Systematic Review and Meta-Analysis

Medicine®

OPEN

The role of fluorescence in situ hybridization to predict patient response to intravesical Bacillus Calmette–Guérin therapy for bladder cancer

A diagnostic meta-analysis and systematic review

Yige Bao, MD[a], Xiang Tu, MD[a], Tiancong Chang, MD[b], Shi Qiu, MD[a], Lu Yang, MD[a], Jiwen Geng, MD[b], Liuliu Quan, MD[b], Qiang Wei, MD[a,*]

Abstract

Background: The aim of the study was to systematically review the relevant studies to assess the role of fluorescence in situ hybridization (FISH) test for predicting patient response to Bacillus Calmette–Guérin (BCG) therapy after transurethral resection of bladder tumor (TURBT).

Methods: We searched PubMed, Embase, and the Cochrane Library from inception to July 5, 2018, and used Quality Assessment Tool for Diagnosis Accuracy Studies (QUADAS-2) to assess the quality. We pooled sensitivity, specificity, and area under curve (AUC) of baseline and post-BCG FISH test for predicting tumor recurrence. Hazard ratio (HR) with 95% confidence intervals (95% CIs) and a Fagan nomogram were applied to assess predictive accuracy of post-BCG FISH test.

Results: A total of 6 studies with 442 participants for post-BCG test and 404 participants for baseline BCG test were included. The pooled analysis for post-BCG FISH test revealed the sensitivity of 0.54 (95% CI 0.38–0.69), specificity of 0.84 (95% CI: 0.72–0.91), and area under the curve (AUC) of 0.78 (95% CI: 0.74–0.81) for predicting tumor recurrence. Patients with positive post-BCG FISH test were more likely to recur during follow-up (HR 3.95, 95% CI 2.72–5.72). The Fagan nomogram revealed the "post-test" probability of tumor recurrence increased by 29% for patients with positive post-BCG FISH test. The baseline FISH test had a pooled sensitivity of 0.70 (95% CI 0.55–0.81), specificity of 0.41 (95% CI: 0.26–0.58), and AUC of 0.60 (95% CI: 0.56–0.64) for predicting recurrence.

Conclusion: The post-BCG FISH test can predict BCG failure with high specificity and patients with positive post-BCG FISH test were more likely to recur. However, the relatively low sensitivity of post-BCG FISH test and unsatisfactory performance of baseline FISH test may limit their mono-use.

Abbreviations: AUA = American Urological Association, AUC = area under the curve, BCG = Bacillus Calmette–Guérin, CIs = confidence intervals, FISH = fluorescence in situ hybridization, HR = hazard ratio, NMIBC = nonmuscle-invasive bladder cancer, QUADAS = Quality Assessment Tool for Diagnosis Accuracy Studies, SROC = summary receiver operating characteristic, TURBT = transurethral resection of bladder tumor.

Keywords: Bacillus Calmette–Guérin therapy, BCG, bladder cancer, FISH, fluorescence in situ hybridization, meta-analysis

1. Introduction

Nonmuscle-invasive bladder cancer (NMIBC) is a group of superficial tumors of the bladder (stage Ta, T1, and carcinoma in situ), which accounts for 70% to 75% newly diagnosed bladder cancer.[1] Depending on prognostic factors, patients are categorized into low-, intermediate-, and high-risk groups to predict tumor recurrence and progression.[2] The most effective

Editor: Leonidas G. Koniaris.

YB, XT, and TC contributed equally to this work and should share the cofirst author.

Funding/support: This study was supported by the National Natural Science Foundation of China (Grant No.81370855, No. 81200551, No. 81300627, and 81500522).

This study did not need consent of ethics committee or institutional review board, because the research was a meta-analysis, which belonged to a review article.

The authors have no commercial or financial incentive associated with the writing and publishing of this work.

The authors of this work have nothing to disclose and the authors report no conflicts of interest.

Supplemental Digital Content is available for this article.

[a] Department of Urology, Institute of Urology, [b] West China School of Clinical Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, P.R. China.

[*] Correspondence: Qiang Wei, Department of Urology, Institute of Urology, West China Hospital of Sichuan University, No. 37, Guoxue Lane, Chengdu, Sichuan 610041, P.R. China (e-mail: weiqiang933@126.com).

Medicine (2018) 97:36(e12227)

Received: 11 May 2018 / Accepted: 12 August 2018

http://dx.doi.org/10.1097/MD.0000000000012227

treatment for intermediate- or high-risk NMIBC is transurethral resection of bladder tumor (TURBT) combined with intravesical instillation of Bacillus Calmette–Guérin (BCG).[3] Nevertheless, as high as 42% of patients developed BCG failure in 1 year and a large portion of these tumors recur or progress into muscle-invasive disease despite the combined therapy.[4]

For patients not responding to intravesical BCG, accurate prediction BCG treatment failure is critical to help decide early cystectomy as well as avoid overtreatment.[5] Conventional cytology can detect high-grade urothelial carcinomas with high diagnostic accuracy. However, it has difficulty distinguishing inflammatory and reactive changes from the recurrent tumor, especially in patients being treated with intravesical BCG.[6] The cystoscopy during follow-up is an important prognostic indicator.[3] But cystoscopy mainly depends on subjective visible changes and relies on detection of actual tumor recurrence, which made it also a poor predictor for early intravesical BCG therapy failure.[7]

The UroVysion FISH test uses fluorescently labeled DNA probes to identify chromosomal alterations.[8] As the chromosomal integrity is not affected by hematuria, infections of urinary tract, or any other instrumentation process, FISH is reported to have better accuracy and earlier detection of tumor recurrence than cytology or cystoscopy.[9,10] A recent update of the American Urological Association (AUA) guideline mentioned that the UroVysion FISH test may be used to assess response to intravesical BCG therapy.[3] However, the evidence was limited to expert opinion. It remains unclear whether a review of the current literature would lead to a revision of clinical guidance. Therefore, we performed a diagnostic meta-analysis to assess the predictive accuracy of the UroVysion FISH test for predicting tumor recurrence in bladder cancer patients receiving regular intravesical BCG after TURBT.

2. Materials and methods

2.1. Search strategy

The systematic search was performed according to the PRISMA statement.[11] PubMed (Medline), Embase database, and the Cochrane Library were searched up to July 5, 2018. We also manually screened the references of included studies for additional citations. The search strategy was applied to identify all trials by using medical subject headings terms in combination with keywords of urinary bladder neoplasms, bladder cancer, BCG vaccine, fluorescence in situ hybridization, and FISH. We limited studies to human.

2.2. Selection criteria

Two authors (Y.B and X.T.) evaluated all potential articles independently. The inclusion criteria included a cross-sectional study that assessed the accuracy of FISH test (baseline FISH test: the specimens of urine were collected before starting the first BCG instillation; and post-BCG FISH test: the urine samples were collected when finishing the 6-week course of BCG instillation) for predicting BCG response. Positive FISH test was defined that at least 4 cells showed polysomy on at least 2 chromosomes (3, 7, or 17) and/or there were at least 12 cells with no signal (homozygous deletion) for 9p21.[12] Recurrence/progression status were used as endpoints. Tumor recurrence was defined as biopsy-proven NMIBC during the follow-up time, and tumor progression was defined as the development of muscle-invasive disease. Reporting data were available to calculate the true-positive, true-negative, false-positive, and false-negative rates of the FISH test. Review articles, editorial comments, conference reports, and low-quality studies were excluded. Any discrepancies were resolved by a third reviewer (Q.W.).

2.3. Data extraction

Two authors (Y.B. and X.T.) performed data extraction independently. We extracted data, including the first author, publication year, country, study design, participant details (number of patients, age, sex, and pre-instillation parameters), FISH test details (FISH system, sample number, and collecting time), follow-up time, and outcome data (recurrence and progression). Outcome data of predictive results detected by baseline and post-BCG FISH test were extracted in 2×2 contingency tables.

2.4. Evidence quality assessment

The Quality Assessment Tool for Diagnosis Accuracy Studies (QUADAS-2) was used by 2 authors (Y.B. and X.T.) separately to evaluate the quality of each trial, which included 4 domains: patient selection; index test conduct; reference test conduct; and participant flow and timing.[13] We judged a study to have "low risk of bias" if it was evaluated as "low" on all 4 domains or the first 3 terms concerning applicability. A study might be evaluated as a high risk of bias if more than 1 domain (including one) was judged "high" or "unclear." Any discrepancies were resolved by a third reviewer (Q.W.).

2.5. Statistical analysis

The pooled sensitivity, specificity, and the summary receiver operating characteristic (SROC) curve with an area under the curve (AUC) of baseline FISH test and post-BCG FISH test for predicting tumor recurrence were calculated using the STATA, version 12.0 (Stata Corporation, College Station, TX), respectively. The hazard ratio (HR) with 95% confidence intervals (95% CIs) were synthesized to compare the prediction capacity of tumor recurrence for positive and negative post-BCG FISH test. A Fagan nomogram was used to assess the predicting value of the post-BCG FISH test for tumor recurrence using likelihood ratios to calculate a post-test probability based on Bayesian theorems. Heterogeneity was valued with the Chi-square and the Higgins–Thompson I^2 method. The pronounced heterogeneity was indicated by a P value $< .05$ and an $I^2 > 50\%$.[14]

3. Results

3.1. Characteristics of the included studies and participants

The initial search identified 151 records in total. We identified 11 records for full-text review after screening titles and abstracts. Among these records, 4 studies were reviews, and 1 study was a duplicate. Finally, data from 6 studies[15–20] were synthesized in this diagnostic meta-analysis (Fig. 1). We summarized the patient clinical features and essential data in Table 1.

3.2. Predictive accuracy of post-BCG FISH test for tumor recurrence

Overall, 442 participants received the post-BCG FISH test with 31.9% (141/442) resulting in FISH positive and 37.3%

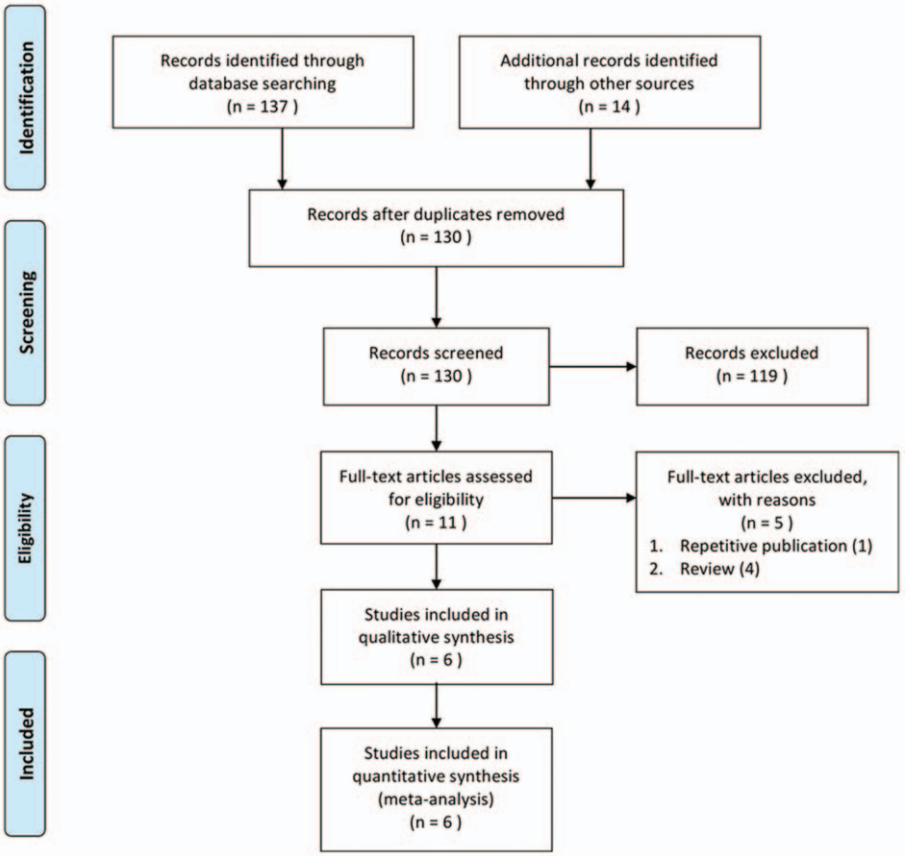

Figure 1. Flow diagram illustrating numbers of studies in the meta-analysis.

(165/442) developing tumor recurrence during the follow-up time. The statistical analysis revealed the pooled sensitivity of 0.54 (95% CI 0.38–0.69) and pooled specificity of 0.84 (95% CI: 0.72–0.91) (Fig. 2). An overall accuracy was revealed by the SROC curve with AUC of 0.78 (95% CI: 0.74–0.81) (S. Figure 1). Patients with a positive post-BCG FISH test were more likely to develop recurrence than patients of the negative post-BCG FISH result (HR 3.95, 95% CI 2.72–5.72). There was no heterogeneity identified ($I^2 = 0.00$, $P = .552$) (Fig. 3). The Fagan nomogram illustrated that with a positive post-BCG FISH result, there was a 66% "post-test" probability of a subsequent tumor recurrence episode, and the "post-test" probability of tumor recurrence dropped to 24% while with a negative post-BCG FISH test (Fig. 4).

Table 1

Characteristics of the included studies and participants.

Ref.	Country	Study design	No. of patients (F/M)	Age (range, y)	Cancer stage (pts.)	FIFH system	Samples collecting time (sample number)		Median follow-up time (range, mo)
							Pre-BCG	Post-BCG	
Kipp et al[15]	USA	Prospective	37 (1/36)	50–86	Ta (17) Tis (15) T1(5)	UroVysion	Before first instillation of IVT (31)	Before 6th instillation of IVT (31) + within 2 months after 6th instillation (6)	16(9)
Mengual et al[16]	Spain	Prospective	65 (8/57)	33–86	Ta (21) Tis (11) T1(22) Tx (11)	Multitarget, multicolor FISH Test UroVysion (Vysis Inc., Downers Grove, IL)	Before first instillation (65)	Two to six months after 6th instillation (65)	16.4* (8.9–26.6)
Savic et al[18]	Switzerland	Prospective	68 (8/60)	37–87	Ta (20) Tis (31) T1(17)	Multitarget UroVysion FISH Assay (Abbott/Vysis, Des Plaines, IL)	Before TURBT (18) + before first instillation (50)	3.3–16.1 weeks after 6th instillation (68)	19.5 (7.7–45.1)
Whitson and Berry[17]	USA	Retrospective	42 (NA)	41–97	NA	UroVysion	Before first instillation (NA)	Immediately after 6th instillation (42)	21 (–53)
Kamat et al[19]	USA	Prospective	126 (30/96)	NA	NA	UroVysion Bladder Cancer Recurrence Kit	Before first instillation (126)	Before 6th instillation (124)	23.4 (A)
Liem et al[20]	Netherlands	Prospective	114 (26/88)	42–94	Ta (43) Tis (23) T1(48)	Multitarget UroVysion Bladder Cancer Kit	Before first instillation (114)	Before 6th instillation (106)	23(–32)

FISH = Fluorescence in situ hybridization, IVT = intravesical therapy, NA = not available, TURBT = transurethral resection of bladder tumor.
* Mean time.

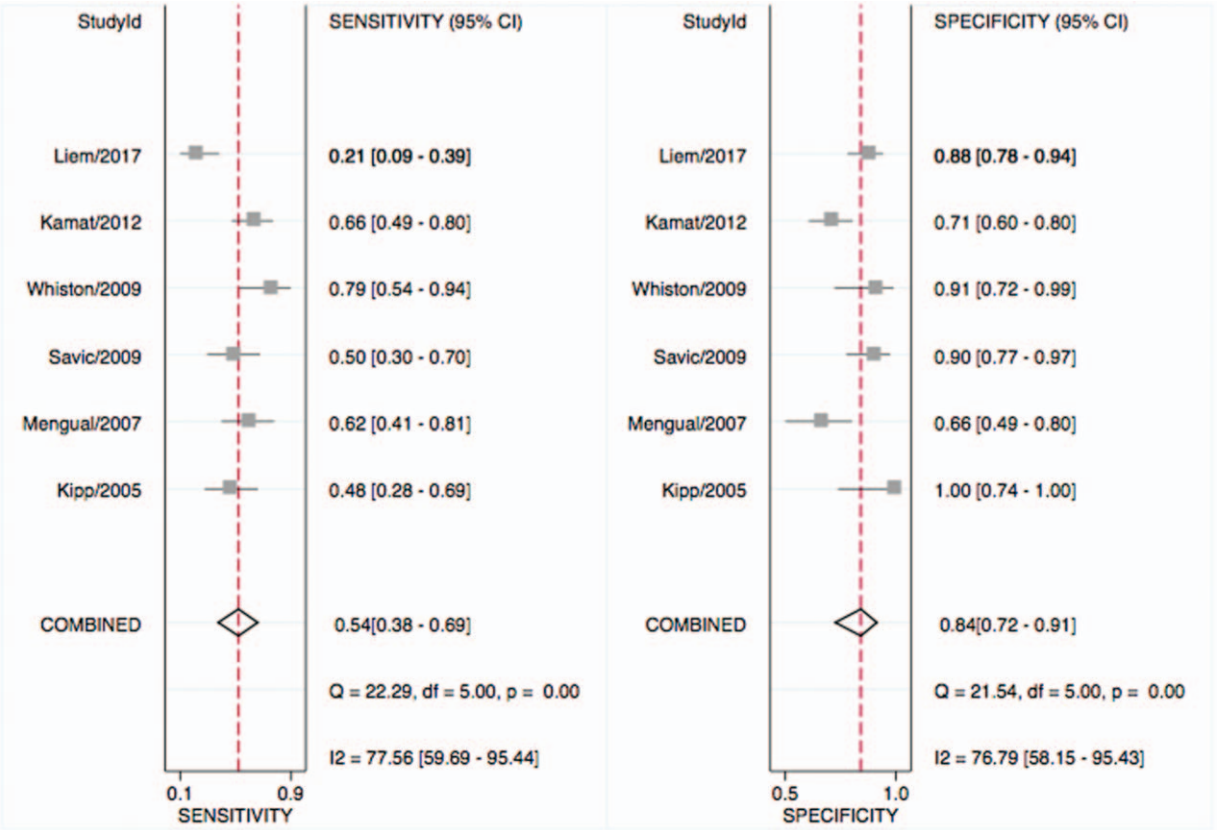

Figure 2. Forest plots of sensitivity and specificity for post-BCG FISH test predicting tumor recurrence.

3.3. Predictive accuracy of baseline FISH test for tumor recurrence

Of the 404 participants examined by the baseline FISH test, 60.9% (246/404) resulted in FISH positive, and 36.1% (146/404) developed recurrence. The sensitivities were between 0.44 and 0.79, while the specificities were between 0.12 and 0.70. The statistical analysis revealed the pooled sensitivity of 0.70 (95% CI 0.55–0.81) and pooled specificity of 0.41 (95% CI: 0.26–0.58) (Fig. 5). An overall accuracy was revealed by the SROC curve with the AUC of 0.60 (95% CI: 0.56–0.64) (S. Figure 2, http://links.lww.com/MD/C454).

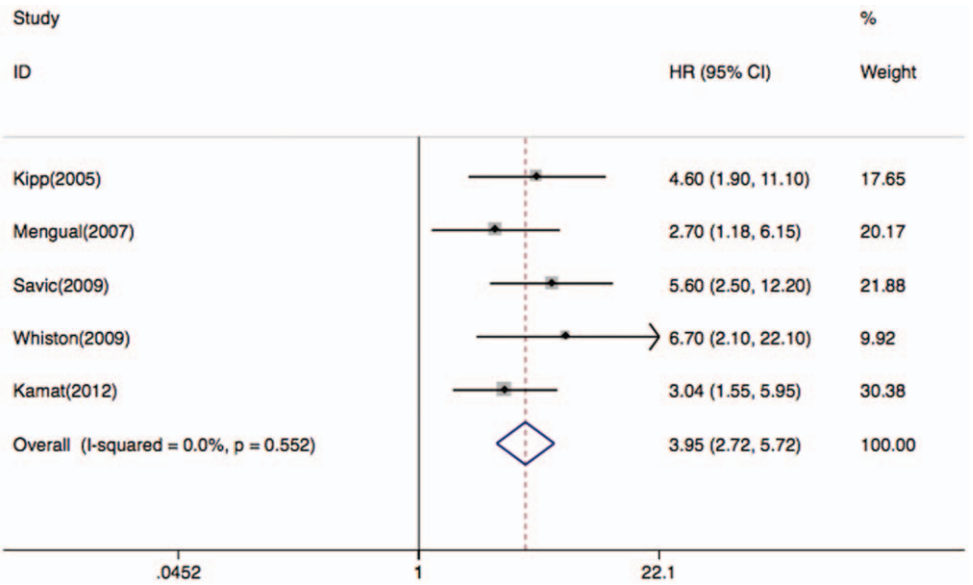

Figure 3. Forest plot of hazard ratio (HR) of tumor recurrence for positive and negative post-BCG FISH test. CI = confidence interval.

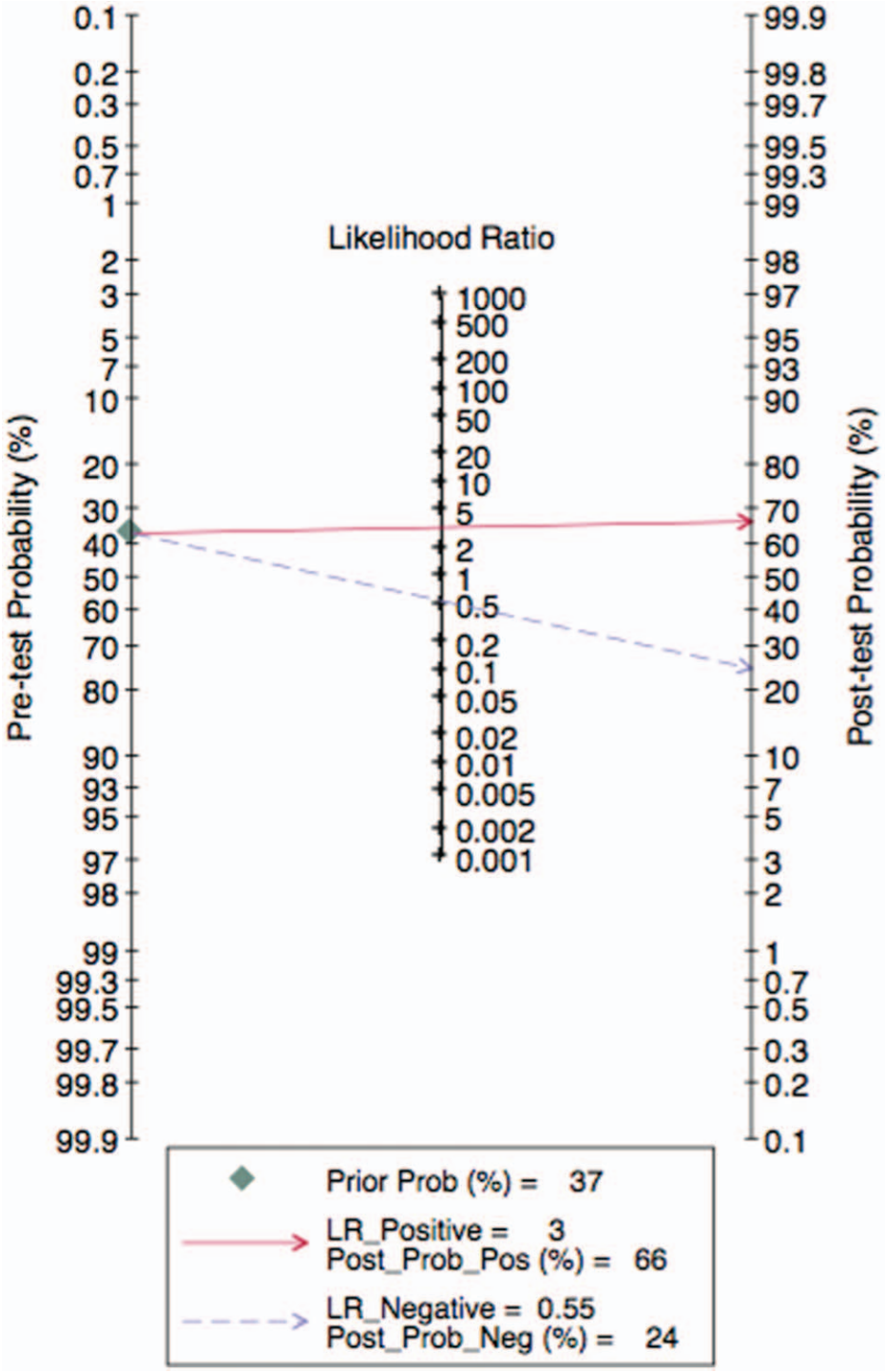

Figure 4. Fagan nomogram of post-BCG FISH for predicting tumor recurrence. With a positive post-BCG FISH result, there was a 66% "post-test" probability of a subsequent tumor recurrence episode, and the "post-test" probability of tumor recurrence dropped to 24% while with a negative post-BCG FISH test. LR = likelihood ratio.

3.4. Predictive accuracy of combined baseline and post-BCG FISH test for tumor recurrence

Three studies[15,16,19] have investigated the predictive capacity of tumor recurrence when regarding the combination of baseline and post-BCG FISH test (Table 2). Overall, simultaneously, positive results for both baseline and post-BCG test predicted a higher risk to recur. When regarding the impact of combined tests on recurrence rate, all 3 studies observed the lowest recurrence rate in patients with simultaneously negative tests, while the portion of recurrence cases remained highest in patients with negative baseline FISH result but transforming to positive after receiving instillation of BCG compared with other 5 groups.

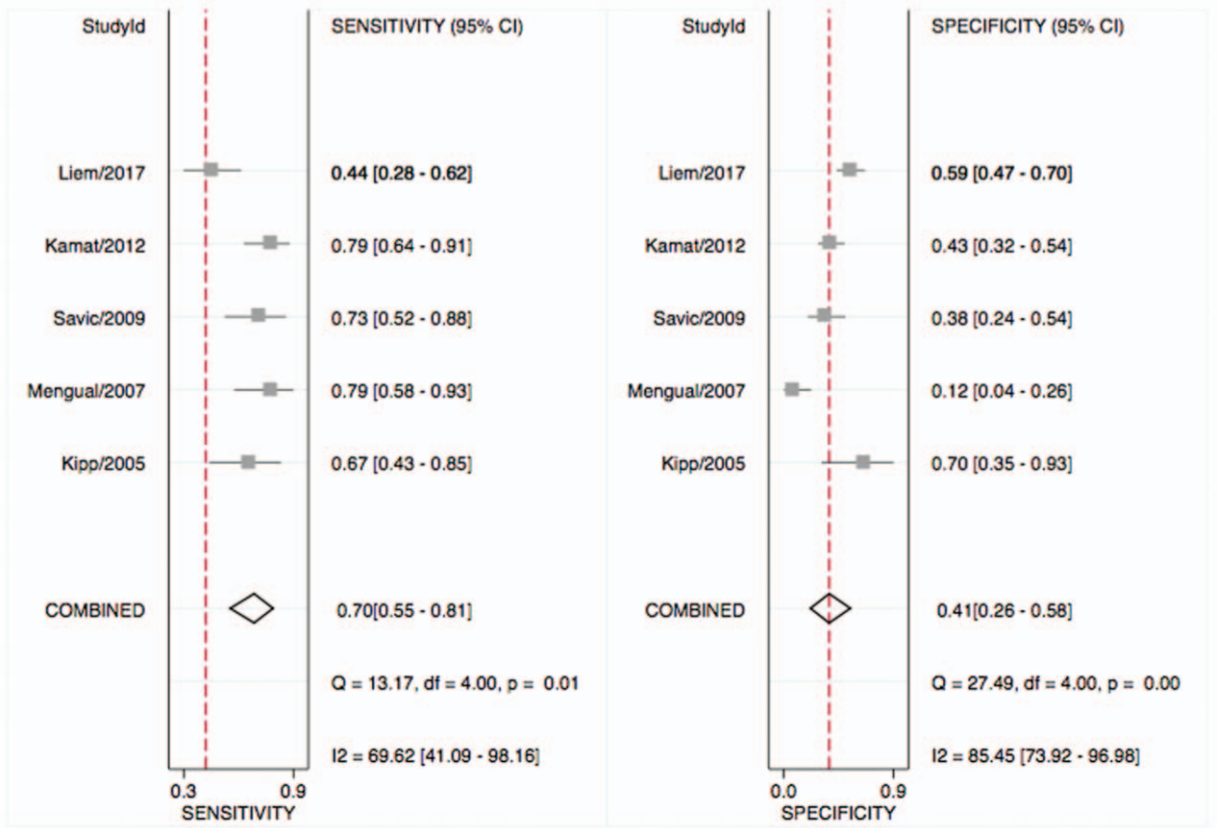

Figure 5. Forest plots of sensitivity and specificity for baseline FISH test predicting tumor recurrence.

3.5. Predictive accuracy of baseline and post-BCG FISH test for tumor progression

Three studies[15,16,19] have reported the predictive capacity of baseline and post-BCG FISH test for tumor progression during follow-up. However, a pooled analysis was not available due to the limited number of studies. We therefore extracted necessary data for 2×2 table and calculated the sensitivities and specificities separately. All studies reported that post-BCG FISH can predict tumor progression with both sensitivity and specificity above 0.50. For baseline FISH, the specificities varied; however, all 3 studies revealed that the sensitivity can reach above 0.50 (S. Table 1, http://links.lww.com/MD/C454).

3.6. Quality assessment of the included studies

Quality evaluation of individual studies is summarized in Table 3. In the patient selection domain, 1 study[17] was considered to be at a high risk for its retrospective design. For the flow and timing domain, we considered 2 studies[15,17] at a high risk of bias for existing withdrawals during the follow-up period. All of the other domains were considered to be at a low or unclear risk.

3.7. Evaluation of heterogeneity and sensitivity analysis

There was substantial heterogeneity between studies. Although post-BCG FISH test was defined that the urine samples for test

Table 2

Predictive accuracy of combined baseline and post-BCG FISH test for tumor recurrence.

	Cox proportional HR (95% CI)					
Ref.	**Neg - Neg**	**Neg - Pos**	**Pos - Neg**	**Pos - Pos**	**Pos - X**	**X - Pos**
*Kipp et al[15]	1 (reference)	4.3 (0.48–38.1)	2.8 (0.9–9.1)	5.3 (1.7–16.4)	NA	NA
†Mengual et al[16]	1 (reference)	1.6 (0.26–9.76)	1 (reference)	2.96 (1.17–7.54)	NA	NA
			Recurrence rate‡			
Kipp et al[15]	46.2% (6/13)	100% (1/1)	66.7% (6/9)	100% (8/8)	82.4 (14/17)	100% (12/12)
Mengual et al[16]	33% (2/6)	75% (3/4)	23% (7/30)	48% (12/25)	35% (19/55)	52% (15/29)
Kamat et al[19]	12.8% (NA)	60% (NA)	NA	48.9% (NA)	38% (31/81)	50% (25/50)

HR = hazard ratio, NA = not available, Neg = negative, Neg-Neg = negative baseline FISH test and negative post-BCG FISH test, Neg-Pos = negative baseline FISH test and positive post-BCG FISH test, Pos = positive, Pos-X = positive baseline FISH test and positive/negative post BCG test, X-Pos = negative/positive baseline FISH test and positive post-BCG FISH test.

* The HR was calculated using the Neg-Neg as the reference.

† The HR was calculated using the Neg-Neg as the reference for Neg-Pos patients, and Pos-Neg for Pos-Pos patients.

‡ Number of recurrence/number at risk.

Table 3

Quality assessment of the included studies.

	Risk of bias				Applicability concerns		
Ref.	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Kipp et al[15]	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear
Mengual et al[16]	Low	Low	Low	Low	Low	Low	Low
Whitson and Berry[17]	High	Low	Low	High	High	Low	Low
Savic et al[18]	Unclear	Unclear	Low	Low	Unclear	Unclear	Low
Kamat et al[19]	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Liem et al[20]	Unclear	Unclear	Low	Unclear	Low	Low	Low

The table summarizes the risk of bias and applicability concerns.

were collected immediately after finishing the 6-week course of BCG instillation in most studies. In 2 studies,[16,18] the urine samples were collected a period of time after the last instillation of BCG at sixth week. The sensitivity analysis by removing the 2 studies revealed that the pooled sensitivity of 0.53 (95% CI 0.30–0.74) and specificity of 0.86 (95% CI, 0.70–0.94), which indicated the short interval after BCG therapy may not have much impact on the final results (S. Figure 3, http://links.lww.com/MD/C454). Similarly, sensitivity analysis by removing the study by Savic et al[18] in which a small portion of urine specimens of baseline FISH collected before TURBT revealed consistent results for baseline FISH test with a sensitivity of 0.69 (95% CI 0.51–0.82) and a specificity of 0.42 (95% CI 0.22–0.65) (S. Figure 4, http://links.lww.com/MD/C454). Sensitivity analysis (data not shown) by removing the studies[15,17] of high risk revealed pooled specificity of 0.80 (95% CI 0.68–0.88) for post-BCG test, pooled sensitivity of 0.71 (95% CI 0.54–0.84) for baseline FISH test, and a similar trend to recur for patients with positive post-BCG FISH test (HR 3.80, 95% CI 1.98–5.61). Because there were less than 10 studies available, we did not assess the publication bias.

4. Discussion

In this diagnostic meta-analysis, we found that the post-BCG FISH test can predict tumor recurrence with high specificity and acceptable sensitivity. Patients with a positive post-BCG FISH were more likely to develop recurrence than patients of the negative post-BCG FISH test.

Intravesical BCG instillation is well known for its antitumor effect in bladder cancer. However, BCG failure does happen, and patients recur or progress. Attempts have been made to identify good predictors such as surveillance cystoscopy and cytology for tumor recurrence during intravesical BCG treatment.[21,22] However, due to the fact reactive urothelial changes could compromise the accuracy of cytology or cystoscopy,[6] currently, no diagnostic tool is available to discriminate between BCG responders and BCG failures. The FISH test combines the morphological changes of conventional cytology with molecular DNA alterations and was reported to have better performance than cytology in the detection of noninvasive papillary tumors in the bladder.[12,23] Considering that the integrity of chromosome is not affected by BCG, the FISH test could be a candidate tool to predict BCG failure and predict tumor recurrence.

In our study, the relatively higher specificity revealed the post-BCG FISH test seemed a better predictor for assessing response to intravesical BCG therapy compared with baseline FISH test. The difference was hypothesized that patients did not have benefitted from BCG induction therapy yet at baseline time.[20,24] And multiple studies[25–27] have reported the persistence of genetically aberrant cells after TURBT, which necessitated adjuvant therapy but not eventually progress to recurrence. Meanwhile, as the median time to recurrence after BCG reported was reported to be 26 months,[28] the median follow-up time of 16 to 23.4 months in this pooled study may not be long enough to detect all recurrences, which may also contribute to the false-positive rates.

The relatively low sensitivity of the post-BCG FISH test meant that there would still be nearly 46% negative patients with probability of recurrence, but still better than cytology.[16] And it was interesting to observe that post-BCG FISH test would have a lower sensitivity than pre-BCG FISH. On the one hand, the restriction to 4 chromosomes (3, 7, 9, 17) in FISH test, which is only part of chromosomal alterations in patients with bladder tumors, may contribute to the low sensitivity.[29] On the other hand, FISH test relies on sufficient malignant cells in the urine sample. The aggressive exfoliation of the vesical mucosa instead of tumor cells during BCG therapy could preclude the fulfillment of the positive criteria, which may lower the sensitivity of post-BCG FISH test.[30] Anyhow, previous studies reported the false-negative results mostly appeared in low-grade (grade 1 and 2) bladder tumor patients because these tumors had relatively few, if any, chromosomal abnormalities.[31,32] It might not to be a major concern because the 5-year progression rate is only 2% to 4% for these low-grade tumors.[33]

Considering the better predictive role when combing baseline and post-BCG FISH test together, multiple FISH tests that were longitudinally taken during a patient's follow-up may be of more value. For example, a patient with negative baseline FISH test but transforming to positive after receiving instillation of BCG recur easily even when compared with a patient with simultaneously positive FISH tests. This indicates that doctors should pay more attention to those patients with inconsistent FISH tests and provide necessary interventions especially for those transformed from negative to positive. However, no sufficient data can be pooled for synthesizing in current studies. More studies are needed to figure out the true role of combined FISH tests. And as tumor progression is more precise to identify patients who are going to need a cystectomy, more studies assessing the role of FISH test in predicting tumor progression are needed in terms of better implication for practice.

As far as we know, this was the first meta-analysis to assess the predictive accuracy of the UroVysion FISH test in predicting response to intravesical BCG therapy in patients with NMIBC. Nevertheless, limitations existed in our study, with the most obvious one being the substantial heterogeneity in varied aspects. However, the sensitivity analysis revealed that the minor interval for FISH test had a little impact on the final results. And as the diagnostic property of the study and FISH test depends mainly on

the chromosomal alterations, varied criteria for intravesical BCG therapy, the different protocol for intravesical therapy as well as tumor prevalence may have a little impact on the final results. Second, the limited number of studies available to synthesize was also one major limitation of our study. However, we have conducted a comprehensive search and included all studies available to synthesize the results.

In summary, we analyzed the current clinical evidence to assess the predictive accuracy of the UroVysion FISH test for predicting BCG response in patients with NMIBC. We found that the post-BCG FISH test can predict tumor recurrence with high specificity and patients with a positive post-BCG FISH were 3.95 times more likely to develop recurrence. However, the relatively low sensitivity of post-BCG FISH test may limit its utility. The combination of post-BCG FISH test with cystoscopy/cytology as well as baseline FISH test may be a promising method to help detect bladder cancer recurrence as early as possible. And more studies assessing the role of FISH test in predicting tumor progression are needed in terms of better implication for practice.

Acknowledgments

We thank Ian Charles Tobias (Western University of Ontario) for reviewing the manuscript.

Author contributions

Conceptualization: Yige Bao, Qiang Wei.
Data curation: Xiang Tu, Tiancong Chang, Shi Qiu, Lu Yang, Jiwen Geng, Liuliu Quan.
Formal analysis: Yige Bao, Xiang Tu, Shi Qiu, Liuliu Quan.
Funding acquisition: Yige Bao, Qiang Wei.
Methodology: Yige Bao, Xiang Tu, Shi Qiu.
Software: Tiancong Chang, Lu Yang, Jiwen Geng.
Supervision: Qiang Wei.
Writing – original draft: Yige Bao, Xiang Tu.
Writing – review & editing: Yige Bao, Xiang Tu, Tiancong Chang, Shi Qiu, Lu Yang, Jiwen Geng, Liuliu Quan, Qiang Wei.

References

[1] Lee R, Droller MJ. The natural history of bladder cancer. Implications for therapy. Urol Clin N Am 2000;27:1–3, vii.
[2] Babjuk M, Oosterlinck W, Sylvester R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008;59:303–14.
[3] Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016;196: 1021–9.
[4] Mungan NA, Witjes JA. Bacille Calmette-Guérin in superficial transitional cell carcinoma. Br J Urol 1998;82:213–23.
[5] Thalmann GN, Markwalder R, Shahin O, et al. Primary T1G3 bladder cancer: organ preserving approach or immediate cystectomy? J Urol 2004;172:70–5.
[6] Highshaw RA, Tanaka ST, Evans CP, et al. Is bladder biopsy necessary at three or six months post BCG therapy? Urol Oncol 2003;21:207–9.
[7] van der Aa MN, Steyerberg EW, Bangma C, et al. Cystoscopy revisited as the gold standard for detecting bladder cancer recurrence: diagnostic review bias in the randomized, prospective CEFUB trial. J Urol 2010;183:76–80.
[8] Meloni AM, Peier AM, Haddad FS, et al. A new approach in the diagnosis and follow-up of bladder cancer. FISH analysis of urine, bladder washings, and tumors. Cancer Gene Cytogenet 1993;71: 105–18.
[9] Grossman HB. Comparison of multitarget fluorescence in situ hybridization in urine with other noninvasive tests for detecting bladder cancer. Br J Urol Int 2003;92:911–4.
[10] Sarosdy MF, Schellhammer P, Bokinsky G, et al. Clinical evaluation of a multi-target fluorescent in situ hybridization assay for detection of bladder cancer. J Urol 2002;168:1950.
[11] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Rev Esp Nutr Hum Diet 2009;18:e123.
[12] Halling KC, King W, Sokolova IA, et al. A comparison of BTA stat, hemoglobin dipstick, telomerase and Vysis UroVysion assays for the detection of urothelial carcinoma in urine. J Urol 2002;167:2001–6.
[13] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[14] Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–60.
[15] Kipp BR, Karnes RJ, Brankley SM, et al. Monitoring intravesical therapy for superficial bladder cancer using fluorescence in situ hybridization. J Urol 2005;173:401–4.
[16] Mengual L, Marín-Aguilera M, Ribal MJ, et al. Clinical utility of fluorescent in situ hybridization for the surveillance of bladder cancer patients treated with Bacillus Calmette-Guérin therapy. Eur Urol 2007;52:752–9.
[17] Whitson J, Berry AP. A multicolour fluorescence in situ hybridization test predicts recurrence in patients with high-risk superficial bladder tumours undergoing intravesical therapy. BJU Int 2009;104:336–9.
[18] Savic S, Zlobec I, Thalmann GN, et al. The prognostic value of cytology and fluorescence in situ hybridization in the follow-up of nonmuscle-invasive bladder cancer after intravesical Bacillus Calmette-Guérin therapy. Int J Cancer 2009;124:2899–904.
[19] Kamat AM, Dickstein RJ, Messetti F, et al. Use of fluorescence in situ hybridization to predict response to bacillus Calmette-Guérin therapy for bladder cancer: results of a prospective trial. J Urol 2012;187:862–7.
[20] Liem EIML, Baard J, Cauberg ECC, et al. Fluorescence in situ hybridization as prognostic predictor of tumor recurrence during treatment with Bacillus Calmette–Guérin therapy for intermediate- and high-risk non-muscle-invasive bladder cancer. Med Oncol 2017; 34:172.
[21] Smith PJ, Lotan Y, Raj GV, et al. Assessing treatment response after induction Bacillus Calmette-Guerin for carcinoma in situ of the urinary bladder: can post-induction random bladder biopsies be avoided? Cytopathology 2014;25:108–11.
[22] Haase RN, Harving N. Are cystoscopy and urinary cytology sufficient to identify candidates for subsequent biopsy after bacillus Calmette-Guerin treatment in patients with bladder carcinoma in situ? Scand J Urol 2015;49:338–40.
[23] Halling KC, King W, Sokolova IA, et al. A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma. J Urol 2000;164:1768–75.
[24] Ghi NM, Alvaro M, Lamm DL. Bacillus Calmette–Guérin immunotherapy for genitourinary cancer. BJU Int 2013;112:288–97.
[25] Pycha A, Mian C, Hofbauer J, et al. Does topical instillation therapy influence chromosomal aberrations in superficial bladder cancer? J Urol 1998;159:265–9.
[26] Miladi M, Peyromaure M, Zerbib M, et al. The value of a second transurethral resection in evaluating patients with bladder tumours. Int Braz J Urol 2003;29:181–2.
[27] Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? J Urol 2001;165:808–10.
[28] Böhle A, Jocham D, Bock PR. Intravesical bacillus calmette-guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90–5.
[29] Steidl C, Simon R, Bürger H, et al. Patterns of chromosomal aberrations in urinary bladder tumours and adjacent urothelium. J Pathol 2002; 198:115–20.
[30] Skacel M, Fahmy M, Brainard JA, et al. Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. J Urol 2003;169:2101–5.
[31] Bittard H, Lamy B, Billery C. Clinical evaluation of cell deoxyribonucleic acid content measured by flow cytometry in bladder cancer. J Urol 1996;155:1887–91.
[32] Richter J, Jiang F, Görög JP, et al. Marked genetic differences between stage pTa and stage pT1 papillary bladder cancer detected by comparative genomic hybridization. Cancer Res 1997;57:2860–4.
[33] Droller MJ. Bladder cancer: state - of - the - art care. CA Cancer J Clin 1998;48:269.