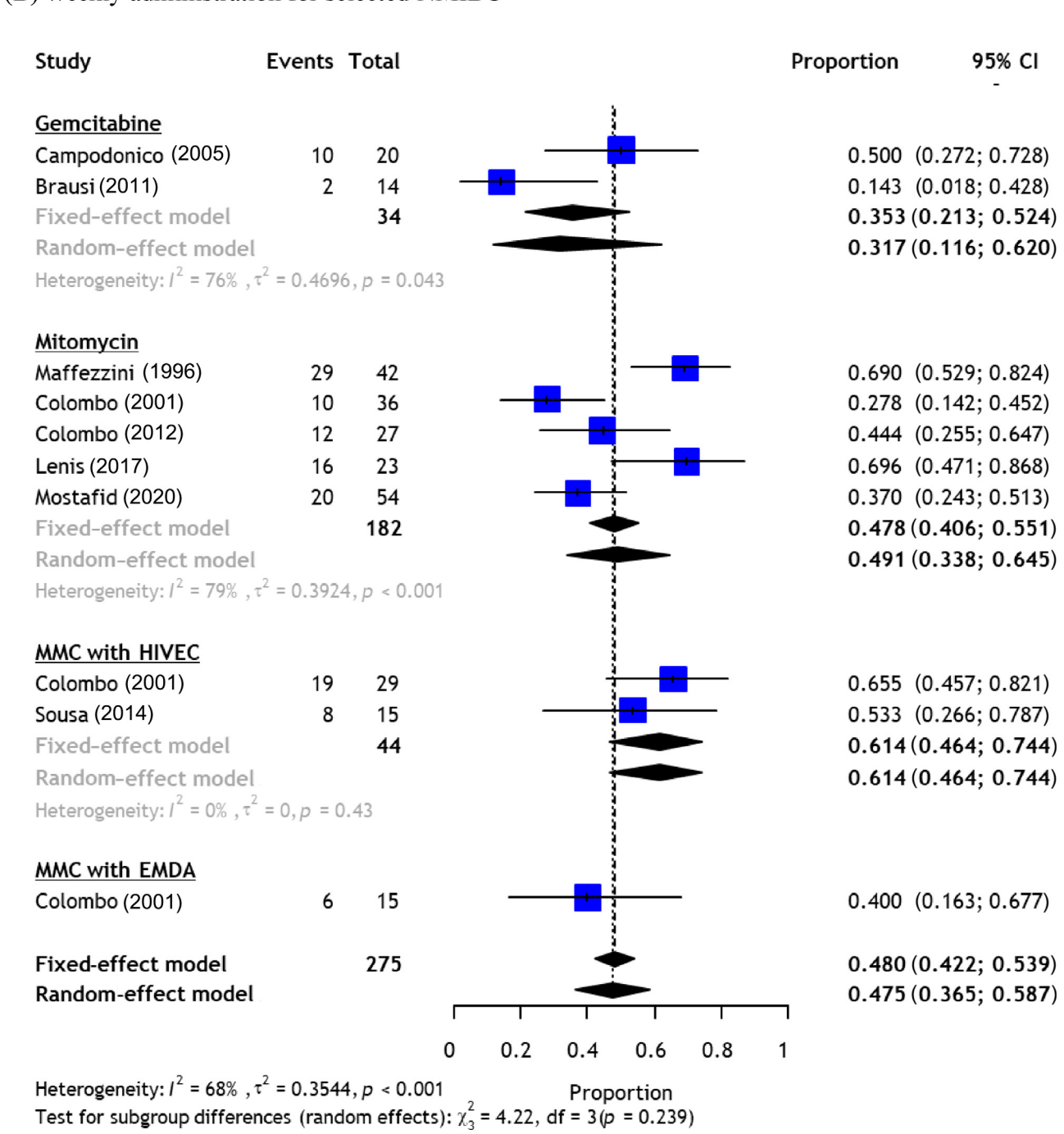


Fig. 2 (continued)

3.3.3. Meta-analysis of treatment-related AEs of MMC chemoablation versus standard treatment

Three comparative studies provided data on differential AEs between MMC chemoablation and. standard surgical treatment [14–16]. As shown in Figure 4, there were no differences in the incidence of cystitis (pooled OR: 0.48, 95% CI: 0.08–2.97), hematuria (pooled OR: 0.73, 95% CI: 0.39–1.37), incontinence (pooled OR: 0.72, 95% CI: 0.38–1.39), and pelvic pain (pooled OR: 0.75, 95% CI: 0.31–1.81) between the two treatments. On the contrary, even in patients treated with an intensive MMC regimen, chemoablation was associated with a lower incidence of dysuria (OR: 0.43, 95% CI: 0.20–0.93) and frequency (pooled OR: 0.49, 95% CI: 0.25–0.97) than the standard treatment. The Cochrane's Q (p = 0.035) and I^2 (I^2 = 70%) tests revealed significant heterogeneity only in the analysis of cystitis.

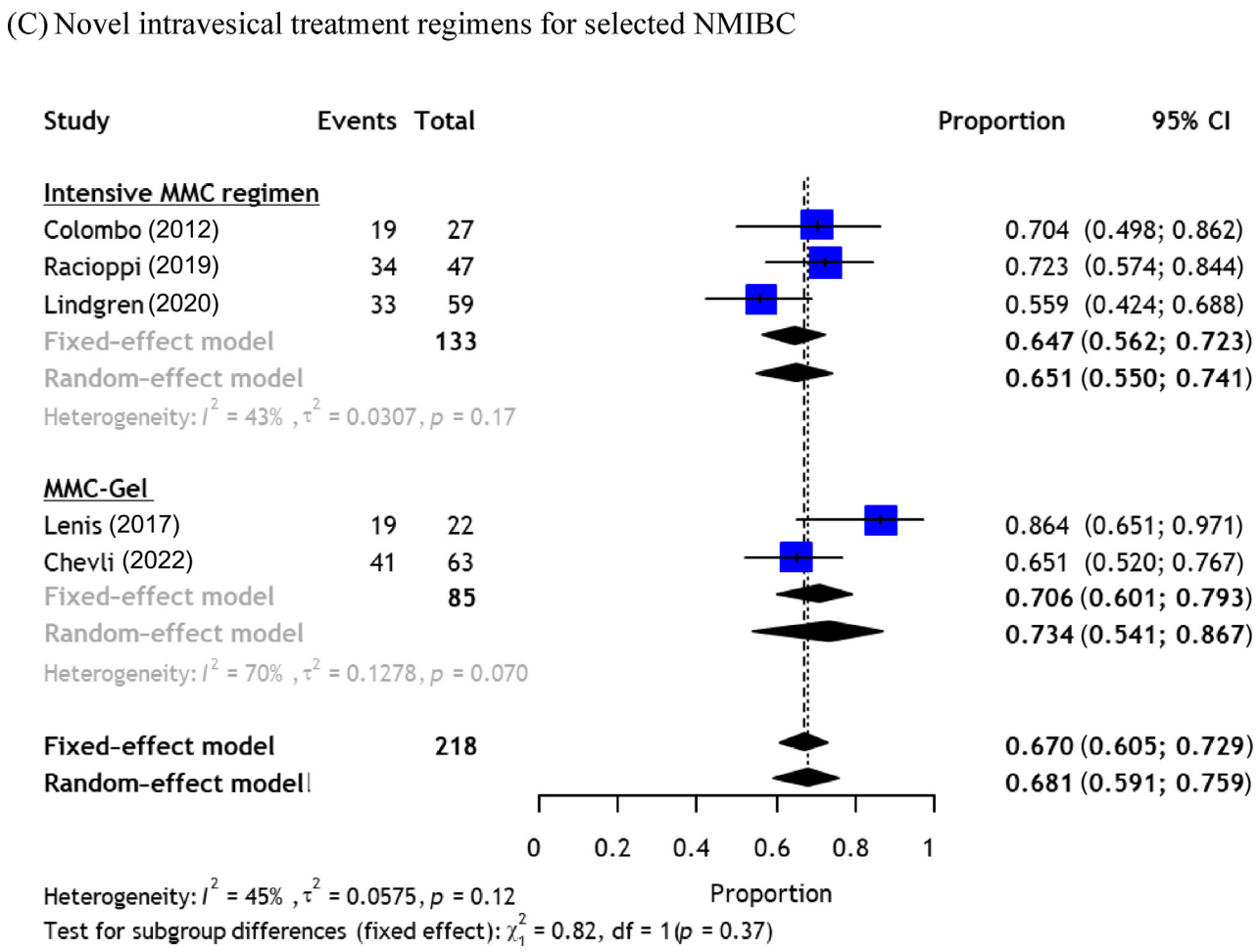


Fig. 2 (continued)

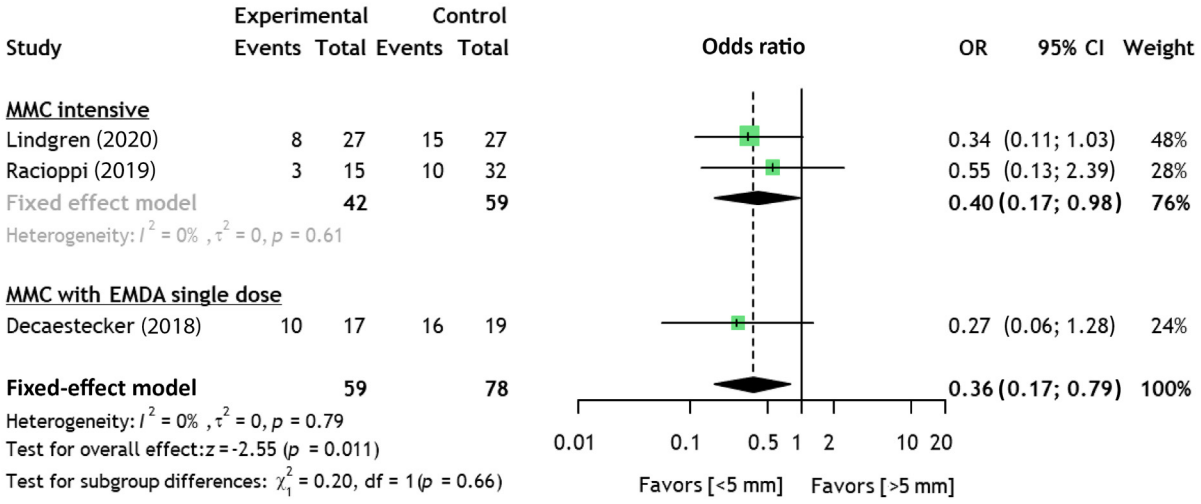
3.4. *Discussion*

This is the first meta-analysis to analyze the clinical efficacy and safety of chemoablation in patients with NMIBC. Although the included studies had preliminary results, there are several key findings to be noted. First, among patients treated with weekly intravesical instillation therapy, chemoablation achieved a CR rate of approximately 50% at the initial assessment for well-selected tumors. Second, as novel forms of chemoablation, MMC-gel and intensive MMC regimen achieved high CR rates with no statistically significant differences between the two procedures. Third, the efficacy of chemoablation was comparable irrespective of tumor multiplicity, whereas tumor size of <5 mm resulted in a higher CR rate than tumor size of ≥5 mm. Finally, the novel intensive MMC regimen was associated with lower rates of dysuria and frequency than the standard treatment with TURBT followed by intravesical therapy.

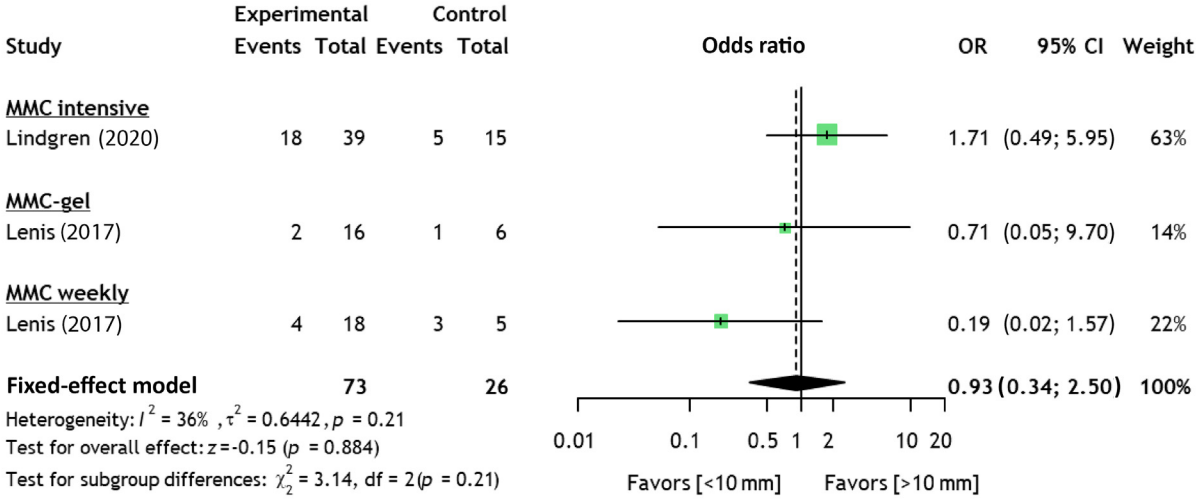
We found approximately 50% CR rates for well-selected NMIBC patients even with a conventional weekly instillation regimen. In addition, the novel forms/regimens of chemoablation achieved higher CR rates despite expanding the inclusion criteria to multiple or larger tumors. Hence, theoretically, approximately half of patients with small tumors and/or a small number of tumors may avoid TURBT, suggesting the clinical applicability of neoadjuvant intravesical therapy followed by TURBT only for those who did not achieve a CR at a predetermined time. Indeed, the DaBlaCa study showed that 29% of patients in the chemoablation group avoided the surgical procedure [43]. Although the optimal number of cycles prior to calling failure remains unknown with the concept of partial responses being facilitated by precise mapping of the tumors in the bladder, neoadjuvant intravesical treatment has a potential impact on avoiding unnecessary surgical procedures.

In addition, an RCT comparing the long-term oncologic outcomes between neoadjuvant MMC with EMDA + TURBT versus TURBT + immediate MMC versus TURBT alone revealed a significantly lower recurrence rate in the neoadjuvant MMC group [45]. These results suggest that neoadjuvant MMC therapy could treat an unrecognized tumor or prevent the implantation of viable cancer cells during TURBT, reducing the recurrence rate [45]. The results from the CALIBER trial showed that the long-term recurrence rate was better for the chemoablation with weekly MMC instillation than for the standard treatment, which further supports the potential efficacy of neoadjuvant intravesical therapy [15]. To date, chemoablation for NMIBC is mentioned in the EAU guidelines; however, it has not yet been adopted into clinical practice [1]. Further investigation with more patients is needed to establish the value of chemoablation in our armamentarium; however, satisfactory mid- or long-term oncologic outcomes provided by the recent two RCTs will enrich the success of its standardization [15,43].

(A) Tumor size <5 vs ≥5 mm



(B) Tumor size <10 vs ≥10 mm



(C) Tumor multiplicity

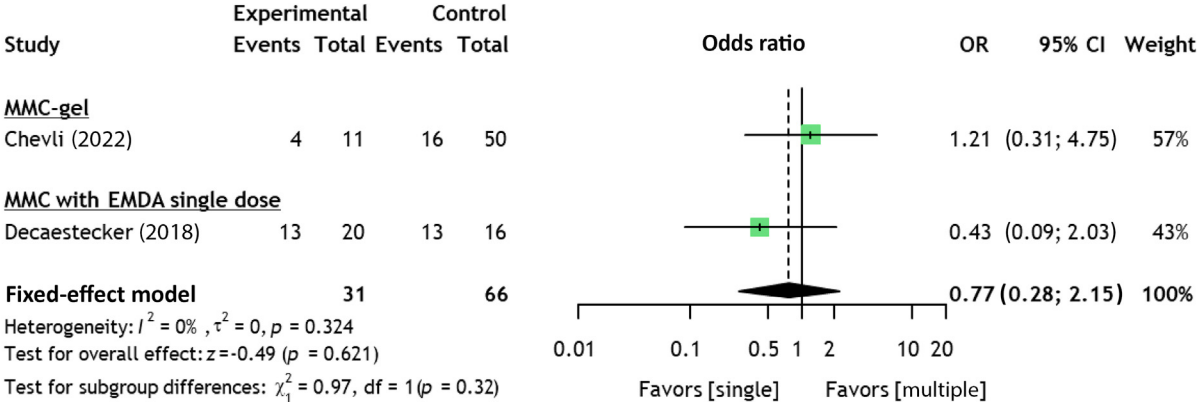
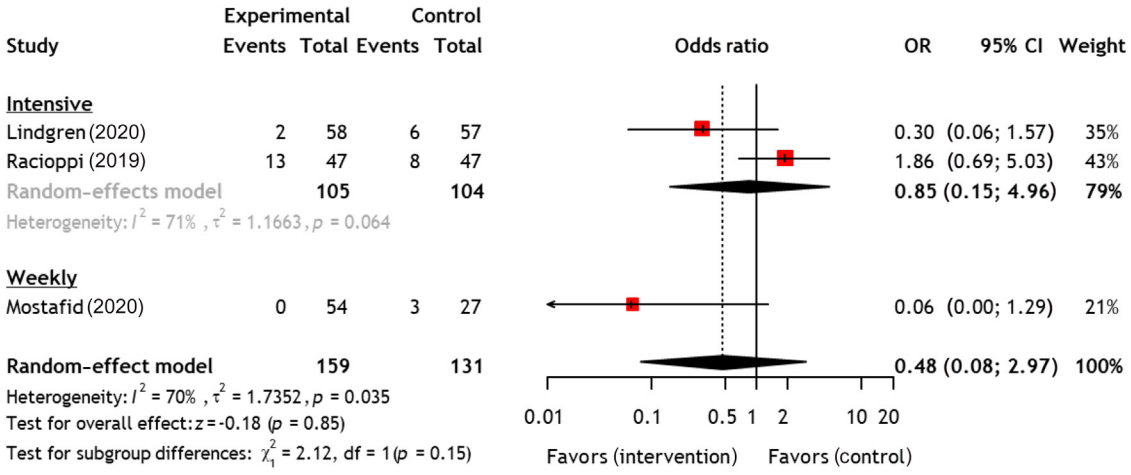
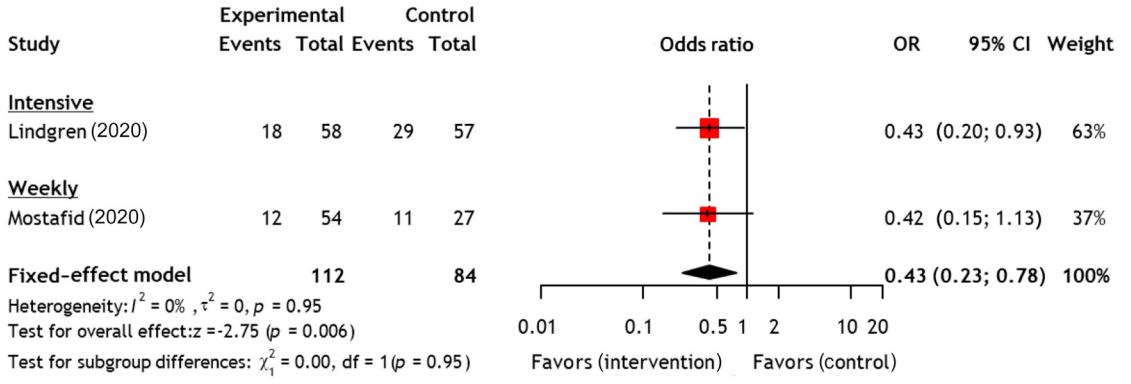


Fig. 3 – Forest plots showing the association of non-CR rates of chemoablation for NMIBC at initial assessment and tumor demographics: (A) tumor size 5 versus ≥5 mm, (B) tumor size <10 versus ≥10 mm, and (C) tumor multiplicity. CI = confidence interval; CR = complete response; df = degree of freedom; EMDA = electromotive drug administration; MMC = mitomycin C; MMC-gel = MMC-containing reverse thermal gel; NMIBC = non–muscle-invasive bladder cancer; OR = odds ratio.

(A) Cystitis



(B) Dysuria



(C) Frequency

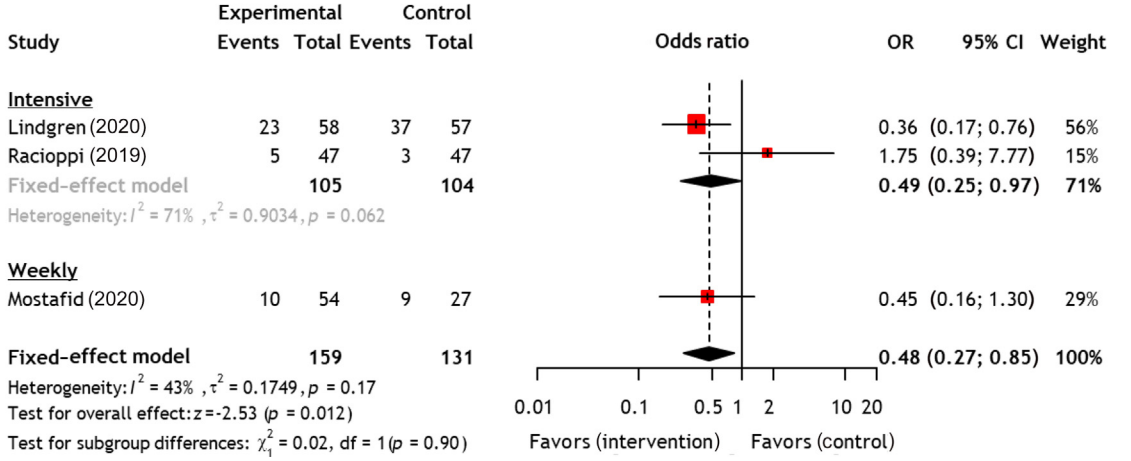
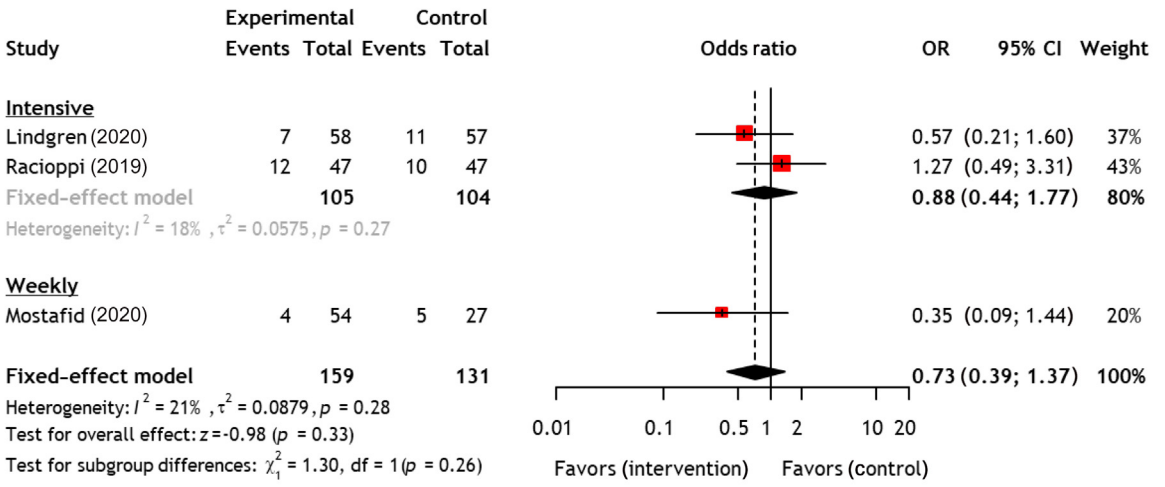
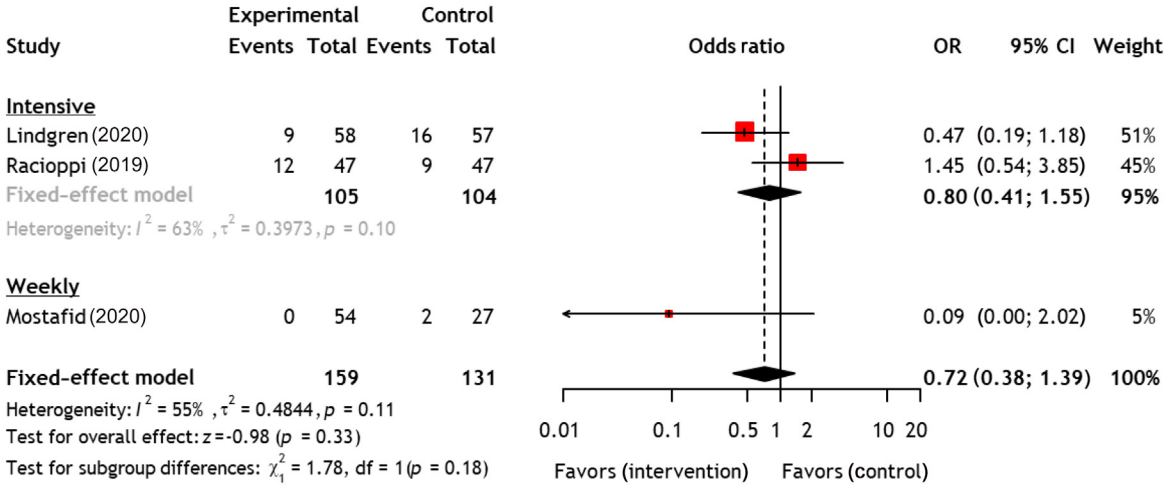


Fig. 4 – Forest plots showing the differential treatment-related AEs between chemoablation with intensified MMC therapy and conventional treatment: (A) cystitis, (B) dysuria, (C) frequency, (D) hematuria, (E) incontinence, and (F) pelvic pain. AE = adverse event; CI = confidence interval; df = degree of freedom; MMC = mitomycin C; OR = odds ratio.

(D) Hematuria



(E) Incontinence



(F) Pelvic pain

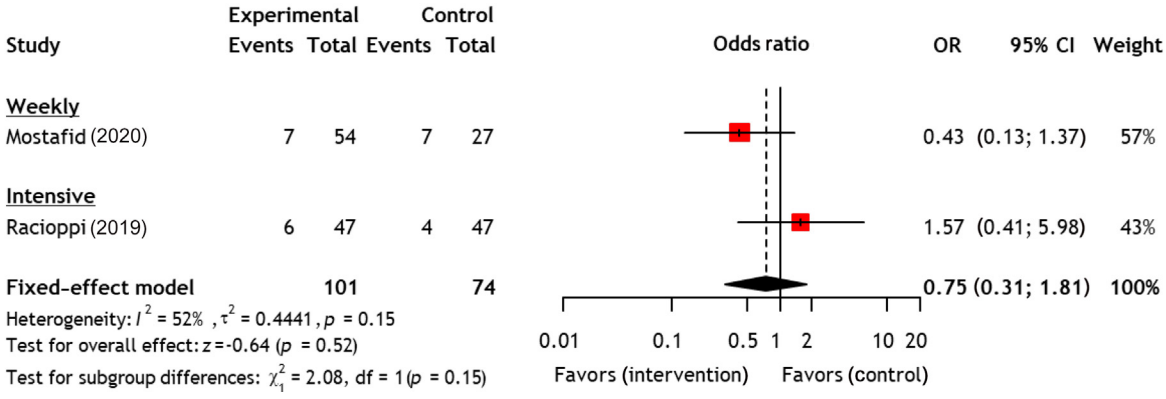


Fig. 4 (continued)

Key to this success will also be the selection of adequate candidates who are most likely to benefit from chemoablation with regard to efficacy and tolerability.

Our analyses revealed similar efficacy of chemoablation irrespective of tumor multiplicity, while superior performance in tumors sized <5 mm having higher CR rates than those sized ≥5 mm. This result aligns with the hypothesis that the ablative efficacy might be prominent in smaller tumors; most chemoablation studies set tumor size as one of their inclusion criteria. However, recurrent tumors sized <5 mm are also safe candidates for observation and/or fulguration [46,47]; a well-designed comparative study is needed to establish optimal management for such small recurrent tumors. On the contrary, it was demonstrated that MMC-gel achieved a CR rate of 41% (7/17) in patients with tumors >3 cm [29]. Furthermore, a prospective study conducted by Raber et al [48] assessing the efficacy of a neoadjuvant intensive MMC regimen for large unresectable tumors (mean: 51 mm) showed that neoadjuvant intensive MMC downsized the tumors by a mean of 17 mm of tumor diameter in all patients, which in turn improved the possibility of achieving complete resection. Taken together, if a CR is the aim, the efficacy of chemoablation appears to be best in small tumors; however, the novel forms of intravesical treatment such as MMC-gel showed a promising ablative impact on larger tumors as well. Furthermore, a neoadjuvant intensive MMC therapy might also improve the rates of complete resection and resection quality; therefore, further studies with more patients with not only recurrent but also primary tumors and longer follow-up are needed to clarify the true efficacy of neoadjuvant intravesical therapy for large tumors.

Recently, there have been increasing investigations regarding the efficacy of enhancement in bladder drug delivery [1]. Promising oncologic outcomes in NMIBC patients treated with device-assisted intravesical therapy, such as EMDA and HIVEC, have been demonstrated in several systematic reviews and meta-analyses [49–52]. Although our analyses did not show the statistical superiority of device-assisted MMC therapy over MMC monotherapy in terms of CR rates (pooled CR rates: 56% vs 49%; Supplementary Fig. 5), better absolute CR rates for device-assisted MMC therapy were reported in some studies included, and this analysis suffered from the inclusion of a small number of studies/patients. Further investigations are needed to clarify the potential impact of enhancement techniques on the efficacy of chemoablation.

As a part of a novel enhancement technology in bladder drug delivery, we found that MMC-containing reverse thermal gel achieved the highest CR rates of 71.2%; this is a novel form of chemoablation formulation with polymers designed to prolong the dwell time of MMC on the bladder mucosa, thereby potentially improving the exposure and kill time (ie, ablative efficacy) [29]. The ablative efficacy of this formulation of MMC was also evaluated in upper tract urothelial carcinoma, with 41 of 71 patients (56%) having had a CR and 23 patients (56%) remaining cancer free at 12 mo [53]. While the efficacy of MMC-gel was highly promising, the high ureteral stricture rate was a treatment-limiting AE [29,53]. Although MMC-gel for NMIBC did not cause deterioration in patient-reported urinary symptoms [54], the treatment outcomes, as well as AEs of an ongoing phase 3 RCT (NCT04688931), are awaited.

Our review confirmed that the intensive MMC regimen, which consists of three instillations per week for 2 wk, also resulted in a high CR rate, which was not significantly different from that of the standard treatment (ie, TURBT). Other than the satisfactory ablative effect of this novel regimen, notably MMC chemoablation outperformed standard treatment in terms of AE rates such as dysuria and frequency even with the intensive MMC regimen. The demonstrated safety profile of this regimen is in line with the results of the phase 2 trial of the intensive MMC regimen [30]. Although the CALIBER trial showed similar health-related quality of life (QoL) between the two treatments [15], the safety and efficacy of the intensive MMC regimen, including the potential for omitting unnecessary TURBT, will surely improve the patient QoL and cost effectiveness of this treatment approach. Furthermore, a surveillance study of treatment preference in NMIBC patients who experienced TURBT one or more times revealed that a significant proportion of patients preferred chemoablation to TURBT [55]. Considering the safety, consecutive patient QoL, possible cost-benefit, as well as patient preference, chemoablation can be a valuable treatment option if introduced into clinical practice in the near future, specifically for the elderly, in cost-saving environments, and/or in case of limited access to healthcare or capacity such as in a pandemic.

Despite the demonstrated benefits of chemoablation in this study, our study has several limitations that need to be addressed. First, most included studies were preliminary; therefore, the number of patients is limited. Second, we included different intravesical regimens such as MMC, BCG, EPI, and GEM [56]. In addition, the inclusion criteria were somewhat different between included studies; therefore, we carefully stratified these different agents and regimens based on evaluable tumor characteristics. Moreover, we pooled the results of the studies published in different eras from 1982 to 2022; therefore, our analyses must be considered to have different diagnostic/treatment standards such as different clinical guidelines, tumor grading systems, or advancement of cystoscopy. Therefore, we performed sensitivity analyses of CR rates stratified by published year (Supplementary Fig. 6) and carefully set the inclusion criteria (limiting studies to those published in the past 5 yr) for an analysis of the risk of non-CR at initial assessment stratified by tumor demographics. Although our sensitivity analyses revealed no differences irrespective of published years, different study demographics, possibly due to temporal biases, might cause heterogeneity in some analyses. Hence, we adopted random-effect models in case of significant heterogeneity; thus, these results need to be interpreted with caution. Third, in our analyses regarding the risk of non-CR at initial assessment stratified by tumor characteristics, we did not consider possible confounders for analysis. Therefore, a well-designed analysis for predictive/prognostic factors with a multivariable analysis is warranted to select adequate candidates who are most likely to benefit from chemoablation.

4. Conclusions

Although our analyses lack long-term outcomes, we confirmed the powerful ablative effect of intravesical therapy in well-selected NMIBC patients. Although chemoablation cannot replace the current standard treatment such as

TURBT followed by postoperative intravesical therapy, neoadjuvant intravesical therapy may lead to the omission of unnecessary TURBT or to the improvement in the chance of achieving a complete resection, leading to better long-term oncologic outcomes. Further investigation with many patients and long-term oncologic outcomes is needed to establish more reliable evidence for changing clinical practice, making chemoablation a standard strategy in the management of well-selected NMIBC patients.

***Author contributions*:** Takafumi Yanagisawa 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: Yanagisawa, Shariat.
Acquisition of data: Yanagisawa, Quhal, Kawada.
Analysis and interpretation of data: Yanagisawa, Quhal, Kawada.
Drafting of the manuscript: Yanagisawa, Quhal, Kawada.
Critical revision of the manuscript for important intellectual content: Mostafaei, Motlagh, Laukhtina, Rajwa, von Deimling, Bianchi, Pallauf, Majdoub, Pradere, Moschini).
Statistical analysis: Yanagisawa, Kawada.
Obtaining funding: None.
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Supervision: Karakiewicz, Teoh, Miki, Kimura, Shariat.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.12.003.

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