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Meta-analysis of relationship between pathological substaging and prognosis of superficial bladder cancer

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Abstract: **To systematically evaluate the value of pathological substaging of different superficial bladder cancer. This is a meta-analysis of retrospective cohort studies. The main outcome measures were progression and recurrence percentage. Computer-based online search was carried out in EMBASE, PubMed, CNKI (China National Knowledge Infrastructure), Wanfang and Google Scholar and case-control studies related to the application of pathological subtstaging in the prognosis of superficial bladder cancer. The quality of the studies included was assessed by Newcastle-ottawa scale. Data were extracted from the studies by two independent reviewers. The Meta-analysis was performed by following the specific steps described in Stata 12.0 A total of 14 case-control studies involving 2388 patients were included. These 14 studies were divided into three groups (T1mVS T1e, T1aVST1bc and T1abVST1c) according to the different substages of bladder cancer. There were no statistically significant differences in the association of pathological substaging with disease recurrence, while two groups showed statistically significant difference in the association of pathological substaging with disease progression (T1m VS T1e, HR=2.27, 95%CI=1.44-3.69, T1aVS T1BC, HR=2.22, HR 95%CI=1.68-2.95>1, suggesting statistical significance). For normuscle invasive bladder cancer, different substages of bladder cancer had no significant differences in the association of pathological substaging with disease recurrence, but two groups showed statistically significant differences in in the association of pathological substaging with disease progression. This suggests that the new methods of pathological substaging have a positive meaning for predicting the progression of bladder cancer. However, we still need larger prospective clinical randomized controlled trials to confirm our conclusion.**

Keywords: Bladder neoplasms; Substage; Prognosis; Meta analysis

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1. Introduction

Bladder cancer is one of common tumors of the urogenital system, ranking the fourth place in malignant tumors in western countries. About 80% of the first diagnoses of bladder cancer are normuscle invasive bladder cancers (NMIBC) [1]. Many T1 lesions are of high risk with a potential to infiltrate locally and infiltrate outside the bladder. It has been reported that the progression rate of superficial bladder cancer ranges from 20% to 40% [2]. According to foreign literature, for most of patients with high-risk superficial bladder cancer, conservative surgery combined with BCG bladder irrigation is still regarded as the treatment of choice. Even with the application of BCG, bladder cancer is still one of the biggest problems that trouble urological surgeons due to its high recurrence rate and progression rate.

Many foreign researches on the causes of the recurrence and progression of bladder cancer have indicated that among all prognostic factors of normuscle invasive bladder cancer, many factors, such as staging, grading, size, and form of cancer as well as carcinoma in situ, were confirmed to be associated with the prognosis of bladder cancer [3]. Based on the depth of tumor infiltration, some scholars put forward a new staging system-pathological substage. There are mainly two ways of substaging at present: (1) Tumors are divided into three different levels (T1a, T1b and T1c) depending on whether they invade mucosal muscle-vessel layer (MM-VP) or not. T1a is defined as no invasion to MM-VP, T1b as depth of invasion reaching MM-VP, and T1c as depth of invasion going beyond MM-VP; (2) Tumors are classified into two types (T1m and T1e) relying on whether the depth of lamina propria under the tumor-invasion mucosa of certain specimen is more than 0.5mm or not. T1e (micro-invasion) is defined as a depth of invasion less than 0.5mm in a single site (one filed under 40×microscope), and T1e (extensive infiltration) as a depth of invasion greater than 0.5mm in multiple sites (one filed under 40×microscope). New methods of staging have been applied to better predict the prognosis of superficial bladder cancer. As the new ways of staging have not been widely accepted and applied yet, we conducted a meta-analysis to study the influences and values of pathological substage on the prognosis of superficial bladder cancer.

2. Materials and Methods

2.1. Research objects

Published case-control research literatures on pathological substage of superficial bladder cancer were collected to analyze the differences in prognoses of different pathological substage. Pathological substage was done by pathologists through secondary pathological examination. All patients with superficial

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bladder cancer were treated with conservative surgery combined with BCG bladder irrigation. The outcome indicators included tumor procession, tumor recurrence, progression-free survival, recurrence-free survival and so on.

2.2. Searching strategy

All articles related to superficial bladder cancer and published from 1994 to 2005 were retrieved in Pubmed, EMbase, Google Scholar, Chinese Biomedical Literature Database, Wanfang Database, and China National Knowledge Infrastructure. Chinese search keywords included "bladder cancer", "substage", "urinary bladder neoplasm", "prognosis", and so on. English search keywords included "urinary bladder neoplasm", "bladder cancer", "TURBT", "substage", "substaging", etc. Titles and summaries were evaluated by two independent reviewers. They were expected to determine whether to include these publications and enlarge the retrieval range by manual searching. The retrieval languages were English and Chinese.

Table 1 The characteristics of literature included in T1MvsT1E group.

Study	Case	Mean-age	Follow-up	Country	Outcome
Van Rhijn[4]	134	68.5	Median：6.4	Canada	PFS DSS
Nishiyama[5]	79	68.5	Median:6.2	Japan	PFS RFS
De Marco[6]	40	69.9	NA	Italy	P DSS
Hanyu[7]	56	60	Median:4.4	China	PFS RFS
Ptariarca[8]	314	72	Median:3.8	Italy	PFS R
Total	623				

(P=Progression, R=Recurrence, DSS=Disease-specific survival, PFS=Progression-free survival, RFS=Recurrence-free survival）

2.3. Inclusion criteria and exclusion criteria

Inclusion criteria: (1) The research content involves pathological substaging of superficial bladder cancer as well as case-control studies of various groups under different substages; (2) The research content has pathological evidences, and secondary pathological examinations are conducted by pathologists to clarify different pathological substages; (3) All research groups must have appropriate outcome measures, including at least one of the following: progression rate, recurrence rate, progression-free survival, recurrence-free survival .

Exclusion criteria: (1) researches with no control group; (2) researches involving no relevant prognostic indicators; (3) researches with no sufficient outcome data.

2.4. Document selection and quality evaluation

Related articles were selected by browsing titles and abstracts. Then, we sought and read through the whole passage to exclude those failing to meet the inclusion criteria and selected those likely to conform to the criteria. Finally, we determined whether the article met the criteria by reading through the whole passage again. Since all articles included were retrospective case-control studies, we conducted quality evaluation on literature included in accordance with Newcastle-ottawa scale (NOS). The evaluation indicators included alternate assessment, comparability assessment as well as outcome assessment.

Table 2 The characteristics of literature included in T1A vs T1BC group.

Study	Year	Case	Mean-age	Follow-up	Country	Outcome
Orsola[9]	2005	85	68.5	Median:4.4	Spain	P R
Andius[10]	2007	121	74	Median:4.4	America	DSS P
Van Rhijn[4]	2011	134	68.5	Median：6.4	Canada	PFS DSS
Lee[11]	2012	183	63.5	Median:3	Korea	PFS RFS
Orsola[12]	2014	200	71	Median:5.9	UK	P R
Soukup[13]	2014	166	68.8	Median:3.1	Czech	P DSS
Patschan[14]	2015	154	74	Median：6.5	Sweden	PFS
Total		1042				

(P=Progression, R=Recurrence, DSS=Disease-specific survival, PFS=Progression-free survival, RFS=Recurrence-free survival）

2.5. Data extraction

By reading these literature included that had been elected carefully, we extracted the basic information of patients including the age and gender as well as prognosis-related data. Some survival data unavailable in the original were calculated using survival curves.

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2.6. Statistical analysis

Stata 12.0 was used to conduct a meta-analysis. The value of I2 was used to reflect the degree of heterogeneity between various groups. If the statistical homogeneity existed between different researches (I2<50%), a fixed effect model would be used for data analysis; Otherwise, a random effects model would be selected. The effect size and HR95% confidence intervals were calculated.

3. Results

3.1. General characteristics of literature included

Preliminary retrieval found 221 articles that might be associated. A total of 12 articles with 1667 cases were included by reading abstract and full text. All articles included were divided into two groups according to different ways of substaging. T1MvsT1E group included 5 articles with a total of 623 cases; T1AvsT1BC group included 7 articles with a total of 1042 cases (Table 1 and 2).

General characteristics of literature included:

Table 3 Newcastle-ottawa scale (NOS) of literature included.

Study	Year	Selection	Comparability	Outcome	Score	Quality
Orsola	2005	4	2	2	8	High
Andius	2007	4	2	2	8	High
Van Rhijn	2011	4	2	1	7	High
Lee	2012	4	2	2	8	High
Nishiyama	2013	4	2	3	9	High
Orsola	2014	4	2	4	10	High
Soukup	2014	4	2	2	8	High
De Marco	2014	4	2	1	7	High
Patschan	2015	4	2	2	8	High
Hanyu	2015	4	2	1	7	High
Ptariarca	2016	4	2	3	9	High

3.2. The Results of Meta-analysis

3.2.1. T1MvsT1E

Statistical analyses were carried out with stata 12.0 to compare the progression of disease of T1M vs T1E group and analyze the association with progression of disease. There were four researches (I~2=0%). Because of their homogeneity, a fixed effect model was selected and the effect size was merged (HR= 2.27; 95% CI=1.44-3.69; z= 3.50, p=0.000, significance test). All confidence intervals of HR95% were greater than 1, suggesting that the substaging methods of T1M vs T1E subtype were associated with the prognosis of disease progression, with statistical significance (Figure 1).

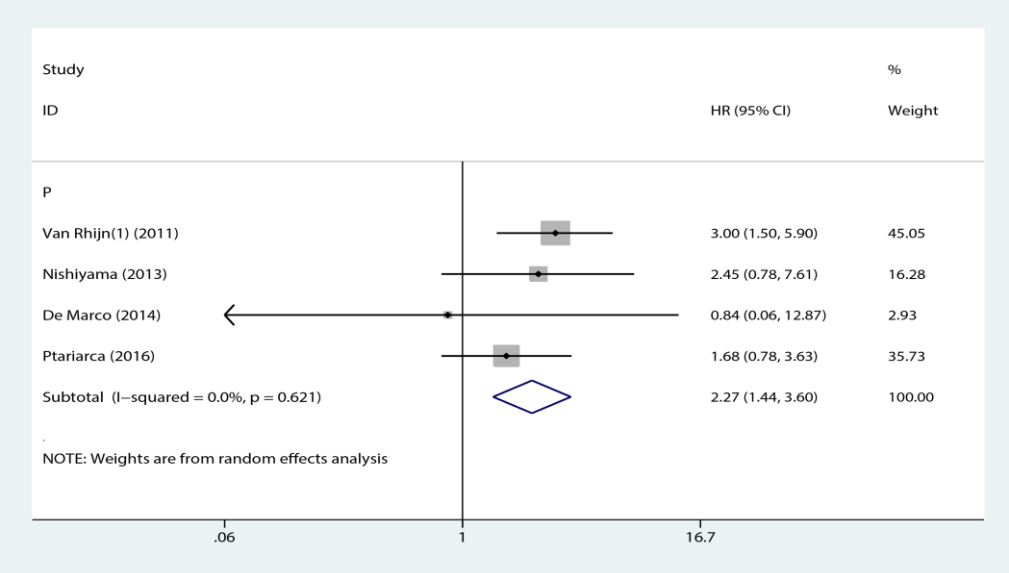

Figure 1. A comparison of disease progression of T1M vs T1E Group.

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There were three researches on the association with disease recurrence about T1M vs T1Ecp group (I~2=73.1%). Because of their heterogeneity, a random effect model was selected and the effect size was merged (HR=1.02; 95%CI=0.75-1.38; z= 0.43, p=0.667>0.05, significance testing). HR95%CI included 1. With few literature included and greater heterogeneity, the heterogeneity may come from data extraction. Since some original data were not available, these data could only be extracted by relevant software. Some subjective errors would definitely occur during data extraction. Therefore, no evidence suggested the correlation between T1m-e and disease recurrence (Figure 2).

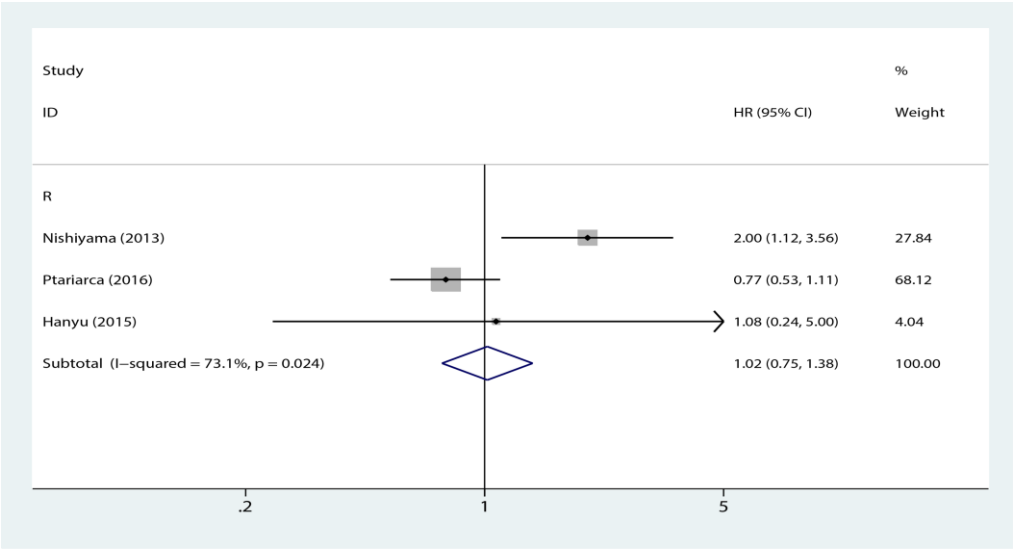

Figure 2. A comparison of disease recurrence of T1M vs T1E group.

3.2.2. T1A vs T1BC

For T1A vs T1BC group, researches on the association with disease progression were analyzed (I~2=0%). Owning to their homogeneity, a fixed effect model was employed (for disease progression, HR=2.22, 95%CI=1.68-2.95; for disease recurrence, HR=1.30, 95%CI=0.90-1.87), suggesting that T1A vs T1BC was associated with the prognosis of disease progression. This conclusion was reliable with statistically significance, but the evidence was not enough to prove the correlation between T1A vs T1BC and disease recurrence (Figure 3).

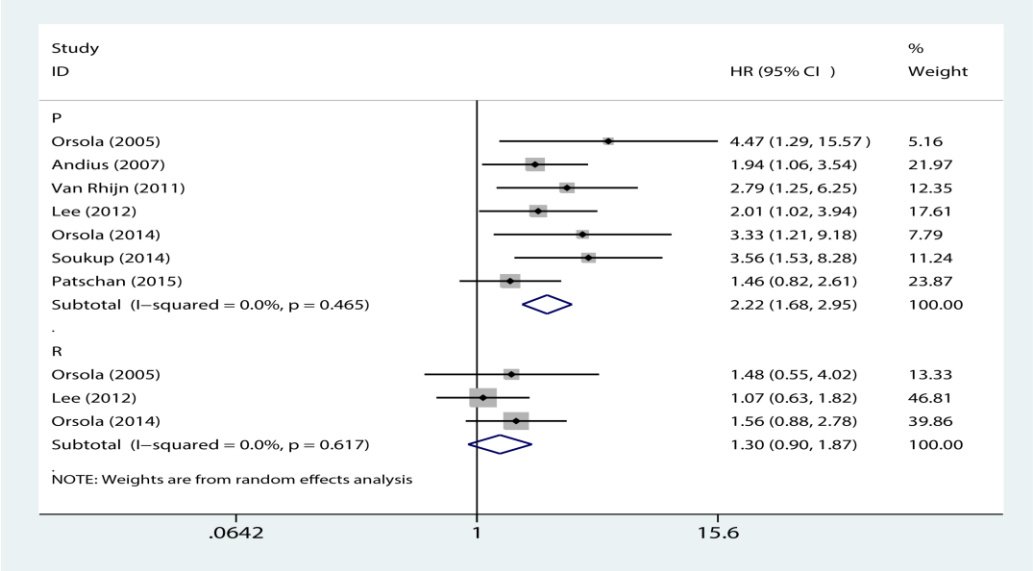

Figure 3. Comparison of disease progression and disease recurrence of T1A vs T1BC group.

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4. Discussion

Two groups were discussed in the meta-analysis. The substaging methods of T1M vs T1E were related with progression of superficial bladder cancer (HR=2.27, 95%CI=1.4-3.69), while the substaging methods of T1AvsT1BC were related with progression of superficial bladder cancer (HR=2.2, 95%CI=1.68-2.95), showing statistically significant differences. Generally speaking, the new ways of pathological substaging has certain correlation with the disease progression of superficial bladder cancer and can provide more theoretical foundation for the treatment methods of high-risk superficial bladder cancer. The refined staging methods can provide prognostic information with greater accuracy.

Problems in the meta-analysis: (1) Most of cases included in the analysis were retrospective case-control studies, prospective randomized controlled studies were difficult to conduct. (2) Different pathologists had subjective differences when judging the samples, which would have an influence on the final results. (3) Some data derived from the K-M survival curves in literature, with HR and CI converted with software by discontinuity point method, which might affect their accuracies.

In conclusion, the methods of pathological substages (T1MvsT1E, T1A vsT1BC) have positive meaning for predicting the progression of superficial bladder cancer and provide more precise prognosis. The new substaging methods are expected to effectively supplement the WHO staging hierarchy .We should look at the substaging methods objectively because they allows us to predict the prognosis of superficial bladder cancer more subjectively, such that both patients and physicians can choose more appropriate surgical methods at the right time. Also, the substaging methods remind patients with later staging that conservative treatment should be given more prudently. With limited literature included in this study, it is necessary to conduct prospective, randomized, multicenter researches with larger sample size in order to draw more reliable conclusions.

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