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REVIEW ARTICLE

The effect of holmium laser resection versus standard transurethral resection on non-muscle-invasive bladder cancer: a systematic review and meta-analysis

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Abstract

To explore the advantages and limitations of holmium laser resection of the bladder tumor (HOLRBT) versus standard transurethral resection of the bladder tumor (TURBT) in the treatment of non-muscle-invasive bladder cancer (NMIBC), the eligible studies were selected from the following databases: PubMed, Cochrane Library, and Embase. Studies comparing HOLRBT and TURBT for patients with NMIBC were included. The outcomes of interest were time of operation, catheterization and hospitalization, rates of recurrence, and perioperative complications, including obturator nerve reflex, bladder perforation, bladder irritation, and urethral stricture. Results of all data were compared and analyzed by Review Manager 5.3. A total of 9 comparative studies were finally included for this analysis. Pooled data demonstrated that HOLRBT significantly reduced the time to catheterization and hospitalization, the rate of recurrence in 2 years of follow-up, obturator nerve reflex, bladder perforation, and bladder irritation, compared with those in TURBT, respectively. However, no significant difference found between HOLRBT and TURBT in the time of operation, rate of recurrence in 1-year follow-up, and urethral stricture. The results of this research reached that HOLRBT would be a better choice than TURBT for patients with NMIBC.

Keywords Non-muscle-invasive bladder cancer · Holmium laser · Transurethral resection · Meta-analysis

Background

Bladder cancer is the tenth most common cancer worldwide, with estimated 549,000 new cases and 200,000 deaths in 2018 [1]. According to the depth of invasion, bladder cancer was divided into two types, non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive disease, and 75% of bladder cancer belongs to the former [2]. NMIBC is defined as the tumor is confined to the mucosa or submucosa of bladder.

Previously, the patients with NMIBC were usually treated by transurethral resection of the bladder tumor (TURBT) combined with intravesical chemotherapy or immunotherapy [3]. This strategy above was the "golden standard" according to the guideline of European Association of Urology [4]. However, the limitations of TURBT were gradually presented, such as the occurrences of obturator nerve reflex, bladder perforation, bladder irritation, and postoperative bleeding. Holmium laser resection of the bladder tumor (HOLRBT) was applied to overcome these shortages, which showed satisfactory outcomes, especially in tissue cutting, vaporization, and hemostasis [5]. The aim of our study was to compare the safety and effectiveness of HOLRBT and TURBT for patients with NMIBC.

Methods

Search strategy

This study was performed following the principle of preferred reporting items for systematic review and meta-analysis protocols (PRISMA) [6]. The databases included PubMed, Cochrane Library, and EMBASE and were respectively searched with the term in title/abstract: "superficial bladder cancer," "non-muscle-invasive bladder cancer," "holmium

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laser," and "transurethral resection" up to March 2019. The reference lists from the identified documents were also searched. To avoid data duplication, the latest report was used if multiple studies described the same population.

Inclusion and exclusion criteria

All comparative studies, including randomized controlled studies (RCT), cohort studies (CS), and case-control studies (CCS), focusing on HOLRBT and TURBT for patients with NMIBC were included. On the other hand, studies would be excluded if (1) studies included patients with muscle-invasive-bladder cancer or distant metastasis; (2) none of the following outcomes of interest were reported, including time of operation, catheterization and hospitalization, rate of recurrence, and complications, such as obturator nerve reflex, bladder perforation, bladder irritation, and urethral stricture; (3) data of studies were not sufficient for a meta-analysis; and (4) studies presented as conference abstracts.

Data extraction

Data were extracted from these studies by 2 independent reviewers. If the two reviewers disagreed, a consensus was reached after a discussion between them. To keep the baselines as similar as possible, the only comparison between HOLRBT and TURBT was extracted when the patients were divided into ≥ 3 groups in studies. When articles were not written in English, they were translated for data extraction if possible.

Outcomes of interest

The outcomes of interest were time of operation, catheterization and hospitalization, rate of recurrence, and perioperative complications, including obturator nerve reflex, bladder perforation, bladder irritation, and urethral stricture.

Quality assessment and statistical analysis

The level of evidence of the included studies was graded according to the criteria by the Centre for Evidence-Based Medicine in Oxford, UK [7]. In addition, the quality of each included CS or CCS was evaluated by the Newcastle-Ottawa scale (NOS). The NOS was a widely used quality assessment method in meta-analysis [8]. In the modified Newcastle-Ottawa scale, a score of 1–9 stars was allocated, and more stars stood for higher quality.

The meta-analysis was performed by Review Manager 5.3. The odd ratio (OR) and mean difference (MD) were used for describing results of dichotomous and continuous variables, respectively. All results were reported with 95% confidence intervals (CI). The $P < 0.05$ was regarded to be statistically significant.

In addition, statistical heterogeneities among trials were evaluated by I^2 and χ^2 tests. I^2 value of 25%, 50%, and 75% was corresponded to low, medium, and high levels of heterogeneity, respectively. When $I^2 < 50\%$ and $P > 0.10$, a fixed-effect model was used. Otherwise, the random-effect model was applied.

Results

Study selection

Through the search strategy, a total of 317 articles were initially found. After software and manual checking, 85 papers were excluded because of duplications. Then, 203 documents were excluded after screening of the title and abstract. Of the 29 remaining records, 20 articles were excluded after evaluation of the full text. Finally, 9 studies [9–17] with a total of 1166 patients were included in the meta-analysis, in which

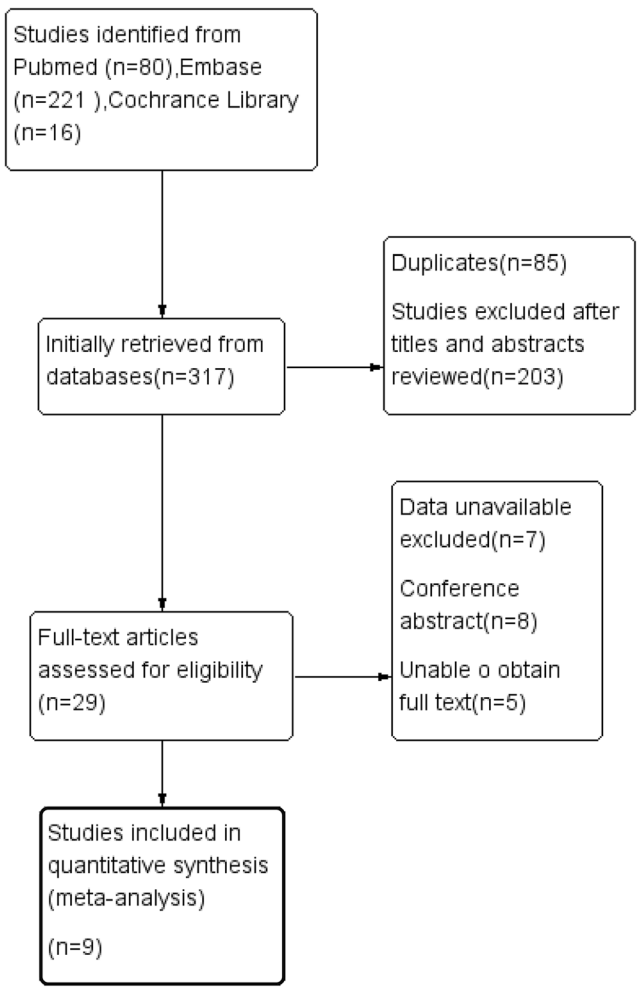


Fig. 1 Flow diagram of study

Table 1 Characteristics of included studies

Study ID	Study type	LOE	Study interval	Treatment	Country	No. of patients	Age of patients	Male (*n*)	Female (*n*)	Tumor size (mm)	Location (n)		T Stage (*n*)		Grade (2004)			NOS
											Lateral	Other	Ta	T1	PUNLMP	Low	High	
D'souza 2016	Prospective	2b	2012–2015	HOLRBT	India	23	66.3 ± 9.8	15	8	15.8 ± 3.1	10	13	15	8	4	16	3	7
				TURBT		27	67.1 ± 8.3	18	9	14.1 ± 2.3	11	16	16	11	5	20	2	
GF. Chen 2015	Prospective	2b	2006–2007	HOLRBT	China	64	61	48	16	NA	30	34	42	22	36	19	9	7
				TURBT		90	65	68	22	NA	36	54	60	30	57	25	8	
Huang 2016	RCT	2b	2009–2013	HOLRBT	China	70	59.97 ± 5.75	45	25	15.8 ± 5.1	28	42	37	33	15	48	7	NA
				TURBT		70	57.87 ± 4.99	48	22	15.3 ± 2.0	25	45	35	35	18	46	6	
Kramer 2015	Retrospective	3b	2010–2014	HOLRBT	Europe	50	62.2 ± 12.3	36	14	26.3 ± 7.9	NA	NA	29	21	0	23	27	8
				TURBT		156	67.5 ± 10.7	125	31	21.8 ± 9.07	NA	NA	83	62	0	72	84	
Luo 2008	Retrospective	3b	2003–2005	HOLRBT	China	26	65	21	5	24 ± 6.25	NA	NA	NA	NA	NA	NA	NA	6
				TURBT		38	57	28	10	27 ± 9.25	NA	NA	NA	NA	NA	NA	NA	
Muraro 2005	Retrospective	3b	NA	HOLRBT	Italy	50	64.5	39	11	NA	NA	NA	43	7	NA	NA	NA	7
				TURBT		50	65.7	40	10	NA	NA	NA	46	4	NA	NA	NA	
Song 2010	Prospective	2b	2005–2009	HOLRBT	China	64	72.5	52	12	18.5 ± 7.75	25	39	36	28	5	39	20	7
				TURBT		109	73.7	87	22	16.2 ± 6.17	46	63	65	44	9	66	34	
Zhong 2010	Retrospective	3b	2006–2007	HOLRBT	China	25	65.76 ± 12.4	NA	NA	13.8 ± 5.8	NA	NA	19	6	3	18	4	8
				TURBT		42	66.26 ± 11.0	NA	NA	15.4 ± 6.6	NA	NA	30	12	7	26	9	
Zhu 2008	Retrospective	3b	2003–2005	HOLRBT	China	101	NA	79	22	NA	NA	NA	67	34	NA	NA	NA	7
				TURBT		111	NA	92	19	NA	NA	NA	70	41	NA	NA	NA	
Total				HOLRBT		473	64.34	335	113	19.14	93	128	288	159	63	163	70	
				TURBT		693	66.17	506	145	18.76	118	178	405	239	96	255	143	

HOLRBT holmium laser resection of bladder tumor; *TURBT* transurethral resection of bladder tumor; *LOE* level of evidence; *NOS* Newcastle-Ottawa scale; *NA* not available

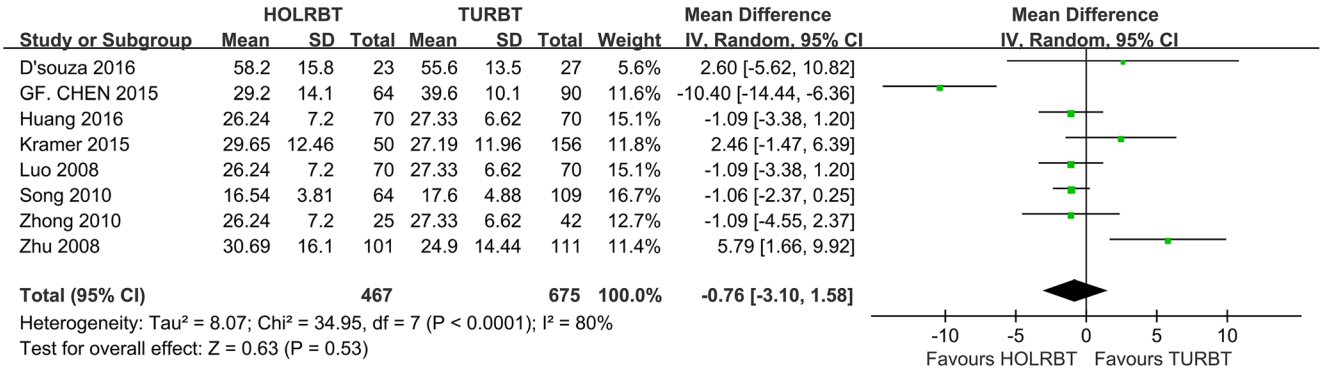


Fig. 2 The results of operation time in meta-analysis

473 patients were treated by HOLRBT and 693 patients were treated by TURBT (Fig. 1).

Eight studies had described the gender of patients, in which 335 were males in HOLRBT group (74.8%) and 506 were males in the TURBT group (77.7%). The chi-square test showed that there was an insignificant difference in gender between two groups ($P = 0.26$). More, the pooled average age of patients between two groups was similar, which was calculated to be 64.34 in HOLRBT group and 66.17 in TURBT group, respectively. The characteristics of all available studies are shown in Table 1.

Totally, 1 RCT, 3 prospective CS, and 5 retrospective CCS were included in this analysis. According to the postoperative intravesical instilled chemotherapy scheme, 4 studies used mitomycin C, 2 studies used epirubicin, 2 studies used pirarubicin, and 1 study did not describe the chemotherapy scheme. Five studies [9–11, 15, 17] described a comparison of ≥ 3 groups, in which only data describing HOLRBT and TURBT for NMIBC were extracted. One study was published in Chinese, however had an English abstract [12].

Outcomes of interest

Operation time

Eight studies including a total of 1142 patients [9–12, 14–17] had evaluated data of operation time, which revealed that there was no significant difference in operation time between two groups (MD = − 0.76, 95% CI [− 3.10, 1.58], $P = 0.53$) (Fig. 2).

Catheterization time

When catheterization time was compared, 8 studies including 1142 patients [9–12, 14–17] were analyzed. Pooled data demonstrated a significantly less time in catheterization time in the HOLRBT group compared to TURBT group (MD = − 1.02, 95% CI [− 1.35, − 0.68], $P < 0.00001$) (Fig. 3).

Hospitalization time

Seven studies including 1002 patients [9–11, 14–17] are pooled, which indicated that hospitalization time was significantly less in HOLRBT group compared to TURBT group (MD = − 1.11, 95% CI [− 1.65, − 0.58], $P < 0.0001$) (Fig. 4).

1-year recurrence

Data describing the rate of 1-year recurrence were pooled from 5 studies [12–14, 16, 17] of 493 patients. Result of meta-analysis showed that there was an insignificant difference between two groups (OR = 0.72; 95% CI [0.45, 1.16], $P = 0.18$). Considering

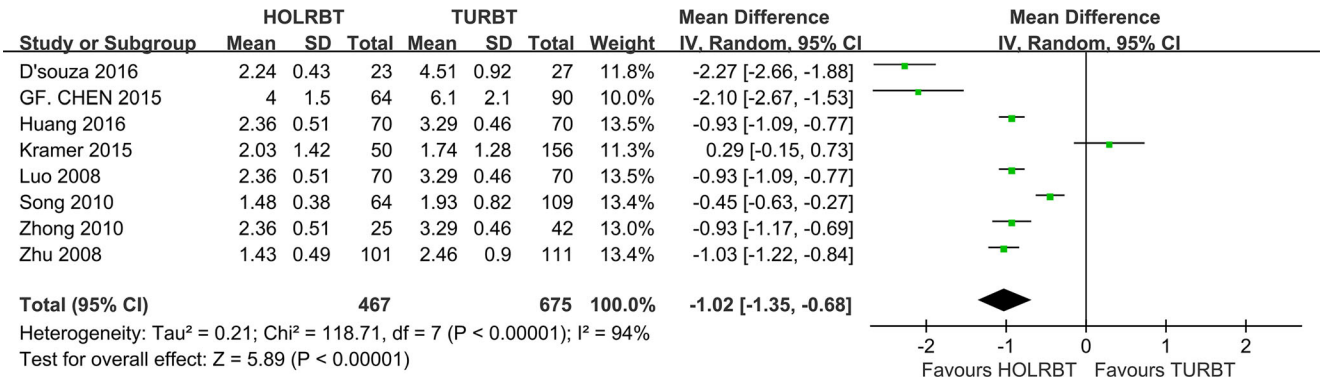


Fig. 3 The results of catheterization time in meta-analysis

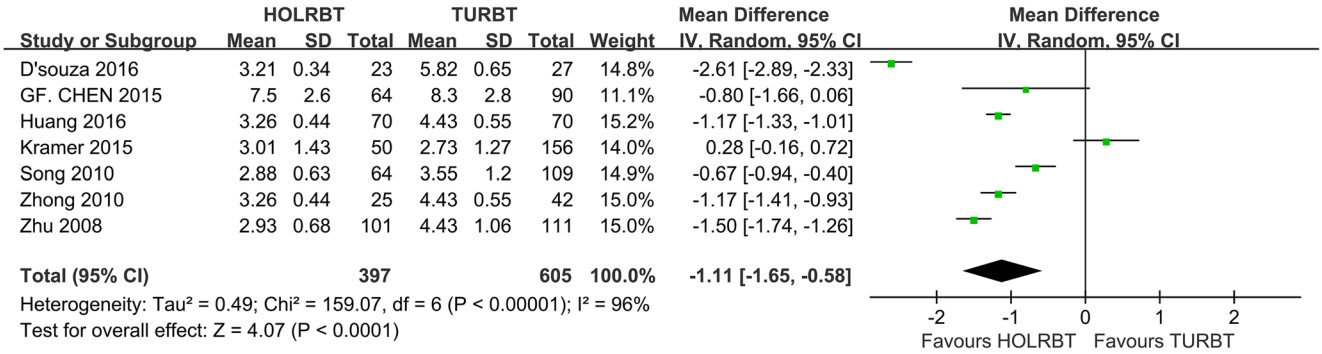


Fig. 4 The results of hospitalization time in meta-analysis

the large impact on recurrence by different chemotherapy schemes, a subgroup analysis was carried out, which showed that there was an insignificance in mitomycin C, epirubicin, pirarubicin, and subgroups that did not mention chemotherapy scheme (Fig. 5).

2-year recurrence

When the rate of 2-year recurrence was compared between two groups, pooled data from 8 studies including a total of 939 patients [9, 10, 12–17] revealed that the recurrence was

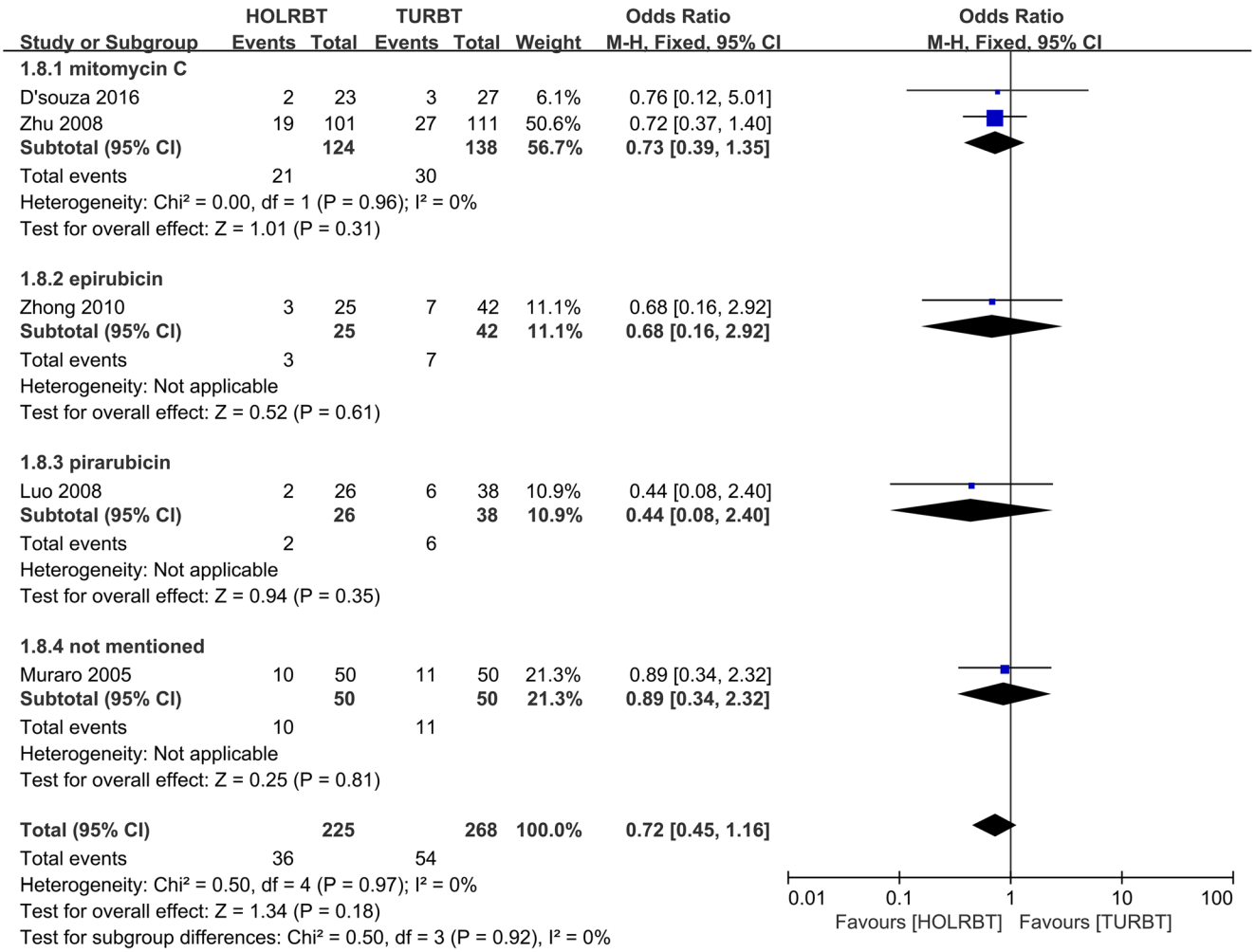


Fig. 5 The results of 1-year recurrence in meta-analysis

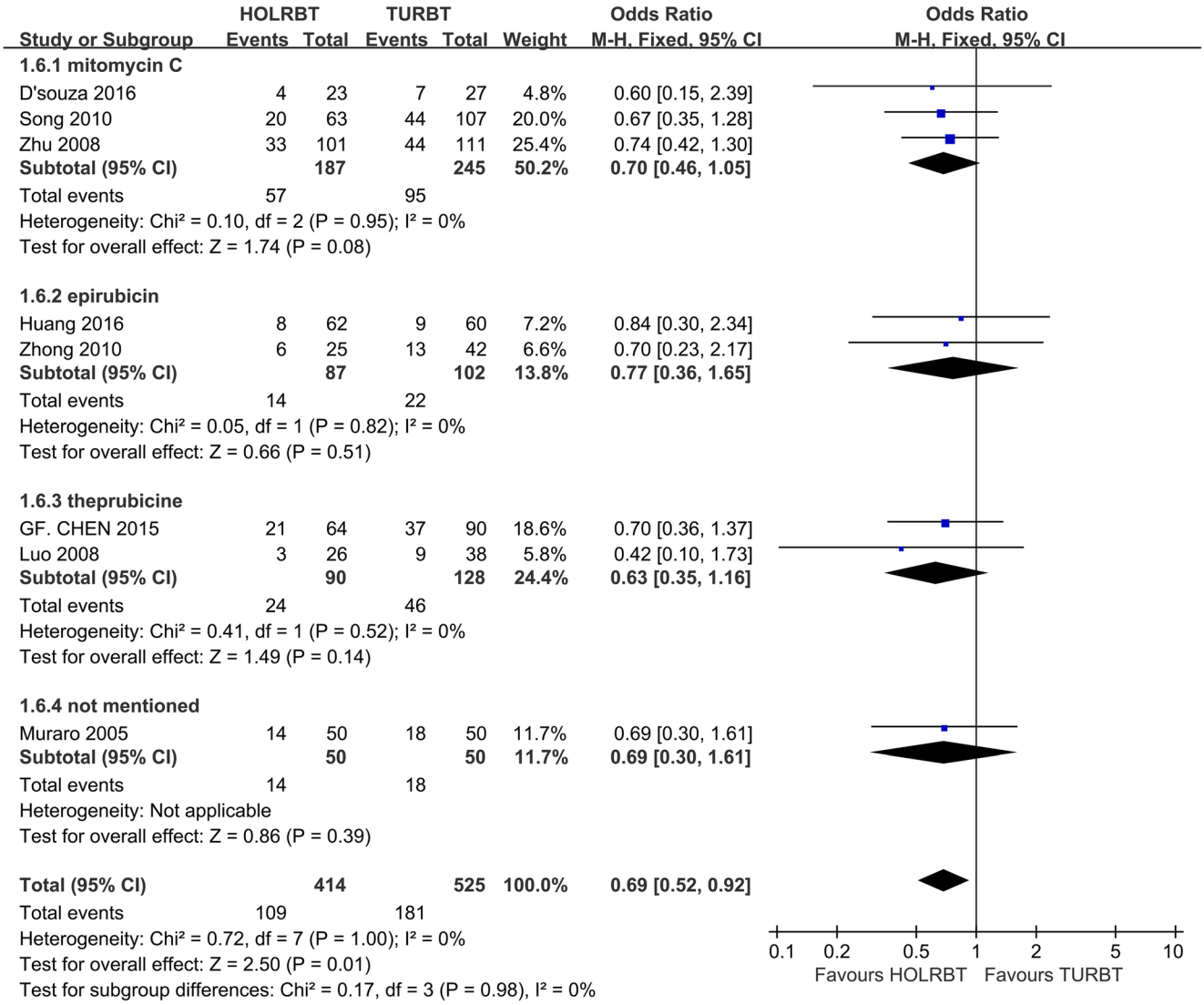


Fig. 6 The results of 2-year recurrence in meta-analysis

significantly higher in TURBT group (OR = 0.69; 95% CI [0.51, 0.94], $P = 0.02$). However, in the subgroup analysis, all results became insignificant in mitomycin C, epirubicin, pirarubicin subgroups, and in the subgroup that did not describe chemotherapy scheme (Fig. 6).

Complications

Four studies [10, 12, 15, 17] evaluated the incidence of obturator nerve reflex, which revealed significantly lower rate of occurrence in the HOLRBT group (OR = 0.06; 95% CI [0.01, 0.23], $P < 0.0001$) (Fig. 7).

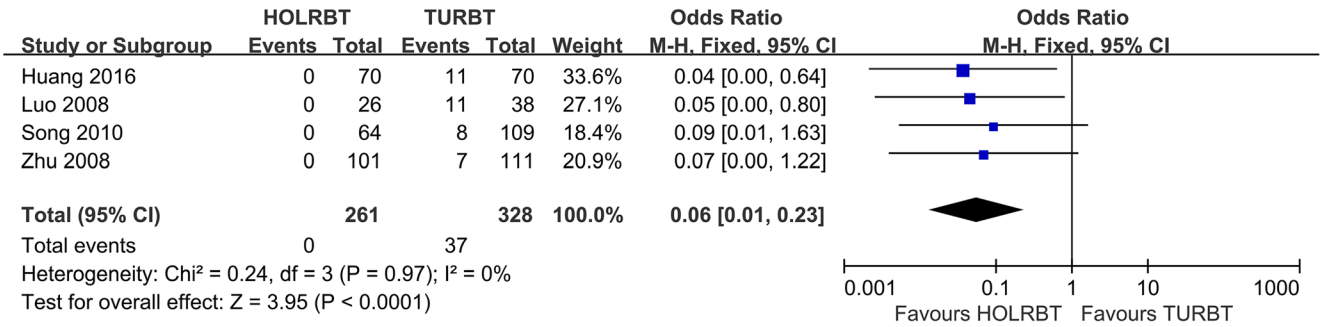


Fig. 7 The results of obturator nerve reflex in meta-analysis

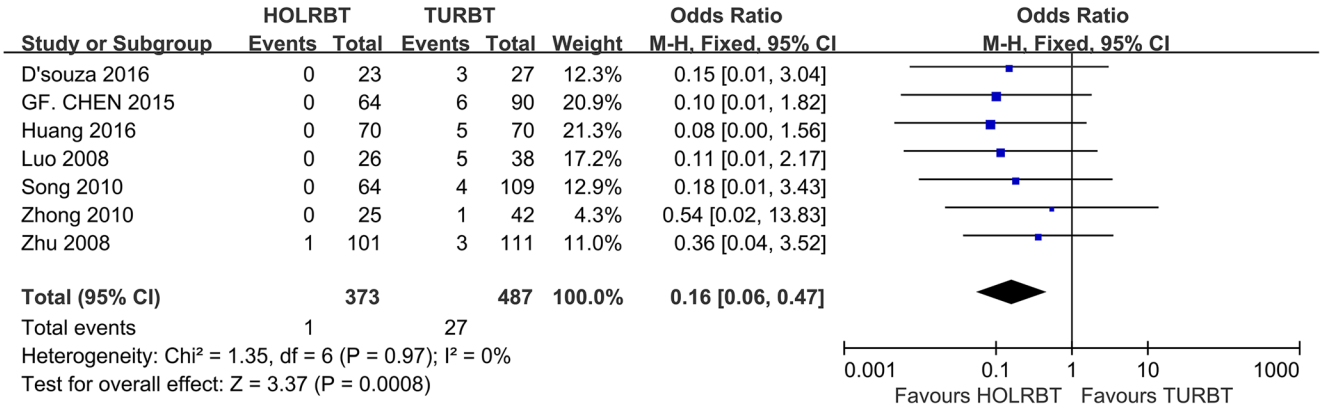


Fig. 8 The results of bladder perforation in meta-analysis

Additionally, seven studies including 860 patients [9, 10, 12, 14–17] were pooled, which presented that the incidence of bladder perforation was significant lower in the HOLRBT group (OR = 0.15; 95% CI [0.05, 0.45], $P = 0.0008$) (Fig. 8).

What is more, six studies including 648 patients [9, 10, 12, 14–16] evaluated the incidence of bladder irritation and revealed a significant difference between two groups and lower incidence of bladder irritation in HOLRBT group (OR = 0.45; 95% CI [0.31, 0.66], $P < 0.0001$) (Fig. 9).

When urethral stricture was compared between HOLRBT and TURBT groups, 4 studies [10, 12, 15, 16] including 444 patients were pooled. The result of meta-analysis showed that there was an insignificance in urethral stricture between two groups (OR = 0.86, 95% CI [0.37, 1.98], $P = 0.73$) (Fig. 10).

Sensitivity analysis and publication bias

To analyze the potential publication bias, a funnel plot of operation time was performed, which revealed that 2 studies had potential publication bias. After the studies were excluded, similar results in all outcomes of interest were shown (Fig. 11).

Discussion

With the increasing of patients with NMIBC, it became a key issue how to improve the survival and quality of patients' life. Nowadays, TURBT still played an important role in the diagnosis and treatment of NMIBC, because it could provide adequate tissue for pathological examination followed with all visible tumors being effectively removed [18, 19]. However, thermal injury was the main factor which leads to complications by TURBT, due to the radiofrequency that had developed an electrical resistance at a temperature that ranged from 100 to 300 °C in the treatment site [20]. According to the reason above, the occurrence of obturator nerve reflex was frequent during TURBT, especially for tumors at the lateral wall of bladder, which possibly leaded to bladder perforation [21]. In order to avoid these complications, inadequate resection depth of the tumors might occur [22]. Meanwhile, the time to catheterization and hospitalization might be longer by thermal injury.

Fortunately, after laser was firstly applied in urology in 1978 [23], holmium laser was gradually used in the resection of bladder tumors since 2001 [24]. In the beginning, the most obvious shortage of laser was unable to reach sufficient tissue

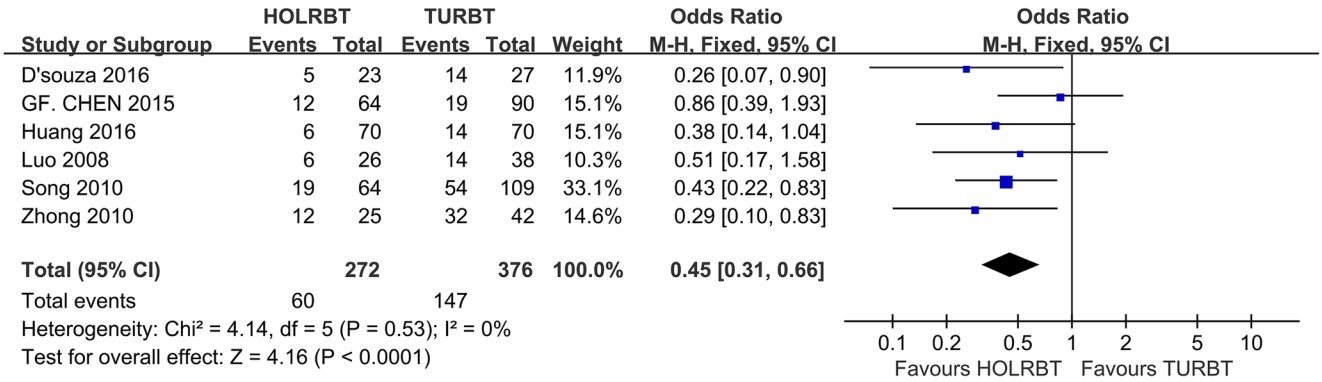


Fig. 9 The results of bladder irritation in meta-analysis

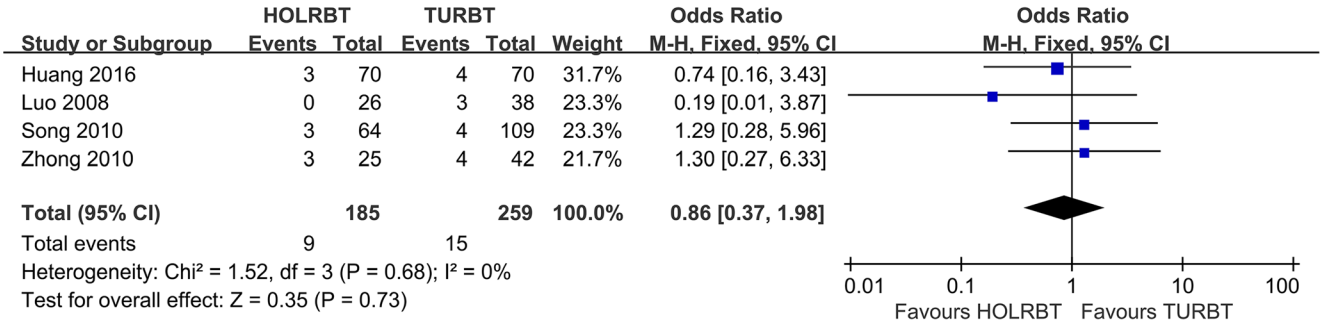


Fig. 10 The results of urethral stricture in meta-analysis

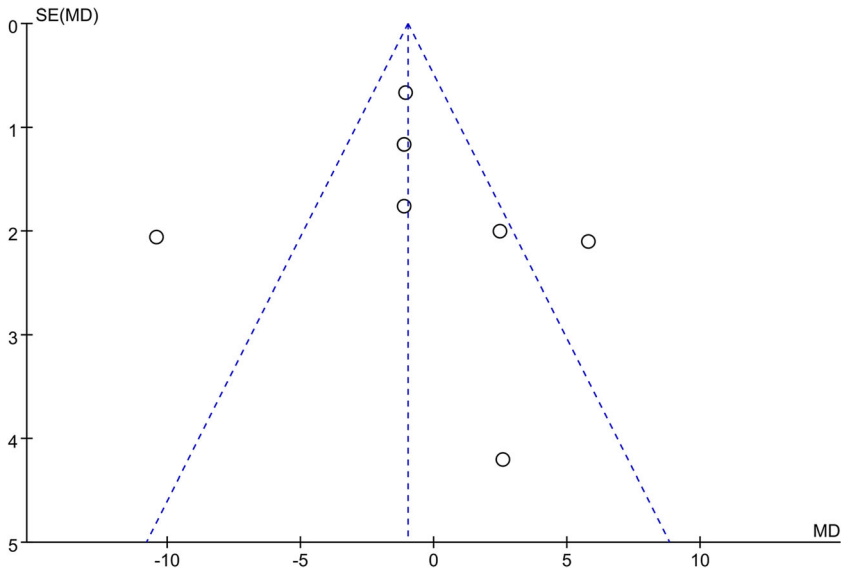
for pathological examination in the treatment of NMIBC. Nonetheless, holmium laser can not only offer adequate tissue for pathological examination, and even accomplish en bloc resection of NMIBC [25, 26]. Holmium laser had a wavelength of 2100 nm. At this wavelength, the tissue penetration depth of the laser was about 400 μm, which was considered safely. The temperature of the treatment regions in HOLRBT ranged from 40 to 75 °C, which was large lower than in TURBT. Thus, the thermal injury in the treatment site was minimal as well [26]. It made a necessary to compare these two technologies.

Our results showed that the time of catheterization and hospitalization was significantly shorter in the HOLRBT group than the TURBT group; however, there was no significant difference in operation time. The same conclusions were reported by Teng et al. [27]. For the time of catheterization and hospitalization, rapider postoperative recovery was shown in the HOLRBT group because of thermal damage caused by TURBT. Nonetheless, significant heterogeneities among studies could be found, and the accuracy of results might be influenced.

Our study revealed that HOLRT had a significant benefit in 2-year recurrence compare with TUBRT, which could be calculated to be 26.1% in HOLRBT group and 34.3% in TURBT group, respectively. In addition, the rate of 1-year recurrence was insignificant. Considering the difference of postoperative intravesical instilled chemotherapy scheme, subgroup analysis was carried out. Though postoperative adjuvant intravesical chemotherapy was an important factor which may affected the recurrence of cancer [28], no significant difference was found in our study. However, more evidence should be discovered to verify this conclusion.

Our study further confirmed the incidences of several perioperative complications, including obturator nerve reflex, bladder perforation, and bladder irritation, which presented large advantages in the HOLRBT group. The rate of obturator nerve reflex, bladder perforation, and bladder irritation could be calculated to be 0%, 0.2%, and 22.0% in HOLRBT group and 11.2%, 5.3%, and 39.1% in TURBT group, respectively. In addition, our study showed that there was an insignificance in the rate of urethral stricture between two groups, which could be calculated to be 4.8% in HOLRBT group and 5.8%

Fig. 11 Funnel plot



in TURBT group, respectively. Based on these results, it seemed that HOLRBT would be safer than TURBT for patients with NMIBC.

Above all, some limitations should be taken into consideration in this study. Firstly, only one RCT was included for analysis, which would lower the quality of pooled results. Secondly, some important parameters were not analyzed because the description of them could not be uniformed, such as pre- and postoperative bleeding. Thirdly, high heterogeneity could be observed in outcomes of operation time, catheterization time, and hospitalization time. These might due to the differences of patient's condition, surgeons' technique and custom, etc.

Conclusions

Based on the results of our meta-analysis, HOLRBT showed similar effectiveness and superior safety than TURBT for patients with NMIBC, though sporadical insignificance between two groups was found. However, more high-quality clinical trials were needed to further confirm our conclusions.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of informed consent Informed consent was obtained from all individual participants included in the study.

Abbreviations HOLRBT, Holmium laser resection of the bladder tumor; TURBT, Transurethral resection of the bladder tumor; NMIBC, Non-muscle-invasive bladder cancer; PRISMA, Preferred reporting items for systematic review and meta-analysis protocols; NOS, Newcastle-Ottawa scale; RCT, Randomized controlled studies; CS, Cohort studies; CCS, Case-control studies; OR, Odd ratio; MD, Mean difference; CI, Confidence intervals; LOE, Level of evidence; NA, Not available

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