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Oncological effectiveness of bladder-preserving trimodal therapy versus radical cystectomy for the treatment of muscle-invasive bladder cancer: a system review and meta-analysis

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Abstract

Objective Radical cystectomy (RC) is the gold standard treatment for muscle-invasive bladder cancer (MIBC). As a bladder-preservation option recommended in guidelines, trimodal therapy (TMT) has become increasingly popular in recent years. However, it is still uncertain whether TMT can provide comparable oncologic outcomes to RC. Therefore, it is imperative to evaluate whether TMT yields comparable outcomes to RC.

Methods We conducted a systematic search of Web of Science, MEDLINE, the Cochrane Library, and EMBASE databases up to June 2023 to identify studies that met our inclusion criteria. The primary outcome measures evaluated in this study were overall survival (OS) and cancer-specific survival (CSS). The study quality was evaluated independently by two authors, and data were extracted accordingly.

Results After excluding duplicates and ineligible articles, our meta-analysis included seven studies involving 3,489 and 13,877 patients in the TMT and RC groups, respectively. Short-term overall survival rates were comparable between the groups, but beyond 5 and > 10-years, the RC group had significantly higher overall survival rates compared to the TMT group. In terms of cancer-specific survival, there was no significant difference between the groups at 1-year follow-up, but from the second year onwards, including the 5-year and > 10-year nodes, the RC group had significantly better outcomes compared to the TMT group.

Conclusion The treatment effect of RC is better than that of TMT. Unless the patient can't tolerate RC or has a strong desire to preserve the bladder, RC should be chosen over TMT in treatment, and patients undergoing TMT should be closely followed up.

Keywords Muscle-invasive bladder cancer, Trimodal therapy, Radical cystectomy, Meta-analysis

Introduction

Bladder cancer is a highly prevalent and lethal tumor of the urinary system [1, 2]. For patients with non-metastatic muscle-invasive bladder cancer (MIBC), radical cystectomy (RC) is currently the recommended standard treatment. However, RC is associated with a significant risk of perioperative morbidity and mortality, with

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up to 67% of patients experiencing complications within 90 days of surgery [3, 4]. This reduces the life expectancy of patients and leads to psychological distress [5]. As a result, trimodal therapy (TMT) has emerged as an alternative treatment option for patients who are unable to tolerate RC or who strongly desire to preserve their bladder [6]. The fundamental treatment strategy of TMT entails performing maximum transurethral resection of bladder tumor (TURBT) followed by concurrent administration of chemotherapy and radiation therapy (RT). Briefly, RT and chemotherapy involve a dose of 55–64 Gy delivered over a period of 4–6 weeks in daily fractions of 2–2.75 Gy, targeting the bladder, distal ureter, and proximal urethra (including the prostate), with concurrent 5-fluorouracil plus mitomycin, gemcitabine, or cisplatin. MRI can aid in precise delineation of the TURBT site for radiotherapy planning [7, 8]. The main advantage of TMT is that it preserves bladder function, allowing patients to have a more satisfactory survival experience. However, compared with RC, TMT s ability to control tumors has been questioned. Several articles have recently analyzed the oncological outcomes of TMT and RC, but their results have been conflicting [9–14]. Therefore, it remains unclear whether TMT can provide comparable oncological outcomes to RC.

To evaluate whether TMT can provide comparable oncologic outcomes to RC, we performed this meta-analysis. By using multifactor regression and propensity score matching (PSM), we aimed to reduce the impact of confounding variables and selection bias on the results of the meta-analysis. As a result, the inclusion criteria of our study were limited to those that used these methods, which helped to improve the reliability of our findings.

Methods

Search strategy and study selection

Adhering to the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15], we conducted an overall thorough selection criteria and statistical analysis of the literature. This study has been registered with the INPLASY registry (registration number: INPLASY202350004). We utilized the following search terms: ("trimodal therapy" OR "radiotherapy" OR "chemoradiotherapy" OR "chemoradiation" OR "bladder-sparing") AND ("radical cystectomy") AND ("bladder cancer" OR "bladder carcinoma") to search for relevant studies in Web of Science, EMBASE, MEDLINE, and the Cochrane Library up to June 2023. To ensure the quality of the included studies, several requirements were satisfied. First, only randomized controlled trials (RCTs) or prospective/retrospective cohort studies were considered. Second, Studies had to compare the effectiveness of trimodal therapy (TMT) and radical cystectomy (RC) in patients diagnosed with muscle-invasive bladder cancer (MIBC). Third, the primary outcome measures had to report overall survival (OS) or cancer-specific survival (CSS). Fourth, multivariable analysis or propensity score matching was required for the survival outcomes analysis. Fifth, letters to the editor, reviews, case-series, and case-reports were not considered. Finally, in the case of multiple studies based on real-world databases, the study providing the most relevant information was selected.

Data extraction and risk of bias

Our team of two independent reviewers conducted a thorough data extraction process from the relevant studies. The extracted data included study demographics, patient baseline characteristics, and the primary outcome measures of OS and CSS. The reviewers meticulously extracted the data to ensure accuracy and completeness. Study demographics comprised the first author's name, publication year, patient country of origin, study design type, and follow-up duration. Patient baseline characteristics included age at diagnosis, sex distribution, Charlson comorbidity score status, tumor stage classification system used for diagnosis or treatment planning purposes, and tumor grade. To assess the quality of individual studies, the two reviewers evaluated them independently using the Downs and Black tool [16], which ranges from 0 to 28. In cases of disagreement, a third investigator was consulted to resolve them. Additionally, to reduce the risk of duplicate data, we carefully examined the included studies and excluded any overlapping data.

Statistical analysis

We employed different statistical methods to analyze the data in our study. For continuous and dichotomous baseline variables, we used weighted mean difference (WMD) and risk ratio (RR), respectively, with 95% confidence intervals (CIs) to compare the TMT and RC groups. To compare the OS and CSS outcomes between the two groups, we used hazard ratios (HR) with 95% CIs. We considered a p-value of less than 0.05 as statistically significant.

To evaluate the heterogeneity among studies, we used Chi-square-based Q tests and I^2 statistics. When high heterogeneity was observed, defined as an I^2 value > 50% and a P value < 0.05, we used a random-effects model (the DerSimonian and Laird method) to determine the pooled effect. If this method was not feasible, we used a fixed-effects method (the Mantel–Haenszel method) for meta-analysis [17]. We assessed possible publication bias by creating Begg's funnel plot and performing Egger's test. Begg's funnel plot evaluates the asymmetry of the distribution of study results and sample sizes, while Egger's test assesses the relationship between the effect size and

its standard error. All statistical analyses were performed using Review Manager version 5.4.

Results

Study selection and characteristics of studies

A flowchart in Fig. 1 illustrates the selection process of relevant literature. Our comprehensive search identified 5378 articles ultimately. We excluded duplicates and studies that didn't accord with our inclusion criteria based on title, abstract scan, and subsequent full-text review. Ultimately, seven articles with data on 3489 and 13877 patients in the TMT and RC groups, respectively, were included in our meta-analysis [13, 18–23]. Table 1 shows the characteristics and quality assessment of the included studies. All seven articles were retrospective cohort designs. Among them, five articles [18–22] used PSM, in which age, gender, tumor stage, and tumor grade were the most frequent matching factors. All seven articles performed multivariable analysis. Based on the quality ratings, the most of the articles included in our analysis were determined to be of moderate quality.

Baseline characteristics of included patients

Five articles presented individual patient data without propensity score matching, as shown in Supplemental Fig. 1. At baseline, the TMT group exhibited significantly older age (WMD: 6.53 years, 95% CI: 3.91–9.16, $P<0.001$, $I^2=97\%$), comparable sex distribution (RR: 1.04, 95% CI: 0.96–1.13, $P=0.34$, $I^2=0\%$), higher rates of comorbidity (RR: 1.56, 95% CI: 1.36–1.80, $P<0.001$, $I^2=0\%$), lower tumor stage (RR: 0.68, 95% CI: 0.48–0.97, $P=0.03$, $I^2=90\%$), and lower tumor grade (RR: 0.98, 95%

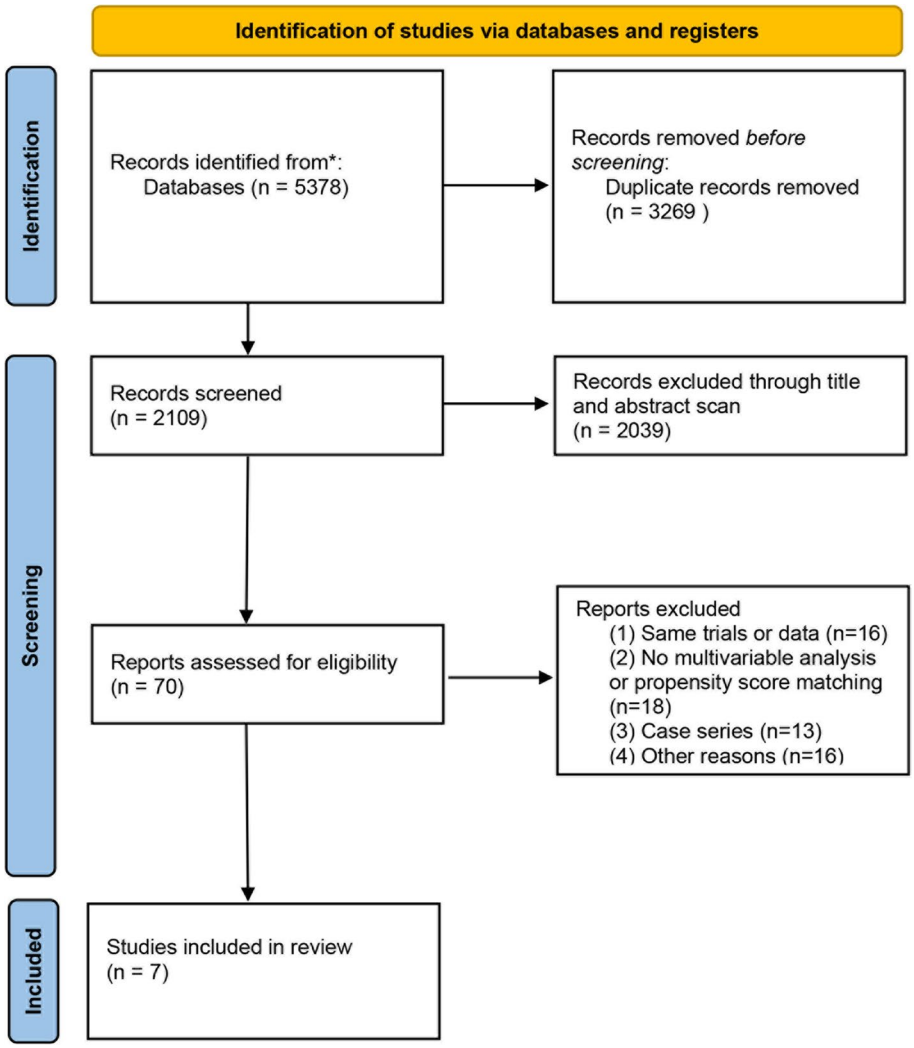

Fig. 1 Flow diagram of selection of eligible studies

Table 1 Characteristic and quality of retrieved studies

Reference	Year	Country, year	Patient Number (after PSM)		Maximum follow up (years)	PSM	Design	Quality score
			TMT	RC				
Bekelman [23]	2013	SEER, 1995–2005	417	1426	9	None	R	15
Kim [22]	2017	Korea, 2007–2014	32 (29)	308 (50)	5	1,2,5,6,10	R	15
Kulkarni [21]	2017	Single-center, 2008–2013	(56)	(56)	6	1,2,5,6,10	R	16
Williams [20]	2018	SEER, 2002–2011	752 (687)	2448 (687)	10	1,2,4,9,5,7,10	R	19
Zhong [19]	2019	NCDB, 2004–2013	1178 (1002)	7276 (1002)	10	1,5,6,7,8	R	18
Kumar [13]	2021	US Veterans, 2000–2017	163	1472	5	None	R	17
Qiu [18]	2022	CaPRICE, 2005–2014	(891)	(891)	15	1,2,3,4,5,6	R	18

1 = age, 2 = gender, 3 = year at treatment, 4 = education achievement, 5 = clinical T stage, and 6 = Charlson Comorbidity Index, 7 = disease site, 8 = facility type, 9 = marital status, 10 = grade

R retrospective, *PSM* Propensity scoring matching

CI: 0.96–0.99, $P=0.01$, $I^2=27\%$). After propensity score matching, there was no difference between the TMT group and the RC group in terms of age, sex, Charlson comorbidity score, tumor stage, and tumor grade (Supplemental Fig. 2).

Overall survival

To compare the OS between TMT and RC, the meta-analysis incorporated data from all seven studies. The findings indicated that the RC group had a higher OS compared to the TMT group (Fig. 2A, HR = 1.33, 95%CI: 1.24–1.42, $P<0.001$, $I^2=36\%$). Further analysis based on the follow-up duration revealed no statistical difference between TMT and RC at 1-year (Fig. 2B, HR = 1, 95%CI: 0.76–1.31, $P=0.99$, $I^2=71\%$) and 2-year (Fig. 2C, HR = 1.24, 95%CI: 0.84–1.82, $P=0.27$, $I^2=84\%$). However, patients in the TMT group had inferior OS at 5-year (Fig. 2D, HR = 1.43, 95%CI: 1.12–1.81, $P=0.004$, $I^2=55\%$) and > 10 year (Fig. 2E, HR = 1.32, 95%CI: 1.15–1.51, $P<0.001$, $I^2=62\%$).

Cancer-specific survival

All seven studies included in the analysis compared the CSS between TMT and RC. The results showed that patients in the RC group had a higher CSS than those in the TMT group (Fig. 3A, HR = 1.4, 95%CI: 1.25–1.56, $P<0.001$, $I^2=10\%$). The analysis also showed no significant difference between TMT and RC in terms of 1-year follow-up outcomes (Fig. 3B, HR = 1.07, 95%CI: 0.88–1.3, $P=0.51$, $I^2=0\%$). However, patients in the TMT group had inferior CSS at 2-year (Fig. 3C, HR = 1.77, 95%CI: 1.46–2.14, $P<0.001$, $I^2=0\%$), 5-year (Fig. 3D, HR = 1.63, 95%CI: 1.09–2.46, $P=0.02$, $I^2=53\%$), and > 10-year follow-up (Fig. 3E, HR = 1.38, 95%CI: 1.07–1.77, $P=0.01$, $I^2=71\%$).

Publication bias

The Begg's funnel plot of OS (Supplemental Fig. 3) showed no clear evidence of asymmetry, indicating no significant publication bias. This finding was consistent with the p-values obtained from Egger's test for all outcomes, which were greater than 0.05, further supporting the absence of significant publication bias. To minimize the risk of duplicate studies, we carefully reviewed the references of the retrieved articles and only included studies that met our predefined criteria for inclusion.

Discussion

The objective of this study was to conduct a comprehensive analysis of the conflicting research regarding the oncologic outcomes of RC and TMT, with the aim of providing an accurate evaluation of their disparities. Our findings indicate that, following PSM, there was no statistically significant discrepancy in OS between the RC and TMT groups in the short term (within 2 years). However, the RC group exhibited a significantly higher OS compared to the TMT group at the 5-year and > 10-year time points. Additionally, there was no disparity in CSS between the RC and TMT groups at the 1-year mark. However, from the second year onwards, including the 5-year and > 10-year intervals, the RC group demonstrated a significantly higher CSS compared to the TMT group. Notably, the most significant difference between the two groups was observed at the 2-year mark ($P<0.001$).

It is noteworthy that a previous meta-analysis (Ding et al. [24]) has evaluated the oncological outcomes of RC and TMT. In their results, TMT had comparable OS and CSS during short-term (1-year, 2-year) and middle-term (5-year) follow-up period, and inferior OS and CSS during long-term follow-up period (> 10 years). However, in our results, TMT had inferior middle-term to long-term

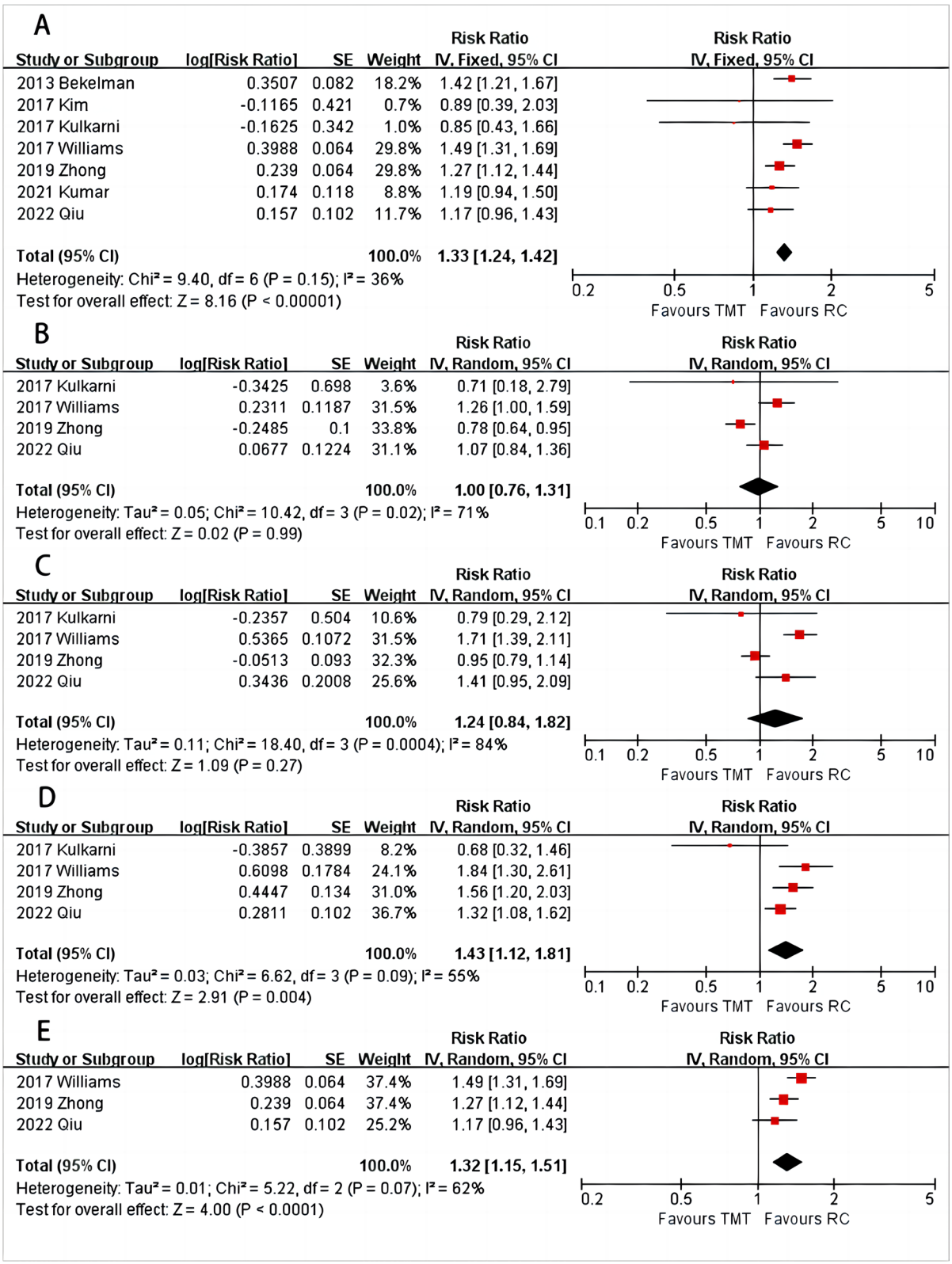

Fig. 2 Forest plot of comparisons of overall OS (**A**) and OS at 1-year (**B**), 2-year (**C**), 5-year (**D**), and > 10 year (**E**)

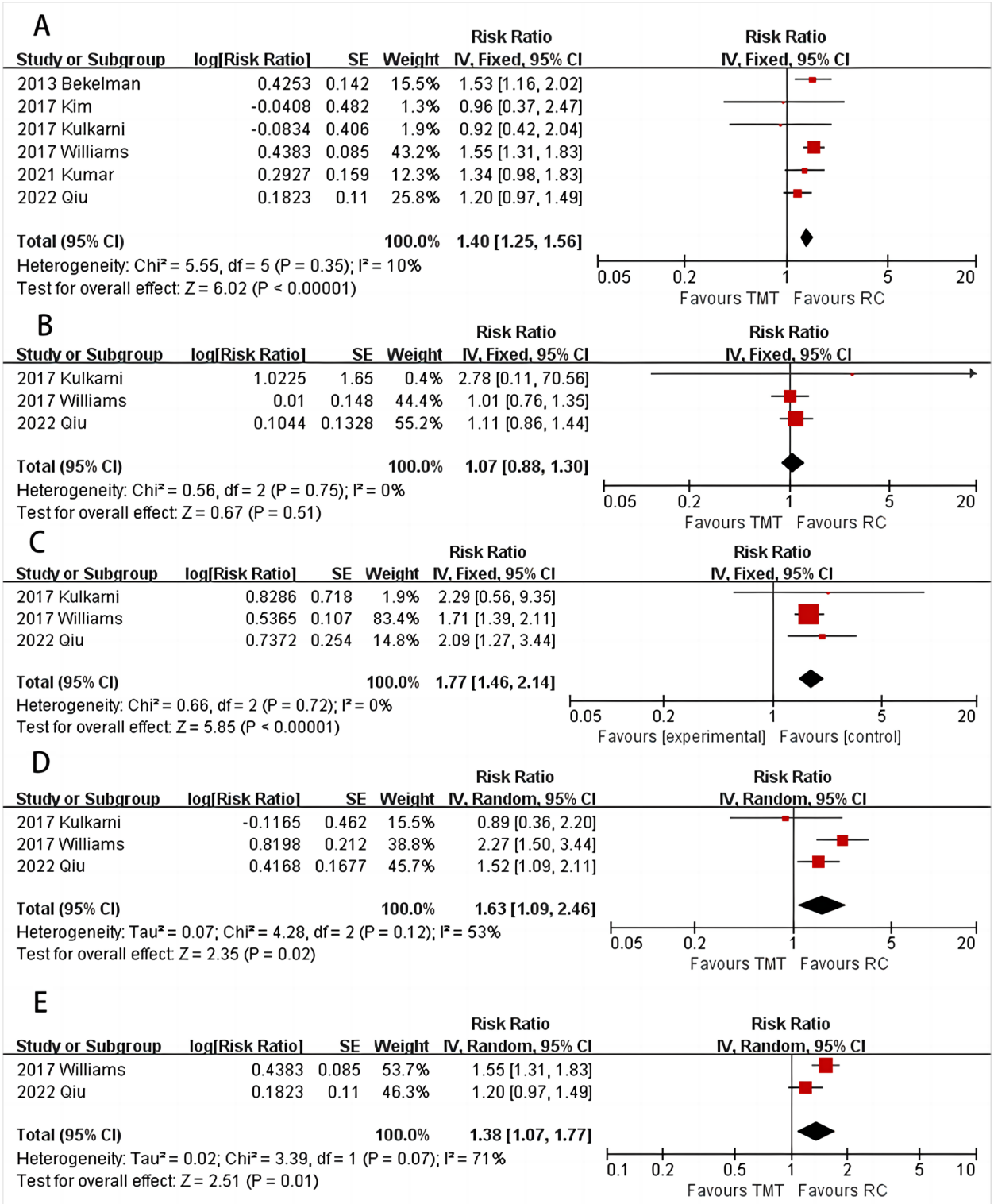

Fig. 3 Forest plot of comparisons of overall CSS (**A**) and CSS at 1-year (**B**), 2-year (**C**), 5-year (**D**), and > 10 year (**E**)

OS and inferior short-term to long-term CSS. At baseline, patients undergone TMT appear to be with lower tumor grade and tumor stage. Considering tumor grade and tumor stage are two dominant risk factors of oncological outcomes, the difference of baseline characteristic between two groups may result in bias of final results.

Unfortunately, the previous meta-analysis conducted by Ding et al. [24] e extracted several oncological data without PSM or Multivariate regression analysis. To minimize the influence of baseline characteristics between patients undergone TMT and those undergone RC, we only included studies with PSM or Multivariate regression analysis. As can be seen from our results, various characteristics were similar between the two groups after PSM. Apparently, our study has more evidence-based reliability than the previous meta-analysis.

The current selection criteria for TMT rely on clinical and pathological factors; however, a single-institution retrospective study demonstrated that 73% of 212 patients with clinical T2 tumors who underwent RC and did not receive neoadjuvant chemotherapy were found to have pathological T3/T4 or lymph node positivity [25]. This suggests that underestimation of tumor stage before TMT treatment may contribute to the poor long-term prognosis of TMT. In recent years, researchers have explored new biomarkers or molecular markers for patient classification and selection, and immunotherapy is being increasingly used. More and more studies have explored the value of biomarkers in the early diagnosis of bladder cancer. Some proteins in urine such as NMP22, Complement factor H-related protein, BLCA-4, and apolipoproteins [26] as well as various metabolites such as taurine, citrate, succinate [27, 28], desaminotyrosine, erythritol, d-ribose, ribitol, d-fructose, d-mannose, and d-galactose [29] have been found to be biomarkers for the early diagnosis of bladder cancer, and circulating MicroRNA have also been found to be used for the early diagnosis of bladder cancer [30]. Biomarker analysis has suggested that DNA damage response markers, such as MRE11 and ERCC1/2, may predict cancer-specific survival among two independent TMT cohorts [31, 32]. Transcriptome sequencing analysis has also indicated that oncologic outcomes may vary based on different molecular subtypes, and neuroendocrine tumor gene expression signature has been identified in MIBC, which differs from traditional basal/luminal MIBC [33]. In contrast, biomarkers in urine are more specific and less sensitive. Therefore, simultaneous detection of biomarkers in urine and circulation may improve the early detection of bladder cancer. These findings will impact future clinical decisions.

Furthermore, while neoadjuvant chemotherapy has been shown to improve survival in MIBC patients undergoing radical cystectomy, its efficacy in TMT therapy remains uncertain [34, 35]. One study explored the potential of consolidative partial cystectomy and pelvic lymph node dissection to preserve bladder function after TMT treatment and achieved complete remission [36]. Among the patients, 10% had residual tumor invasion and 2% had lymph node metastasis. The 5-year metastasis-free survival, CSS, and OS rates were 97%, 93%, and 91%, respectively. Partial cystectomy did not affect bladder function or quality of life. These findings suggest that consolidation surgery may have a role in TMT therapy.

Our study suggests that in the real world, TMT is mainly used in older patients with relatively early tumor stage and grade [4, 6, 8]. There is no doubt that patients with relatively low-grade and earlier-stage tumors have better tumor prognosis, which is why we emphasize in our study that we must include studies that only do multivariate analysis or PSM, which will make the study results more credible.

Our study also has certain shortcomings. First, all the studies selected by us for inclusion belong to retrospective studies rather than RCT studies, but unfortunately, it is difficult to conduct RCT studies on the comparison of TMT therapy and RC therapy at present. Second, all included studies did not performed subgroup analysis, it is still unclear whether TMT could provide comparable oncological outcomes in specific subgroup patients, and future well- designed studies on this topic is still needed.

In conclusion, our exhaustive investigation and meticulous statistical examination have demonstrated the superiority of RC over TMT in the management of MIBC, particularly with regard to long-term overall survival and specific survival. Consequently, in subsequent clinical treatment decisions, we advocate for the preference of RC over TMT for the treatment of MIBC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12957-023-03161-z.

Additional file 1: Supplemental figure 1. Forest plot of comparisons of age (A), sex (B), Charlson comorbidity score (C), tumor stage (D) and tumor grade (E) before propensity score matching.

Additional file 2: Supplemental figure 2. Forest plot of comparisons of age (A), sex (B), Charlson comorbidity score (C), tumor stage (D) and tumor grade (E) after propensity score matching.

Additional file 3: Supplemental figure 3. Begg's funnel plot of overall OS.

Additional file 4. Literature search strategy.

Authors' contributions

Xiaozhe Su, Caitao Dong, Wenbiao Liao contributed equally to this work and share the first authorship. Wt.L, C.D: data extraction, statistical analysis and wrote the paper. X.S, Wt.L, W.L: statistical analysis, data extraction and wrote the paper. X.S. Wt.L: study design, statistical analysis, revised manuscript, data extraction. All authors approved the submitted version.

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Availability of data and materials

The original data is available upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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