非肌肉層侵犯之膀胱癌病人，經尿道腫瘤切除後，使用鹽水進行膀胱沖洗比化療灌注更能兼顧效果及安全性嗎？

引言人：林怡君
日期：2019/05/14 12:00~13:00

簡介-1
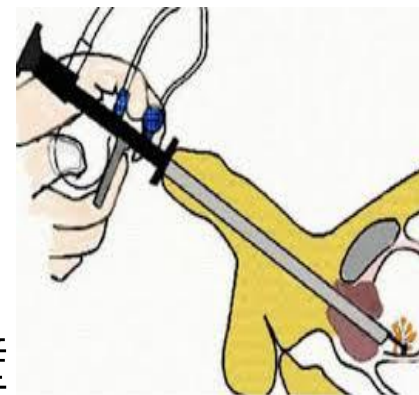

表淺性膀胱癌(非肌肉侵犯型)佔70%	Ta	非侵入性乳頭狀瘤癌
	Tis	受限於黏膜的原位癌
	T1	不越過黏膜下層的腫瘤
肌肉侵犯型佔30%	T2	癌症侵犯肌肉層
	T3	癌症穿出肌肉層，超出膀胱壁
	T4	癌症已經轉移到骨盆腔壁或遠端器官
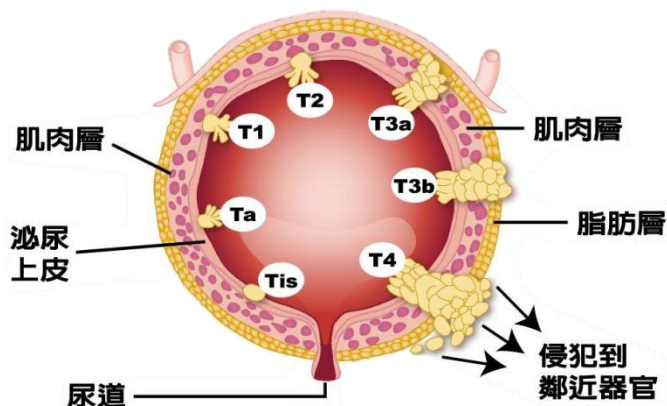
- 膀胱癌是泌尿外科最常見的臨床腫瘤之一。

- 美國每年有81,000例新病例，導致每年17,000人死亡。

- 其中，有**70%為非肌肉侵犯型膀胱癌(表淺性膀胱癌)**。
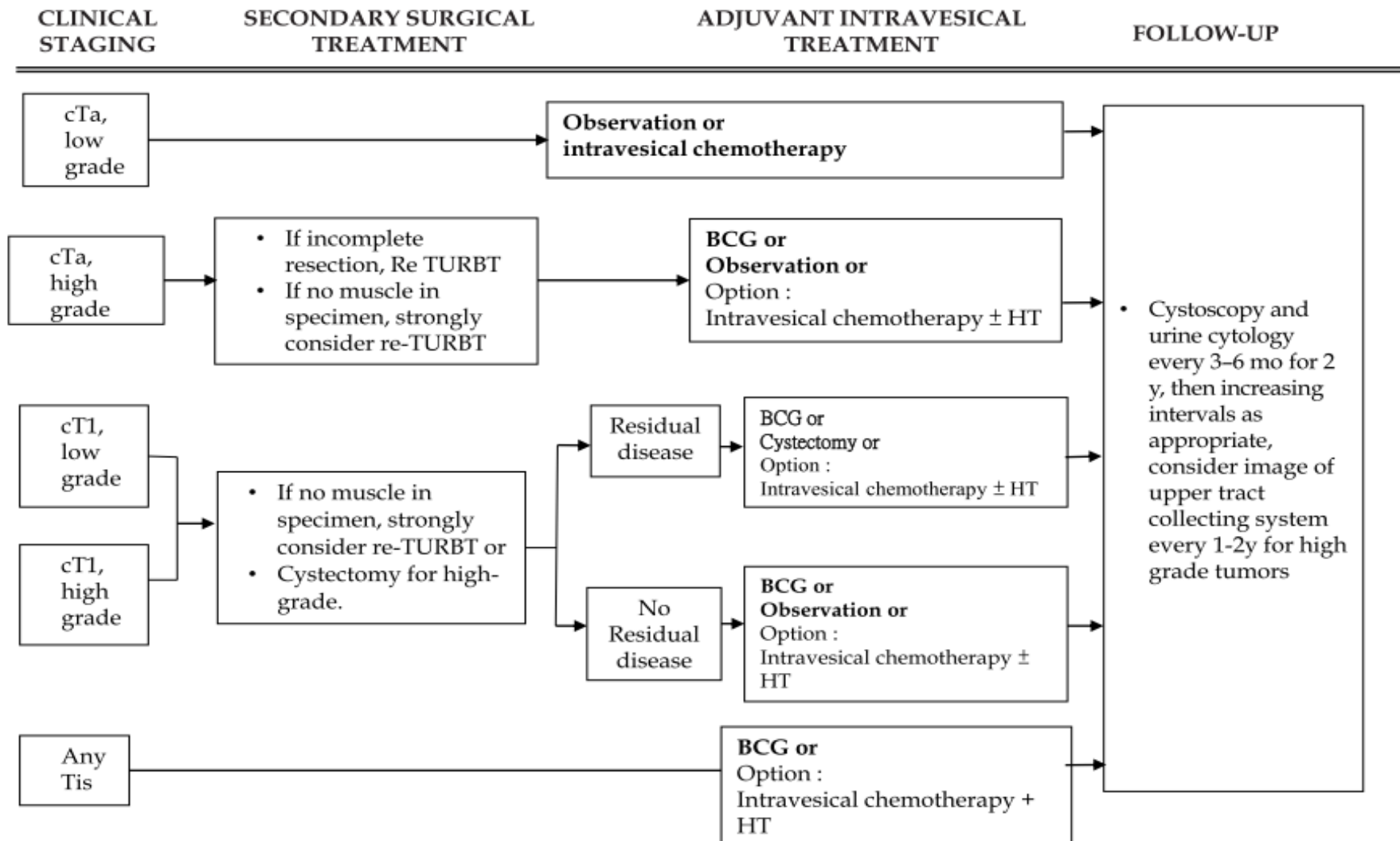
- 最常見臨床表徵：無痛性、肉眼可見血尿。

簡介-2

- **經尿道膀胱腫瘤刮除術** (Transurethral resection of bladder tumors；TUR-BT)：表淺性膀胱癌最主要的治療方法。

- 腫瘤刮除手術後之連續性膀胱灌洗
  - 控制血尿及預防血塊生成
  - 沖出漂浮的癌細胞，避免附著於膀胱壁

- 膀胱灌注化療藥物
  - 手術後常見之輔助治療，常用藥物：Mitomycin
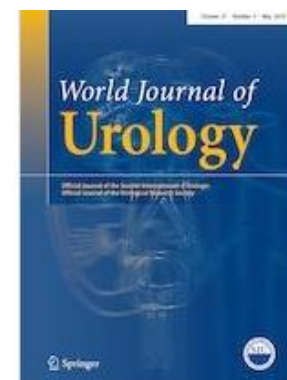 - 若發生不良事件會造成病人極大的風險
  - 副作用：血尿、頻尿

現況

CLINICAL STAGING	SECONDARY SURGICAL TREATMENT	ADJUVANT INTRAVESICAL TREATMENT	FOLLOW-UP
cTa, low grade		**Observation or intravesical chemotherapy**	
cTa, high grade	• If incomplete resection, Re TURBT • If no muscle in specimen, strongly consider re-TURBT	**BCG or Observation or** Option : Intravesical chemotherapy ± HT	• Cystoscopy and urine cytology every 3–6 mo for 2 y, then increasing intervals as appropriate, consider image of upper tract collecting system every 1-2y for high grade tumors
cT1, low grade / cT1, high grade	• If no muscle in specimen, strongly consider re-TURBT or • Cystectomy for high-grade.	Residual disease → BCG or Cystectomy or Option : Intravesical chemotherapy ± HT No Residual disease → **BCG or Observation or** Option : Intravesical chemotherapy ± HT	
Any Tis		**BCG or** Option : Intravesical chemotherapy + HT	

文獻介紹

REVIEW

CrossMark

Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors

Zhongbao Zhou[1,2] · Shikai Zhao[3] · Youyi Lu[2] · Jitao Wu[2] · Yongwei Li[2] · Zhenli Gao[2] · Diandong Yang[2] · Yuanshan Cui[2]

Appraisal sheets(FAITH)

- Appraisal Tool
  - [統合分析 Meta-analysis]
    - 步驟1：研究探討的問題為何 (PICO)
    - 步驟2：研究的品質如何 (內在效度)
    - 步驟3：研究結果之意義為何 (效益)

Appraisal

➢ 步驟 1：系統性文獻回顧探討的問題為何？

研究族群 / 問題 (Population/ Problem)：

- *after transurethral resection for the treatment of non-muscle invasive bladder cancer.*

介入措施 (Intervention)：

- **continuous saline bladder irrigation**

比較 (Comparison)：

- *intravesical chemotherapy*

結果 (Outcomes)：

- *efficacy and safety*

Appraisal sheets(FAITH)

- Appraisal Tool
  - [統合分析 Meta-analysis]
    - 步驟1：研究探討的問題為何 (PICO)
    - 步驟2：研究的品質如何 (內在效度)
    - 步驟3：研究結果之意義為何 (效益)

【F】研究是否找到 (Find) 所有的相關證據？

良好的文獻**搜尋**至少應包括二個主要的**資料庫**(如：Medline, Cochrane 考科藍實證醫學資料庫, EMBASE 等)，並且加上文獻**引用檢索**(參考文獻中相關研究、Web of Science, Scopus或Google Scholar)、試驗登錄資料等。

文獻搜尋應不只限於英文，並且應同時使用 MeSH字串及一般檢索詞彙(text words)。

Search strategy

Our study searched MEDLINE (1970 to Aug 2018), EMBASE (1993 to Aug 2018) and the Cochrane Controlled Trials Register to screen studies investigating CSBI and intravesical chemotherapy after TURBT. The analysis used the search formula: "[continuous AND ("saline solution" OR ("saline" AND "solution") OR "saline solution" OR "saline") AND ("urinary bladder" OR ("urinary" AND "bladder") OR "urinary bladder" OR "bladder") AND ("therapeutic irrigation" OR ("therapeutic" AND "irrigation") OR "therapeutic irrigation" OR "irrigation")] AND [intravesical AND ("drug therapy" OR ("drug" AND "therapy") OR "drug therapy" OR "chemotherapy" OR "drug therapy" OR ("drug" AND "therapy") OR "chemotherapy")]". The study was limited to published research on humans, with no restrictions on language. Furthermore, we have also browsed references of related articles. The authors were contacted to offer further information from their research if necessary.

【F】研究是否找到 (Find) 所有的相關證據？

在文章的方法 (Methods)章節，可以找到詳細**搜尋策略的說明**，包括使用的名詞，結果(Results)章節中可以找到本篇系統性文獻回顧評估的摘要及全文文獻數目、文獻納入與排除的數量及原因。

資料可能會以圖表或 PRISMA 的流程圖呈現。

Inclusion criteria

If study met the following criteria, it would be included: (1) CSBI and intravesical chemotherapy after TURBT was investigated in the article, (2) the article was a randomized controlled study, (3) full-text content and related data can be obtained, (4) the data provided by the article are valid and worthy of study, mainly including the total number of subjects and the valuable results of each indicator. If the same experimental results were published in different journals or at different times, the latest finding would be included in the meta-analysis. However, if a group of subjects participated in multiple studies, each study may be included in the analysis. The flowchart (Fig. 1) details the process of selection and elimination.

【F】研究是否找到 (Find) 所有的相關證據？

在文章的方法(Methods)章節，可以找到詳細搜尋策略的說明，包括使用的名詞，結果(Results)章節中可以找到本篇系統性文獻回顧**評估的摘要及全文文獻數目、文獻納入與排除的數量及原因**。
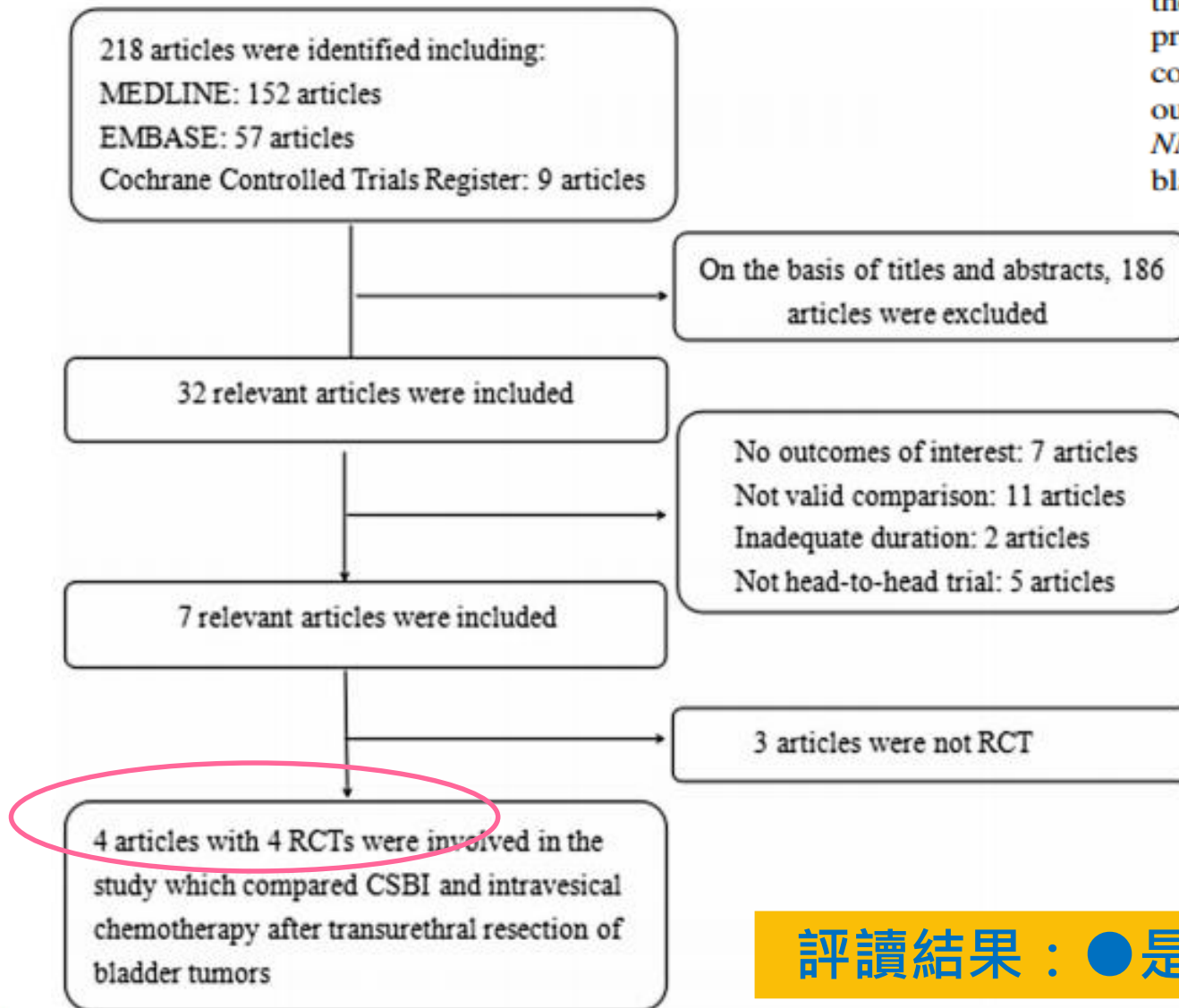資料可能會以圖表或 PRISMA 的流程圖呈現。

Results

Characteristics of individual studies

Two-hundred and eighteen articles were found by retrieval in each database. After screening the titles and abstracts, 186 articles were excluded on the basis of the inclusion criteria. Of the remaining 32 articles, 28 articles were excluded due to lack of available data. Four articles containing 4RCTs [7, 13–15] which compared CSBI and intravesical chemotherapy after TURBT were eventually absorbed into our analysis (Fig. 1). The characteristics of the studies are summarized in Table 1.

PRISMA 流程圖

Fig. 1 The flowchart details the selection and elimination process. *RCT* randomized controlled trials, *CSBI* continuous saline bladder irrigation, *NMIBC* non-muscle invasive bladder cancer

218 articles were identified including:
MEDLINE: 152 articles
EMBASE: 57 articles
Cochrane Controlled Trials Register: 9 articles

On the basis of titles and abstracts, 186 articles were excluded

32 relevant articles were included

No outcomes of interest: 7 articles
Not valid comparison: 11 articles
Inadequate duration: 2 articles
Not head-to-head trial: 5 articles

7 relevant articles were included

3 articles were not RCT

4 articles with 4 RCTs were involved in the study which compared CSBI and intravesical chemotherapy after transurethral resection of bladder tumors

評讀結果：●是 〇否〇不清楚

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

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【A】文獻是否經過嚴格評讀 (Appraisal)？

應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇**研究的品質**(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)。

Quality assessment

The study used the Jadad scale to evaluate the quality of RCTs retrieved [10]. Additionally, relevant research methods, including allocation method of participants, hiding allocation process, double-blinded and termination of results in data loss, were used to analyze the quality of individual studies. Afterwards, individual studies were assessed in line with the guidelines provided with the *Cochrane handbook for systematic reviews of interventions v5.30* [11]. Every article was evaluated and allotted in accordance with three quality classification standards: (A) when the study fulfilled all quality criteria, the study would be considered to have a low risk of bias; (B) when one or more of the quality criteria was just partially met or was fuzzy, the study was considered to have a secondary risk of bias; or (C) when one or more of the criteria were barely met or not included, the study was considered to have a high risk of bias. All authors participated in the quality assessment of RCTs retrieved. Differences regarding this quality assessment were resolved by discussion among the researchers.

評讀結果：●是 ○否 ○不清楚

【I】是否只納入 (Included) 具良好效度的文章？

僅進行文獻判讀是不足夠，系統性文獻回顧只納入至少要有一項研究結果是極小偏誤的試驗。在文章的方法章節，可以找到文章評估的方式，以及是由誰完成評估的，在結果章節則會提供審查者意見一致性的程度。

Quality of individual studies

All four articles complied with the criteria of randomized controlled study and each study indicated the randomization processes. A potent calculation in three RCTs [7, 14, 15] was applied to determine the sample size and the standard of character of these article was A. One RCT [13] without a calculation of sample size was classified as B (Table 2). All studies were included in the analysis regardless of the grade of quality. The funnel plot showed a qualitative estimation of publication bias of the study, the plot was highly symmetrical and four squares were contained in the large triangle, and no evidence of bias was found (Fig. 2).
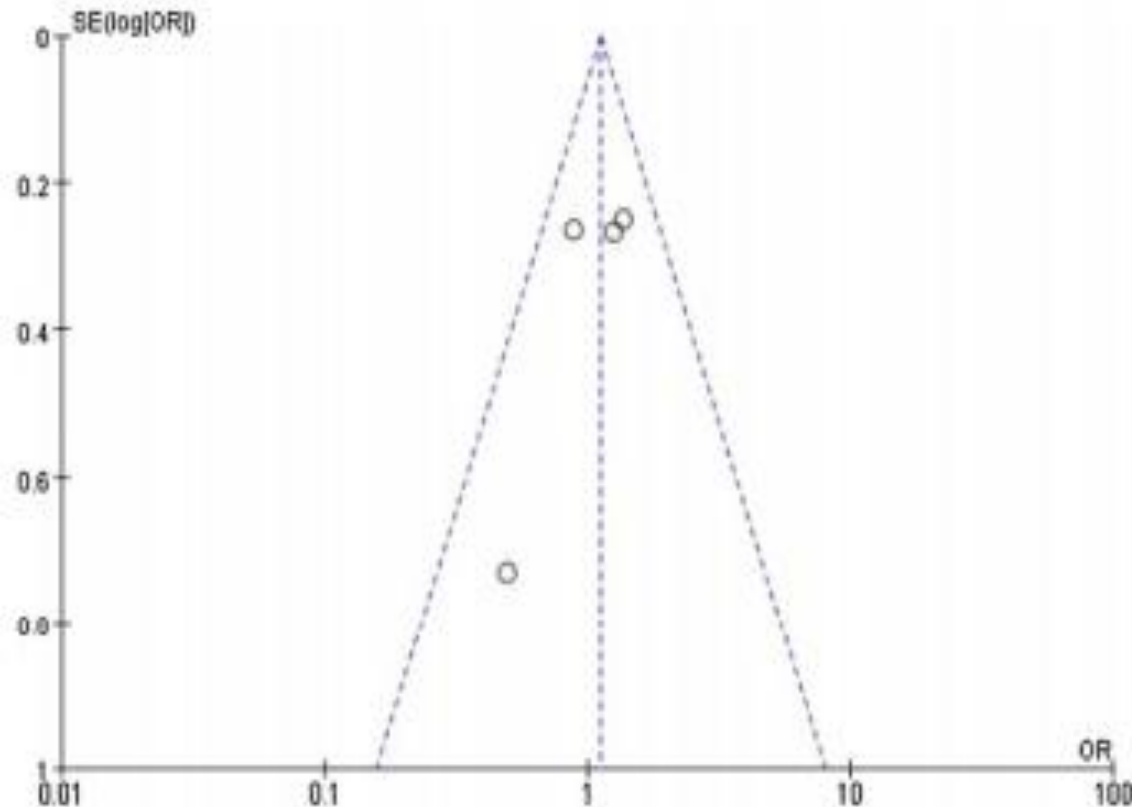
評讀結果：○是 ○否 ●不清楚

Quality of individual studies

Table 2 Quality assessment of individual study

Study	Allocation concealm...	...	...	Level of quality	ITT analysis
[13]	A		ı;	B	No
[14]	A		ı;	A	Yes
[15]	A		ı;	A	No
[7]	A		ı;	A	No

SE(log|OR|)

Fig. 2 Funnel plot of the studies presented in our study. *SE* standard error, *OR* odds ratio

A the study has a lo...   ...intention-to-treat

【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？

應該用至少 1 個**摘要表格呈現**所納入的試驗**結果**。

Table 1 Study and patient characteristics

Study	Therapy in experimental group	Therapy in control group	Sample size Experimental	Control	Administration method	Median follow-up time (year)	Inclusion population	Instillation protocol
[13]	CSBI	Intravesical chemotherapy	24	21	Irrigation	3	Patients with superficial bladder tumor were assigned to two groups before transurethral resection of bladder tumor	Epirubicin solution of 40 ug/ml for 20 h immediately after surgery; continuous irrigation with saline in the same manner
[14]	CSBI	Intravesical chemotherapy	162	166	Irrigation	4	Patients with clinical evidence of primary or recurrent NMIBC (Ta/T1, G1–3)	Gemcitabine (2000 mg/100 ml of saline) or placebo (100 ml of saline) followed by continuous bladder irrigation for ≥20 h
[15]	CSBI	Intravesical chemotherapy	123	115	Irrigation	5	Patients with intermediate risk NMIBC were treated by TUR followed by either CSBI or intravesical instillation of mitomycin C	Mitomycin C (4 weekly instillations starting 1 week after TUR followed by 11 monthly instillations to month 12); CSBI (2000 ml/h for first 1 h, then 1000 ml/h for 3 h, and then 250 ml/h for 14–18 h)
[7]	CSBI	Intravesical chemotherapy	124	126	Irrigation	5	Patients with primary low-to-intermediate-risk tumors were enrolled	Single immediate instillation of 30 mg mitomycin C in 30 ml of saline; CSBI (2000 ml/h for first 1 h, then 1000 ml/h for 2 h, and then 500 ml/h for 15 h)

評讀結果：●是 〇否〇不清楚

CSBI continuous saline bladder irrigation, *NMIBC* non-muscle invasive bladder cancer, *TUR* transurethral resection

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Appraisal

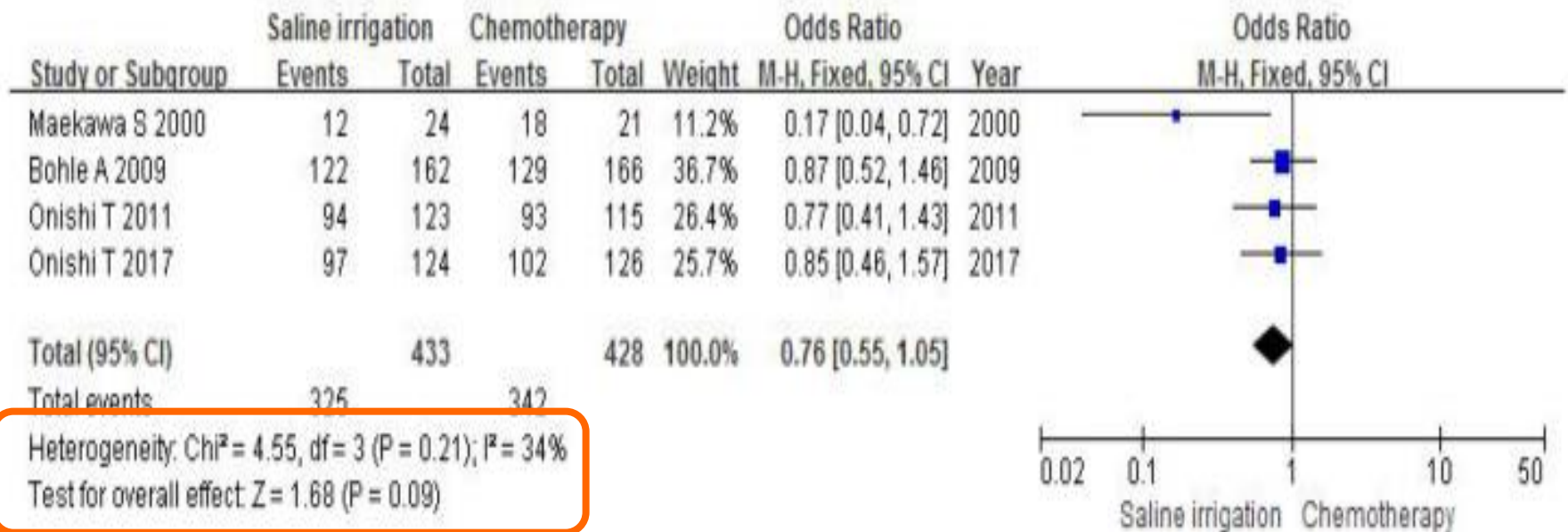## 【T】作者是否以表格和圖表「總結」 (Total up) 試驗結果？

以「**森林圖**」(forest plot) 呈現研究結果，最好再加上異質性分析。

【H】試驗的結果是否相近 - 異質性 (Heterogeneity) ？

在理想情況下，各個試驗的結果應相近或具同質 性，若具有異質性，作者應評估差異是否顯著 (卡方檢定)。根據每篇個別研究中不同的 PICO 及研究方法，探討造成異質性的原因。

【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？
【H】試驗的結果是否相近 - 異質性 (Heterogeneity)？
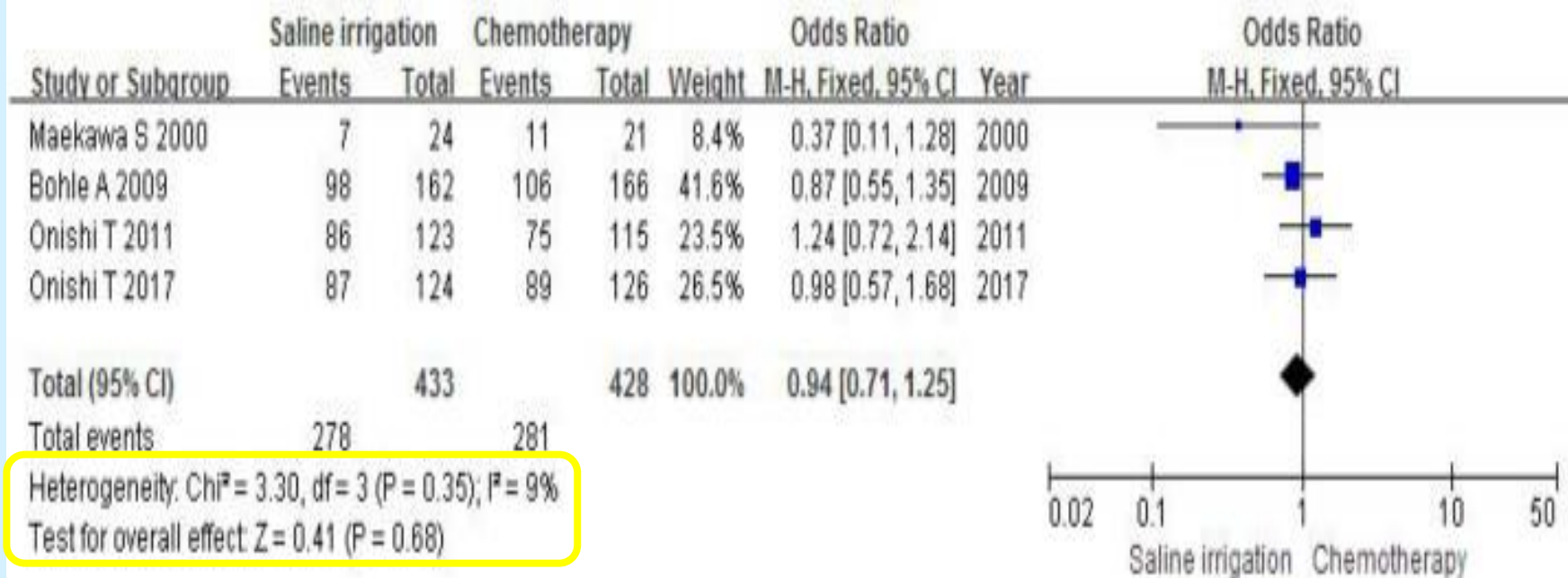

Fig. 3 Forest plots showing a 1-year recurrence-free survival; b 2-year recurrence-free survival; c the median period to first recurrence. M–H Mantel–Haenszel, CI confidence interval, df degrees of freedom

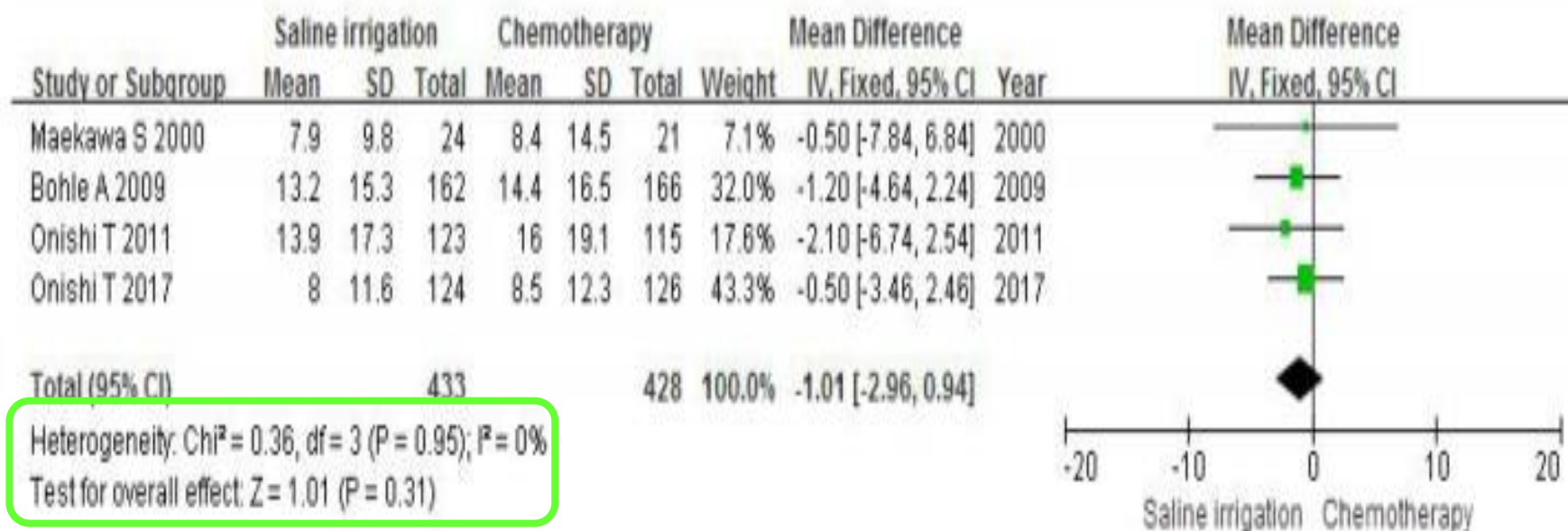## 【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？
【H】試驗的結果是否相近－異質性 (Heterogeneity)？

Fig. 3 Forest plots showing a 1-year recurrence-free survival; b 2-year recurrence-free survival; c the median period to first recurrence. M–H Mantel–Haenszel, CI confidence interval, df degrees of freedom

【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？
【H】試驗的結果是否相近 – 異質性 (Heterogeneity)？

(C)

Fig. 3 Forest plots showing **a** 1-year recurrence-free survival; **b** 2-year recurrence-free survival **c** the median period to first recurrence. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？
【H】試驗的結果是否相近 – 異質性 (Heterogeneity)？

Fig. 4 Forest plots showing **a** the number of tumor progression; **b** the number of recurrence during follow-up. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom
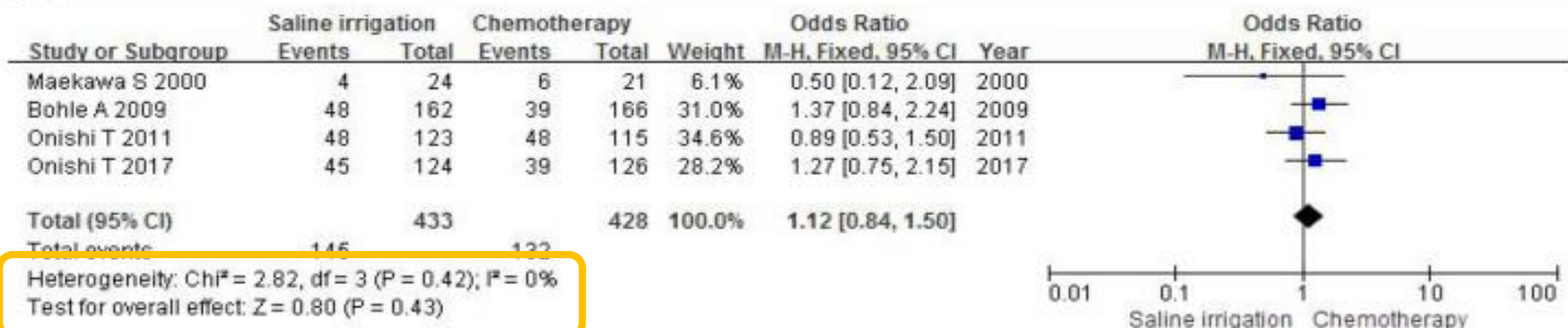
Appraisal FAITH步驟 2：系統性文獻回顧的品質如何 (T-H)

【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？
【H】試驗的結果是否相近 - 異質性 (Heterogeneity)？

Fig. 5 Forest plots showing a macrohematuria; b frequency of urination; c bladder irritation symptoms. M–H Mantel–Haenszel, CI confidence interval, df degrees of freedom

【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？
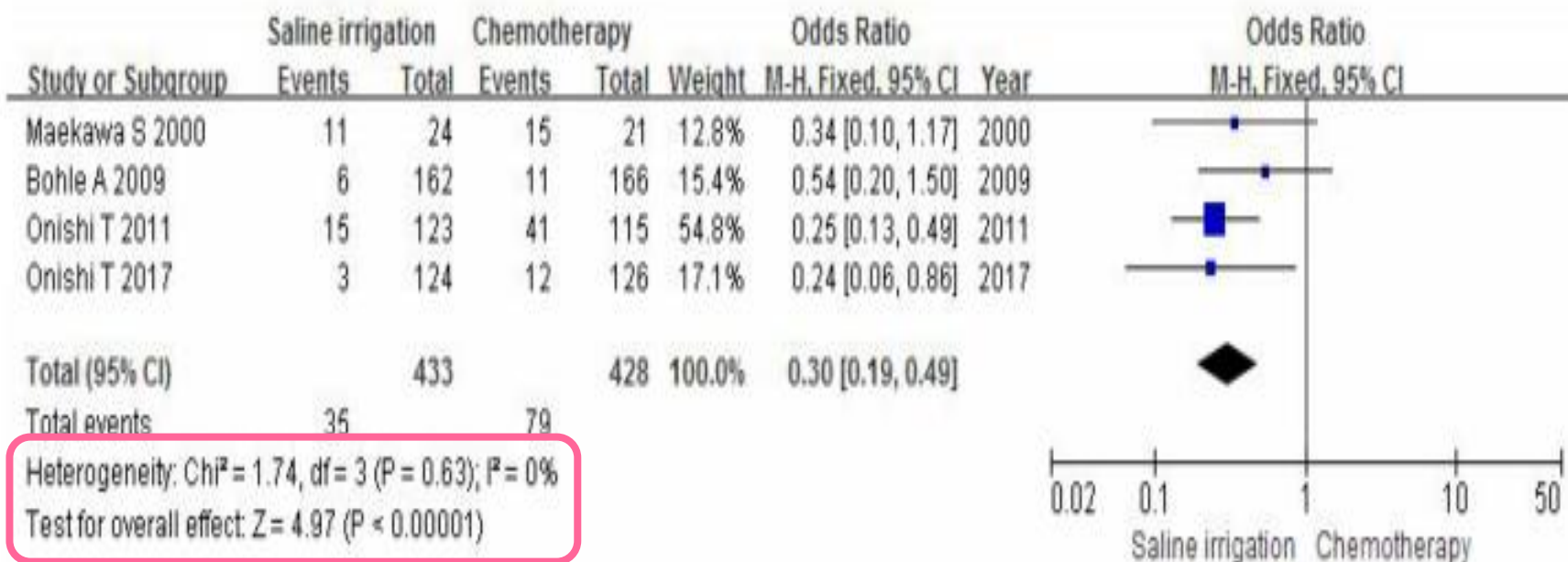## 【H】試驗的結果是否相近 – 異質性 (Heterogeneity)？

Fig. 5 Forest plots showing a macrohematuria, b frequency of urination; c bladder irritation symptoms. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

【T】作者是否以表格和圖表「總結」(Total up) 試驗結果？
【H】試驗的結果是否相近 – 異質性 (Heterogeneity)？

| Study or Subgroup | Saline irrigation | | Chemotherapy | | | Odds Ratio | | Odds Ratio |
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Maekawa S 2000	11	24	15	21	12.8%	0.34 [0.10, 1.17]	2000	
Bohle A 2009	6	162	11	166	15.4%	0.54 [0.20, 1.50]	2009	
Onishi T 2011	15	123	41	115	54.8%	0.25 [0.13, 0.49]	2011	
Onishi T 2017	3	124	12	126	17.1%	0.24 [0.06, 0.86]	2017	
Total (95% CI)		433		428	100.0%	0.30 [0.19, 0.49]		
Total events	35		79					

Heterogeneity: Chi² = 1.74, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 4.97 (P < 0.00001)

(C)

Fig. 5 Forest plots showing **a** macrohematuria; **b** frequency of urination; **c** bladder irritation symptoms. *M–H* Mantel–Haenszel, *CI* confidence interval, *df* degrees of freedom

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

總結

系統性文獻回顧的品質	評讀結果
研究是否找到(Find) 所有的相關證據？	是
文獻是否經過嚴格評讀(Appraisal)？	是
是否只納入(Included)具良好效度?	不清楚
作者是否以表格和圖表「總結」 (Total up) 試驗結果？	是
試驗的結果是否相近－異質性 (Heterogeneity)？	是

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

Appraisal sheets(FAITH)

- Appraisal Tool
  - [統合分析 Meta-analysis]
    - 步驟1：研究探討的問題為何 (PICO)
    - 步驟2：研究的品質如何 (內在效度)
    - 步驟3：研究結果之意義為何 (效益)

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

結論

表淺性膀胱癌經尿道腫瘤切除術後，以「生理食鹽水連續膀胱灌洗」與「化療藥物灌注」相比，其：

✓ 一年復發存活率、二年復發存活率、第一次復發時間、腫瘤進展等療效並無顯著差異。

✓ 生理食鹽水連續膀胱灌洗者，較無血尿、頻尿、膀胱刺激等不適症狀。

✓ 對於表淺性膀胱癌TUR-BT術後相較於化療藥物灌注，生理食鹽水連續膀胱灌洗為更加安全的療法。

討論與限制

➢ 腫瘤需徹底被移除，殘留的腫瘤導致復發，特別在中晚期(T1)高達33.8-36% 術後復發率。

➢ EAU和AUA指出TURBT術後膀胱內化療，4年後復發率降低39%，每種化療藥物機轉都不相同。

➢ CSBI常被用於手術後防止血栓阻塞，但在腫瘤治療，卻是一種新穎的灌注方案。可以去除漂浮的膀胱癌細胞，防止膀胱壁粘附和植入癌細胞，減少腫瘤復發。沒有禁忌症。

➢ CSBI 好處：容易、毒性低、節約成本。

➢ TURBT後，CSBI似乎在預防復發和局部毒性之間提供了比NMIBC膀胱內化療更好的平衡。

【限制】樣本數? 沒有比對單一藥物！

臺北市立萬芳醫院
-委託財團法人臺北醫學大學辦理-

Letter to the Editor

Letter to the Editor regarding the article "Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors".

Haroon UM, Galvin DJ.
World J Urol. 2019 Apr 12. doi: 10.1007/s00345-019-02750-6. [Epub ahead of print]
No abstract available.
PMID: 30980092

Letter to the Editor regarding the article "Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors".

Panahi MH.
World J Urol. 2019 Feb 1. doi: 10.1007/s00345-019-02645-6. [Epub ahead of print]
No abstract available.
PMID: 30707303

Dear Editors in chief, Professor Burchardt and Professor de la Taille,

We read the article by Zhou et al. [1] entitled "Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors" with great interest. Looking at the methodology and papers included for the meta-analysis, we have found a few flaws which must be highlighted.

The authors state in their study design: "Systematic review of Randomized Controlled Trials (RCTs) was carried out using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist" [1]. Their inclusion criteria states: "the article was a randomized controlled study" [1].

The authors include in their analysis a study by Onishi et al. [2] which is a retrospective non-randomised study of 238 patients with non-muscle-invasive bladder cancer. May I ask the authors for clarification on why it was included in the analysis?

The other flaw we see with their analysis is the comparison of different intravesical chemotherapeutic agents: Gemcitabine (Bohle et al.) to epirubicin (Maekawa et al.) to mitomycin c (Onishi et al.) [3, 4, 5]. To get meaningful results which can be applied to clinical practice, the intervention (the chemotherapeutic agent) must be standardised. Hence, conclusions from this study do not represent a high level of evidence and must be viewed with some scepticism.

Best Wishes

Dear Editor,

I recently reviewed the article by Zhou et al. [1] published in the January 2019 issue of the *World Journal of Urology*, entitled "*Meta-analysis of efficacy and safety of continuous saline bladder irrigation compared with intravesical chemotherapy after transurethral resection of bladder tumors*". I assessed its methodological quality using 16-item AMSTAR2 [2] appraisal tool. According to AMSTAR2, the study scored 11 items out of 16 while lost points from items 2, 9, 12, 13 and 14 which were related to the issues of protocol registry, risk of bias (ROB) and heterogeneity, respectively. ROB was well assessed by appropriate tools but its result was not accounted into the analysis through meta-regression/subgroup analysis or sensitivity analysis which may due to the paucity of the included studies. No commentary on the likely impact of ROB in discussion as well. In addition, although no heterogeneity was observed, it was not mentioned in the discussion part.

I suppose there was a typographical error to report "OR of – 1.01 and 95% CI of – 2.96 to 0.94 (p = 0.31)" for the median period to the first recurrence while it was mean difference not odds ratio.

Finally, to evaluate clinical significance, prediction interval (PI) was proposed in contrast to statistical significance presented by confidence interval (CI). I suggest that authors calculate prediction interval for evaluating clinical significances [3] for macrohematuria, frequency of urination and bladder irritation symptoms which were considered statistically significant.

As a conclusion, this was a well-written paper and most items were followed appropriately; non-critical weaknesses were observed there, so based on AMSTAR2, this study is classified as "Moderate" quality.

臨床問題：非肌肉層侵犯之膀胱癌病人，經尿道腫瘤切除後，使用鹽水進行膀胱沖洗比化療灌注更能兼顧效果及安全性嗎？
- 同意：0位
- 需要更多文獻支持：13位
- 不同意：7位