Sub-staging specific differences in recurrence-free, progression-free and cancer-specific survival for patients with T1 bladder cancer: a systematic review and meta-analysis

GuanQiu Chen

Xi'an Jiaotong University Medical College First Affiliated Hospital

Tao Yang

Xi'an Jiaotong University Medical College First Affiliated Hospital

Pu Zhang

Xi'an Jiaotong University Medical College First Affiliated Hospital

Meng-Zhao Zhang

Xi'an Jiaotong University Medical College First Affiliated Hospital

Bo Yang

Xi'an Jiaotong University Medical College First Affiliated Hospital

Jinhai Fan (✉ jinhaif029@126.com)

Xi'an Jiaotong University

Research article

Keywords: Urinary bladder neoplasms, Sub-staging, Muscularis mucosa, Progression, Recurrence, Cancer-specific survival

Posted Date: March 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-17652/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Urologia Internationalis on January 1st, 2020. See the published version at <https://doi.org/10.1159/000506238>.

Abstract

Background: The efficiency of the T1 sub-staging system on categorizing bladder cancer (BC) patients into subgroups with different clinical outcomes was unclear. We summarized relevant evidences, including recurrence-free survival (RFS), progression-free survival (PFS) and cancer-specific survival (CSS), to analyze the prognostic significance of T1 sub-stage.

Methods: Systematic literature searches of MEDLINE, EMBASE and the Cochrane Library were performed. We pooled data on recurrence, progression, and CSS from 35 studies.

Results: The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) indicated the difference in RFS between T1a sub-stage and T1b sub-stage (HR1.28, 95%CI 1.14-1.43). The significant difference was observed in PFS between the two arms (HR 2.18, 95%CI 1.95-2.44). Worse CSS was found in T1b patients than T1a patients (HR 1.45, 95%CI 1.28-1.64).

Conclusions: T1 sub-staging system based on the invasion depth into muscularis mucosae (MM) can be a significant prognostic factor for RFS, PFS, and CSS of patients with T1-BC. Urologists and pathologists are encouraged to work together to give a precise sub-stage classification of T1-BC, and T1 sub-staging system should be a routine part of any histopathological report when possible. Different treatment strategies need to be developed for both T1a-BC and T1b-BC.

1. Background

Up to 75% of bladder cancers (BCs) are non-muscle invasive at initial diagnosis(1). T1-BC, which invades the lamina propria but not the muscularis propria, comprises 20% of non-muscle invasive BC(2). And the prognostic situation is challenging, relected on the relatively high 5-year recurrence rates (39–45%), 5-year progression rates (18–23%) and the cancer-specific mortality (15%)(3). Therefore, some experts recommended that radical cystectomy should be performed for all T1-BC patients(4, 5), while some experts believed that radical cystectomy was an unnecessary treament strategy for non-progressive T1-BC and negatively affected the quality of life(6). However, the predictive value of Tumor Node Metastasis(TNM) stage is limited in T1-BC. The T1 sub-stage may help categorize patients into different subgroups with different clinical outcomes. And T1 sub-stage has been identified as an important prognostic factor(7). The most widely studied sub-staging system for T1-BC is based on muscularis mucosae (MM) invasion. The MM is a discontinuous layer of smooth muscle bundles, approximately situated in the middle between the urothelium and the muscularis propria. Two invasion stages can be defined as invasion above the MM (referred as T1a) and invasion in or through the MM (referred as T1b). The main objective of this review was to analyze the prognostic significance of T1 sub-staging system based on MM invasion in recurrence-free survival (RFS), progression-free survival (PFS) and cancer-specific survival (CSS) for T1-BC patients.

2. Materials And Methods

2.1 Data sources and searches This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. A research librarian searched multiple electronic databases including MEDLINE, EMBASE and the Cochrane Library. The main key words used for the search were (urinary bladder neoplasms OR bladder tumors OR urinary bladder cancer OR bladder carcinoma) AND (sub-stage OR sub-staging) AND muscularis mucosa AND prognosis. The full search algorithm was shown in **(S1 word)**. The search was conducted in September 2019, without limiting the starting time of the literature. We also reviewed reference lists and previous systematic reviews for additional studies and searched documents for unpublished studies. The language was not restricted.

2.2 Study selection The inclusion criteria was as follows: Firstly, the participants must be identified as T1 primary BC patients. Secondly, the category was according to T1 sub-staging system based on MM invasion. Thirdly, the predefined outcomes were differences in RFS, PFS, and CSS between T1a and T1b. Publications were required to report hazard ratios (HRs) and 95% confidence intervals (CIs) or documented data, which allowed an HR to be readily calculable for one of the specified outcomes(8). The recurrence was defined as histological detection of BC after three months of transurethral resection of bladder tumor (TURBT). The progression was defined as later occurrence of any higher stage disease. Two reviewers evaluated each study on the basis of predefined inclusion criteria. Only studies which fulfilled inclusion criteria, evaluation of at least one outcome (RFS, PFS or CSS) after TURBT were included. Case reports, review articles and meta-analyses were excluded.

2.3 Data abstraction and study quality assessment Two reviewers extracted data on baseline characteristics, methods, and outcomes (HRs, number of events for recurrence, progression, and CSS) from included articles. The disagreements were resolved by consensus. We used the Newcastle-Ottawa Scale system to rate the quality of all studies. Studies with scores more than 7 were assessed as “low-risk”, scores of 4 to 6 were assessed as “moderate-risk”, and scores of less than 4 were assessed as “high-risk”. The study quality assessment was independently performed by two reviewers. And the inconsistencies were resolved by consensus.

2.4 Data synthesis and analysis We conducted meta-analyses on HRs and 95% CIs for RFS, PFS, and CSS using Stata software (version 11.0). A random effects model was used to combine the results.

2.5 Heterogeneity and publication bias The Cochrane Q test was used to evaluate statistical heterogeneity ($P < .10$). The I^2 statistic was used to assess the contribution of between-study heterogeneity to overall heterogeneity(9). To evaluate publication bias, Begg’s test was performed. Meta-regression was used to analyze the heterogeneity.

3. Results

900 potentially relevant articles were initially included after database searches. The study flow chart was presented in **(Fig 1)**. We selected 68 articles for full-text review, of which 35 studies met the inclusion

criteria. For each study, the data were extracted (**S2 Table**). Five studies were performed in Asia (10-14), 20 were performed in Europe (2, 7, 15-32), and 10 were performed in North America (33-42). RFS was evaluated in 20 studies, PFS was evaluated in 31 studies and CSS was evaluated in 12 studies. Median follow-up time ranged from 12 to 114 months, with a median of 57.3 months. The 35 studies included 100% of patients with T1-BC.

The difference was found in RFS between T1a and T1b sub-stage (HR1.28, 95%CI 1.14-1.43) (**Fig 2**). The significant difference was observed in PFS between the two arms (HR 2.18, 95%CI 1.95-2.44) (**Fig 3**). And T1b patients had worse CSS than T1a patients (HR 1.45, 95%CI 1.28-1.64) (**Fig 4**).

3.1 Study quality, heterogeneity and publication bias The risk of bias was calculated to be low or moderate for included studies. 33 studies were rated low-risk of bias, and two were moderate-risk. The scale scores were conveyed in (**S3 Table**). We did not find any heterogeneity among studies by evaluating the RFS ($I^2 = 27.9\%$). Heterogeneity was observed for PFS and CSS ($I^2 = 60.7\%$, $I^2 = 50.1\%$). The Begg's funnel plots did not reveal any statistically significant publication bias in studies (that evaluated RFS ($p=0.230$) and CSS ($p=0.150$)) (**Fig 5A, Fig 5B**). When evaluating PFS, statistically significant publication bias was identified by the Begg's funnel ($p=0.002$) (**Fig 5C**).

Discussion

The current classification recommends the reporting of the extent of invasion of T1-BCs. However, the system for sub-staging to be used remains optional. T1 sub-stage based on MM invasion was identified as an important prognostic factor for T1-BC. The T1 sub-staging system may help categorize patients into different subgroups with different clinical outcomes. The typical symptom of MM invasion is the change of MM distribution pattern from a continuous layer to a dispersed smooth muscle cell bundle. It was reported that the presence of MM could be found only in 32% of TURBT specimens, and 17% of biopsy specimens(43–47). In some areas of the bladder, such as trigone, the MM may be difficult to be identified(48), while the rate of MM discovery has increased up to 100% in more recent reports now. Most of them agreed on a 90% discovery rate(15). It is important for urologists and pathologists to work together to identify the MM invasion. Firstly, the urologists need to minimize the cautery injury when performing TURBT, and submit the tumor base separately. These will enable the pathologist to have a better opportunity to identify the MM invasion depth. En-bloc resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is proven to be feasible. It provides resected specimens of high quality with detrusor muscle preserved(49, 50). Secondly, well trained pathologists need to sub-stage the tumor in most patients with stage T1-BC.

Martin-Doyle et al(3) previously conducted a meta-analysis in comparing the recurrence rate between T1a and T1b/c high-grade BC based on six studies published before 2015. They found that T1a high-grade BC patients had no difference in recurrence compared with T1b/c high-grade BC patients (HR, 1.29; 95% CI, 0.93–1.78; $P = 0.127$). We evaluated 20 studies including both T1 low-grade BC and T1 high-grade BC. We found the difference in recurrence between T1a BC and T1b BC patients (HR, 1.28; 95%CI, 1.14–1.43

). The different clinical outcomes in our study was explained as follows: Firstly, the population in our study covered all types of T1-BC, rather than T1 high-grade BC. Secondly, most studies focused on progression rate, with fewer studies reporting the recurrence of BC. Thirdly, the invasion of MM was more frequently discovered.

We analyzed the heterogeneity in studies, which evaluated RFS and CSS with meta-regression. As individual patient data were not accessible, the assessment of heterogeneity was limited. We only analyzed the factors of publication year and race using covariate meta-regression respectively. We found the publication year was related to the heterogeneity in studies which evaluated PFS ($P = 0.014$), while the race was not related to the heterogeneity ($p = 0.822$). We found that neither publication year ($p = 0.538$) nor race ($P = 0.705$) was related to the heterogeneity in studies which evaluated CSS. Although we identified little evidence of publication bias, we might have limited capabilities to detect the bias, given the limitations of available techniques(51). This publication bias might be originated from selective reporting of results.

The treatment of T1-BC remains controversial. For patients receiving no adjuvant intravesical treatment, the progression rate was 9.1% in patients with T1a tumor, whereas it was 50% in patients with T1b tumor (11). Orsola et al (15) reported that in BCG-treated patients, the progression rate was 8% in patients with T1a tumor, whereas it was 34% in patients with T1b tumor. Overall the progression rate of T1b patients was higher than that of T1a patients. In our study, T1b patients had worse RFS, PFS and CSS than T1a patients. So patients with T1a tumor could be managed conservatively with TURBT and intravesical BCG treatment. But patients with T1b tumor should be recommended to receive more aggressive treatment.

There were some limitations in our study. Firstly, all included studies were retrospective observational studies with selection biases. Secondly, insufficient data which lacked details on presence of carcinoma in situ and employment of whether re-TURBT or intravesical treatment, limited further analyses. Thirdly, we did not distinguish between low grade and high grade cancers, which might also influence disease recurrence and progression.

Conclusions

From our meta-analysis, we confirmed that T1 sub-staging system based on MM invasion could be a significant and adverse prognostic factor for RFS, PFS, and CSS of patients with T1-BC. Therefore, urologists and pathologists should be encouraged to work together to evaluate MM invasion. And T1 sub-staging system based on MM invasion should be recognized as a routine part of any histopathological report when possible. And future researches such as multicenter randomized clinical trials should be conducted to confirm our opinions.

Abbreviations

BC: bladder cancer; MM: muscularis mucosae; RFS: recurrence-free survival; PFS: progression-free survival; CSS: cancer specific survival; HRs: hazard ratios; CIs: confidence intervals; TURBT: transurethral resection of bladder tumor

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

JF: Conceptualization, methodology, visualization, supervision, and project administration. GC: Methodology, investigation, data curation, formal analysis, resources, writing-original draft. TY: Investigation, data curation, writing-review and editing. PZ: Investigation, data curation, visualization, writing-review and editing. MZ: Investigation, data curation, editing and visualization. BY: data curation, and editing. All authors read and approved the final manuscript.

References

1. Babjuk M, Bohle A, Burger M, Capoun O, Cohen D, Comperat EM, et al. EAU Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. *European Urology*. 2017;71:447-61.
2. Andius P, Johansson SL, Holmang S. Prognostic factors in stage T1 bladder cancer: tumor pattern (solid or papillary) and vascular invasion more important than depth of invasion. *Urology*. 2007;70:758-62.

3. Martin-Doyle W, Leow JJ, Orsola A, Chang SL, Bellmunt J. Improving selection criteria for early cystectomy in high-grade t1 bladder cancer: a meta-analysis of 15,215 patients. *Journal of Clinical Oncology*. 2015;33:643-50.
4. Sternberg IA, Keren PG, Chen LY, Herr HW, Dalbagni G. Role of immediate radical cystectomy in the treatment of patients with residual T1 bladder cancer on restaging transurethral resection. *Bju International*. 2013;112:54-9.
5. Stein JP, Penson DF. Invasive T1 bladder cancer: indications and rationale for radical cystectomy. *Bju International*. 2008;102:270-5.
6. Cookson MS, Chang SS, Wells N, Parekh DJ, Smith JJ. Complications of radical cystectomy for nonmuscle invasive disease: comparison with muscle invasive disease. *J Urol*. 2003;169:101-4.
7. Rouprêt M, Seisen T, Larre S, Comperat E, Mazerolles C, Fromont G, et al. Prognostic interest to discriminate muscularis mucosae invasion (T1a vs. T1b) in non-muscle-invasive bladder carcinomas: Results from a national multicentre study with a central pathology review. *European Urology Supplements*. 2013;12:e483-4.
8. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine*. 1998;17:2815-34.
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60.
10. Hasui Y, Osada Y, Kitada S, Nishi S. Significance of invasion to the muscularis mucosae on the progression of superficial bladder cancer. *Urology*. 1994;43:782-6.
11. Sozen S, Akbal C, Sokmensuer C, Ekici S, Ozen H. Microstaging of pT1 transitional cell carcinoma of the bladder. Does it really differentiate two populations with different prognoses? (pT1 subcategory). *Urologia Internationalis*. 2002;69:200-6.
12. Lee JY, Joo HJ, Cho DS, Kim SI, Ahn HS, Kim SJ. Prognostic Significance of Substaging according to the Depth of Lamina Propria Invasion in Primary T1 Transitional Cell Carcinoma of the Bladder. *Korean J Urol*. 2012;53:317-23.
13. Turan T, Efiloglu O, Gunaydin B, Ozkanli S, Nikerel E, Atis G, et al. Comparative differences between T1a/b and T1e/m as substages in T1 urothelial carcinoma of the bladder. *International Braz J Urol*. 2018;44:267-72.
14. Chang WC, Chang YH, Pan CC. Prognostic significance in substaging of T1 urinary bladder urothelial carcinoma on transurethral resection. *American Journal of Surgical Pathology*. 2012;36:454-61.
15. Orsola A, Trias I, Raventos CX, Espanol I, Cecchini L, Bucar S, et al. Initial high-grade T1 urothelial cell carcinoma: feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. *European Urology*. 2005;48:231-8, 238.
16. Soukup V, Babjuk M, Duskova J, Pesl M, Szakaczova M, Zamecnik L, et al. Does the expression of fascin-1 and tumor subclassification help to assess the risk of recurrence and progression in t1 urothelial urinary bladder carcinoma? *Urologia Internationalis*. 2008;80:413-8.

17. Bertz S, Denzinger S, Otto W, Wieland WF, Stoehr R, Hofstaedter F, et al. Substaging by estimating the size of invasive tumour can improve risk stratification in pT1 urothelial bladder cancer-evaluation of a large hospital-based single-centre series. *Histopathology*. 2011;59:722-32.
18. Palou J, Sylvester RJ, Faba OR, Parada R, Pena JA, Algaba F, et al. Female gender and carcinoma in situ in the prostatic urethra are prognostic factors for recurrence, progression, and disease-specific mortality in T1G3 bladder cancer patients treated with bacillus Calmette-Guerin. *European Urology*. 2012;62:118-25.
19. Nguyen-Huu Y, Delorme G, Lillaz J, Bedgedjian I, Le Ray-Ferrieres I, Chabannes E, et al. [Muscularis mucosae invasion: prognostic factor for intravesical BCG immunotherapy failure for T1 bladder carcinoma]. *Progres En Urologie*. 2012;22:284-90.
20. DE Marco V, Cerruto MA, D'Elia C, Brunelli M, Otte O, Minja A, et al. Prognostic role of substaging in T1G3 transitional cell carcinoma of the urinary bladder. *Mol Clin Oncol*. 2014;2:575-80.
21. Soukup V, Duskova J, Pesl M, Capoun O, Feherova Z, Zamecnik L, et al. The prognostic value of T1 bladder cancer substaging: a single institution retrospective study. *Urologia Internationalis*. 2014;92:150-6.
22. Patschan O, Sjodahl G, Chebil G, Lovgren K, Lauss M, Gudjonsson S, et al. A Molecular Pathologic Framework for Risk Stratification of Stage T1 Urothelial Carcinoma. *European Urology*. 2015;68:824-32, 835-6.
23. Breyer J, Bertz S, Müller A, Lausenmeyer EM, Mayr R, Gierth M, et al. New pathological features predicting prognosis of early-invasive urothelial carcinoma: Quantitative substaging and tumour invasion pattern should assist WHO 1973 grading classification in predicting cancer-specific survival of stage pT1 bladder cancer. *European Urology Supplements*. 2016;15:e392.
24. Patriarca C, Hurle R, Moschini M, Freschi M, Colombo P, Colecchia M, et al. Usefulness of pT1 substaging in papillary urothelial bladder carcinoma. *Diagnostic Pathology*. 2016;11:6.
25. Colombo R, Hurle R, Moschini M, Freschi M, Colombo P, Colecchia M, et al. Feasibility and Clinical Roles of Different Substaging Systems at First and Second Transurethral Resection in Patients with T1 High-Grade Bladder Cancer. *Eur Urol Focus*. 2018;4:87-93.
26. Jeandin E, Dupont A, Tille JC, Hauser J, Tran SN, Regusci S, et al. Pathological substaging of pT1 urothelial bladder carcinoma is associated with tumor progression. *European Urology, Supplements*. 2018;17:e1069.
27. Smits G, Schaafsma E, Kiemeney L, Caris C, Debruyne F, Witjes JA. Microstaging of pT1 transitional cell carcinoma of the bladder: identification of subgroups with distinct risks of progression. *Urology*. 1998;52:1009-13, 1013-4.
28. Bernardini S, Billerey C, Martin M, Adessi GL, Wallerand H, Bittard H. The predictive value of muscularis mucosae invasion and p53 over expression on progression of stage T1 bladder carcinoma. *J Urol*. 2001;165:42-6, 46.

29. Denzinger S, Otto W, Fritsche HM, Roessler W, Wieland WF, Hartmann A, et al. Bladder sparing approach for initial T1G3 bladder cancer: Do multifocality, size of tumor or concomitant carcinoma in situ matter? A long-term analysis of 132 patients. *International Journal of Urology*. 2007;14:995-9, 999.
30. Queipo-Zaragoza JA, Ruiz-Cerda JL, Vera-Donoso CD, Vera-Sempere F, Budia-Alba A, Jimenez-Cruz JF. Prognostic value of p53, Ki-67, microstaging and microvessel density in pT1G3 bladder tumors: creation of risk groups for progression. *Scand J Urol Nephrol*. 2007;41:283-9.
31. Orsola A, Raventos C, Allue M, Lozano F, Delgado G, Bastarós JM, et al. Optimizing therapeutic strategies in initial high grade T1 bladder cancer: Post-BCG second TUR according to lamina propria invasion microstaging (T1 A/B). *Journal of Urology*. 2011;185:e703.
32. van Rhijn BW, Liu L, Vis AN, Bostrom PJ, Zuiverloon TC, Fleshner NE, et al. Prognostic value of molecular markers, sub-stage and European Organisation for the Research and Treatment of Cancer risk scores in primary T1 bladder cancer. *Bju International*. 2012;110:1169-76.
33. Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. The importance of the depth of invasion in stage T1 bladder carcinoma: a prospective cohort study. *J Urol*. 1997;157:800-3, 804.
34. Cheng L, Neumann RM, Weaver AL, Spotts BE, Bostwick DG. Predicting cancer progression in patients with stage T1 bladder carcinoma. *Journal of Clinical Oncology*. 1999;17:3182-7.
35. Kondylis FI, Demirci S, Ladaga L, Kolm P, Schellhammer PF. Outcomes after intravesical bacillus Calmette-Guerin are not affected by substaging of high grade T1 transitional cell carcinoma. *J Urol*. 2000;163:1120-3.
36. Shariat SF, Weizer AZ, Green A, Laucirica R, Frolov A, Wheeler TM, et al. Prognostic value of P53 nuclear accumulation and histopathologic features in T1 transitional cell carcinoma of the urinary bladder. *Urology*. 2000;56:735-40.
37. Mhawech-Fauceglia P, Fischer G, Alvarez VJ, Ahmed A, Herrmann FR. Predicting outcome in minimally invasive (T1a and T1b) urothelial bladder carcinoma using a panel of biomarkers: a high throughput tissue microarray analysis. *Bju International*. 2007;100:1182-7.
38. Faivre D'Arcier B, Celhay O, Safsaf A, Zairi A, Pfister C, Soulié M, et al. T1 bladder carcinoma: prognostic value of the muscularis mucosae invasion (T1a/T1b). A multicenter study by the French Urological Association (CCAFU). *Progrès en urologie : journal de l'Association française d'urologie et de la Société française d'urologie*. 2010;20:440-9.
39. van Rhijn BW, van der Kwast TH, Alkhateeb SS, Fleshner NE, van Leenders GJ, Bostrom PJ, et al. A new and highly prognostic system to discern T1 bladder cancer substage. *European Urology*. 2012;61:378-84.
40. Brimo F, Wu C, Zeizafoun N, Tanguay S, Aprikian A, Mansure JJ, et al. Prognostic factors in T1 bladder urothelial carcinoma: the value of recording millimetric depth of invasion, diameter of invasive carcinoma, and muscularis mucosa invasion. *Human Pathology*. 2013;44:95-102.
41. Orsola A, Werner L, de Torres I, Martin-Doyle W, Raventos CX, Lozano F, et al. Reexamining treatment of high-grade T1 bladder cancer according to depth of lamina propria invasion: a prospective trial of

- 200 patients. *Br J Cancer*. 2015;112:468-74.
42. Fransen VDPE, Otto W, Hartmann A, Bertz S, Mayr R, Brundl J, et al. Metric substage according to micro and extensive lamina propria invasion improves prognostics in T1 bladder cancer. *Urol Oncol*. 2018;36:361-7.
43. Ro JY, Ayala AG, El-Naggar A. Muscularis mucosa of urinary bladder. Importance for staging and treatment. *American Journal of Surgical Pathology*. 1987;11:668-73.
44. Angulo JC, Lopez JI, Grignon DJ, Sanchez-Chapado M. Muscularis mucosa differentiates two populations with different prognosis in stage T1 bladder cancer. *Urology*. 1995;45:47-53.
45. Cottrell L, Nairn ER, Hair M. Consistency of microstaging pT1 bladder transitional cell carcinoma. *Journal of Clinical Pathology*. 2007;60:735-6.
46. Segal R, Yafi FA, Brimo F, Tanguay S, Aprikian A, Kassouf W. Prognostic factors and outcome in patients with T1 high-grade bladder cancer: can we identify patients for early cystectomy? *Bju International*. 2012;109:1026-30.
47. Lopez-Beltran A, Cheng L. Stage pT1 bladder carcinoma: diagnostic criteria, pitfalls and prognostic significance. *Pathology*. 2003;35:484-91.
48. Dixon JS, Gosling JA. Histology and fine structure of the muscularis mucosae of the human urinary bladder. *Journal of Anatomy*. 1983;136:265-71.
49. Kramer MW, Rassweiler JJ, Klein J, Martov A, Baykov N, Lusuardi L, et al. En bloc resection of urothelium carcinoma of the bladder (EBRUC): a European multicenter study to compare safety, efficacy, and outcome of laser and electrical en bloc transurethral resection of bladder tumor. *World Journal of Urology*. 2015;33:1937-43.
50. Zhang XR, Feng C, Zhu WD, Si JM, Gu BJ, Guo H, et al. Two Micrometer Continuous-Wave Thulium Laser Treating Primary Non-Muscle-Invasive Bladder Cancer: Is It Feasible? A Randomized Prospective Study. *Photomedicine and Laser Surgery*. 2015;33:517-23.
51. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *Journal of Clinical Epidemiology*. 2005;58:882-93.

Figures

Figure 1

The study flow chart. A total of 35 studies met the inclusion criteria.

Figure 2

T1a/b sub-staging: recurrence-free survival. Difference in RFS between T1a and T1b sub-stage.

Figure 3

T1a/b sub-staging: progression-free survival. Difference in PFS between T1a and T1b sub-stage.

Figure 4

T1a/b sub-staging: cancer-special survival. Difference in CSS between T1a and T1b sub-stage.

Figure 5

Publication bias assessment: funnel plots. A: recurrence-free survival; B: progression-free survival; C: cancer-specific survival

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMA2009checklist.doc](#)
- [S2Table.xls](#)
- [S3Table.doc](#)
- [S1word.doc](#)