

Research Article

Cystoscopic Biopsy Should Be a Remedy for The Failing of Post-operative Pathology in Patients with Bladder Urothelial Tumors: A Single Center Study Based on Eight Years' Experience

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Abstract

Objective: The effects of meaningless pathology on postoperative therapy, prognostic prediction and scientific study are our foremost concerns. In this study, we analyzed pathologic findings of patients with Bladder Urothelial Tumors (BUT) and investigated potential factors affecting pathologic accuracy.

Materials and Methods: 289 patients with BUT were included in current retrospective study. Pathologic findings of both biopsy and postoperative specimens were retrieved and analyzed. Sensitivity of pathology in grade and muscle infiltrating was calculated respectively and relational factors were evaluated. Logistic regression models were further performed to screen critical factors.

Results: The sensitivity of biopsy pathology for tumor grade was 65.40%, 66.84% and 62.75% in the total, Transurethral Resection of Bladder Tumor (TUR-BT) and cystectomy groups; however, biopsy pathology remedied up to 9.69%, 13.90% and 1.96% of postoperative pathology in corresponding groups. The detection of invasive muscle was 30.48%, 31.43% and 30.00% for biopsy pathology in total, TUR-BT and cystectomy groups, which rectified nearly 5.71% and 17.14% of postoperative pathology in total and TUR-BT patient groups. Pathology of cystectomy was sufficient to determine muscle infiltrating. TUR-BT and small tumors lead to inaccuracy of postoperative pathology in total patients ($P < 0.05$). Large tumors decreased the grade diagnosis of biopsy pathology ($P < 0.05$). Biopsy pathology was more susceptibility to lower tumor grade. TUR-BT highly impacted muscle infiltrating detection of postoperative pathology ($P < 0.05$). Logistic regression models confirmed tumor grade was an independent factor for successful biopsy pathology, while tumor size and operation means were independent factors for postoperative pathology.

Conclusions: With low sensitivity, biopsy pathology can still significantly remedy the inaccurate findings of postoperative pathology. Biopsy should be suggested to perform routinely before tumor resection, especially in patients with small tumors supposed to receive TUR-BT.

Keywords: Biopsy; Bladder; Pathology; Sensitivity

Introduction

BUC is the malignancy arising from the urothelium of urinary bladder, which is one of most common genitourinary cancers in human [1], and it is the fourth most common type in all cancers word wide [2]. It is estimated to be 73,510, with 14,880 BUC-

associated deaths in USA in 2012 [2]. The incidence of BUC was 6.61/100,000 in China, which is the ninth in all malignant tumors [3]. It is still notorious for high rate of recurrence. Transitional Cell Carcinoma (TCC) is the most common type [4]. Pathology classifications of grade and stage were recommended as credible prognosticators [5]. Therefore, accurately histopathologic diagnosis was of utmost significance. Several studies investigated the methods

of predicting muscle invasion [6] and tumor grade [7,8], but their application was not widespread. Inadequate or missing tissue for pathologic examination in postoperative specimens was a widely known limitation [9,10]. However, most of data were based on cystectomy derived pathology. There is a paucity of information about the assessment of postoperative pathology in patients receiving TUR-BT. How dependable are these pathologies? Who is prerequisite for tumor biopsy?. In present study, biopsy and postoperative pathologic findings of BUT were retrieved and evaluated to assess the diagnostic sensitivity. We then investigate its potential factors to further justify the situation, in which biopsy of bladder tumor was necessary.

Materials and Methods

Patients

Following the approval of the Ethics Committee of Qilu Hospital of Shandong University, we retrospectively collected the clinical and pathological data of 289 patients with pathologically confirmed BUT treated at our department between April 2004 and July 2012. Of 289 included patients, 238 were male and 51 were female. The ratio of male/female was 4.7/1.0. The age ranged from 28 to 90 with the median of 64 years old. 102 patients had pretreatment interval longer than one month, while 187 shorter than one month. Patients with single tumor added up to 172, while those with multiple tumors 117. Among all patients, 217 showed macroscopic hematuria and 116 diagnosed with tumors larger than 3 cm. TUR-BT was performed for 187 patients. Inclusion in the study was determined when patients were able to provide information of both biopsy and postoperative pathologies. We consistently agreed to include the initial treatment when patients visited our department more than once. Cases with squamous cell carcinoma, adenocarcinoma, sarcoma and cancers of complex components were excluded due to the different classification systems in the grade.

All histopathologic diagnoses were performed by two independent pathologists. Histological grade of BUT was

classified according to the 1998 World Health Organization/International Society of Urologic pathologists' classification of papillary urothelial neoplasms [11] as follows: (a) Papilloma, benign tumor;(b) PUNLMP, Papillary Urothelial Neoplasm of Low Malignant Potential; (c) Low grade urothelial carcinoma; (d) High grade urothelial carcinoma. Histological stage of BUC was sorted according to the 2002 American Joint Committee on Cancer TNM staging system [12] as follows: (a) non-muscle-infiltrating Ta-Tis-T1; (b) muscle-infiltrating T2-T3-T4. Pathologic results confirmed as higher grade/stage of either biopsy or postoperative pathology were supposed to be correct, while lower was considered to be incorrect. Consistent findings of both biopsy and postoperative pathology were supposed to be genuine results.

Data Analysis

The Statistical Package for Social Sciences version 16.0 (SPSS Inc, Chicago, IL) was adopted to analyze the database. The Pearson Chi-Square test was used to compare the differences among various groups. Fisher's exact test was used, when more than 20% of cells had expected counts less than five. Logistic regression models were constructed to discriminate prognostic parameters by transforming characteristics into categorical variables. A two-sided $P < 0.05$ was considered to be statistically significant.

Results

Sensitivity of Biopsy Pathology and Postoperative Pathology

The sensitivity of BUT diagnosis in our study was 93.77% for biopsy pathology and 95.16% for postoperative pathology in total patients. Apart from the role in BUT diagnosis, pathology of high quality was sufficient in tumor grade and stage. The sensitivity of biopsy pathology in tumor grade was 65.40%, 66.84% and 62.75% respectively in total, TUR-BT and cystectomy groups; while, the sensitivity of postoperative pathology was 90.31%, 86.10% and 98.04% in corresponding groups (Figure 1).

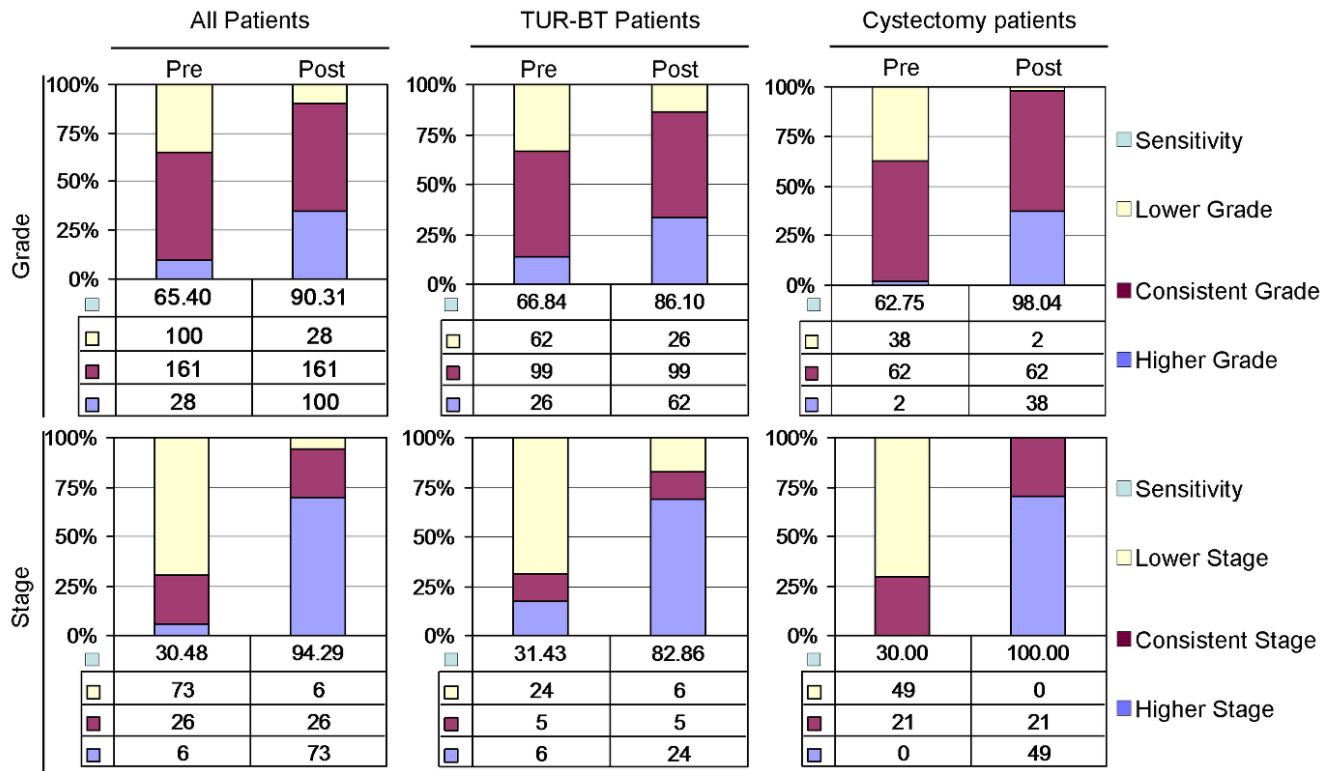


Figure 1: The sensitivity of preoperative and postoperative pathology in grade and stage of bladder urothelial tumor.

Though with a low sensitivity, biopsy pathology remedied up to 9.69%, 13.90% and 1.96% of postoperative pathology. The detection of muscle infiltrating was 30.48%, 31.43%, 30.00% respectively for biopsy pathology in total, TUR-BT and cystectomy groups; while, the sensitivity was 94.29%, 82.86% and 100.00% of postoperative pathology in corresponding groups (Figure 1). Biopsy pathology rectified nearly 5.71% and 17.14% of postoperative pathology in total and TUR-BT patient's groups. Pathology of cystectomy was sufficient to determine muscle invasive status (Figure 1).

Factors Affect the Sensitivity of Biopsy and Postoperative Pathology

We expected to screen clinical and pathological characteristics that decreased the sensitivity of the pathology. Characteristics, such as age, sex, pretreatment interval, macroscopic hematuria, tumor size, tumor number, operation means, tumor grade and stage were grouped accordingly. In the aspect of tumor grade, tumor size and grade significantly correlated with the accuracy of biopsy pathology, while operation means, and tumor diameter were statistically related to the sensitivity of postoperative pathology in total patients ($P < 0.05$) (Table 1).

Characteristics	Total patients						TUR-BT patients						Cystectomy patients		
	Biopsy pathology			Postoperative pathology			Biopsy pathology			Postoperative pathology			Biopsy pathology		
	Correct	Incorrect	P	Correct	Incorrect	P	Correct	Incorrect	P	Correct	Inco rrect	P	Correct	Incorrect	P
Age															
≥ 60	123(68.3)	57(31.7)	0.178#	160(88.9)	20(11.1)	0.293#	84(70.0)	36(30.0)	0.220#	100 (83.3)	20 (16.7)	0.144#	39(65.0)	21(35.0)	0.573#
< 60	66(60.6)	43(39.4)		101(92.7)	8(7.3)		41(61.2)	26(38.8)		61 (91.0)	6 (9.0)		25(59.5)	17(40.5)	
Sex															

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Male	153(64.3)	85(35.7)	0.391#	213(89.5)	25(10.5)	0.436*	98(64.9)	53(35.1)	0.247#	128(84.8)	23(15.2)	0.282#	55(63.2)	32(36.8)	0.812#
Female	36(70.6)	15(29.4)		48(94.1)	3(5.9)		27(75.0)	9(25.0)		33(91.7)	3(8.3)		9(60.0)	6(40.0)	
Pre-treatment Interval															
≤ 1 month	126(67.4)	61(32.6)	0.338#	165(88.2)	22(11.8)	0.106#	91(88.2)	41(43.8)	0.346#	111(84.1)	21(15.9)	0.219#	35(63.6)	20(36.4)	0.840#
> 1 month	63(61.8)	39(38.2)		96(94.1)	6(5.9)		34(61.8)	21(38.2)		50(90.9)	5(9.1)		29(61.7)	18(38.3)	
Macroscopic Hematuria															
Yes	146(67.3)	71(32.7)	0.243#	199(91.7)	18(8.3)	0.164#	93(70.5)	39(29.5)	0.104#	116(87.9)	16(12.1)	0.275#	53(62.4)	32(37.6)	0.855#
No	43(59.7)	29(40.3)		62(86.1)	10(13.9)		32(58.2)	23(41.8)		45(81.8)	10(18.2)		11(64.7)	6(35.3)	
Tumor Diameter															
≥ 3 cm	68(58.6)	48(41.4)	0.047#	113(97.4)	3(2.6)	0.001#	31(64.6)	17(35.4)	0.699#	46(95.8)	2(4.2)	0.024#	37(54.4)	31(45.6)	0.014#
< 3 cm	121(69.9)	52(30.1)		148(85.5)	25(14.5)		94(67.6)	45(32.4)		115(82.7)	24(17.3)		27(79.4)	7(20.6)	
Tumor Number															
Single	111(64.5)	61(35.5)	0.708#	156(90.7)	16(9.3)	0.788#	73(67.6)	35(32.4)	0.800#	92(85.2)	16(14.8)	0.674#	38(59.4)	26(40.6)	0.361#
Multiple	78(66.7)	39(33.3)		105(89.7)	12(10.3)		52(65.8)	27(34.2)		69(87.3)	10(12.7)		26(68.4)	12(31.6)	
Operation Means															
TUR-BT	125(66.8)	62(33.2)	0.484#	161(86.1)	26(13.9)	0.001#	-	-		-	-		-	-	
Cystectomy	64(62.7)	38(37.3)		100(98.0)	2(2.0)		-	-		-	-		-	-	
Grade															
Papilloma & PUN-LMP	26(86.7)	4(13.3)	0.002a#	24(80.0)	6(20.0)	0.797a#	26(86.7)	4(9.9)	0.108a#	24(80.0)	6(20.0)	0.402a#	-	-	0.002a#
Low Grade	105(70.9)	43(29.1)	0.010b#	136(91.9)	12(8.1)	0.054b*	72(67.3)	35(39.5)	0.012b#	95(88.8)	12(11.2)	0.385b*	33(80.5)	8(19.5)	-
High Grade	58(52.3)	53(47.7)	0.000c#	101(91.0)	10(9.0)	0.758c#	27(54.0)	23(46.0)	0.024c#	42(84.0)	8(16.0)	0.617c#	31(50.8)	30(49.2)	-
Muscle Infiltrating															

Muscle Infiltrating	65(61.9)	40(38.1)	0.346#	98(93.3)	7(6.7)	0.190#	22(62.9)	13(11.6)	0.578#	30(85.7)	5(14.3)	1.000*	43(61.4)	27(38.6)	0.684#
Non-Muscle Infiltrating	124(67.4)	60(32.6)		163(88.6)	21(11.4)		103(66.8)	49(33.2)		131(86.2)	21(13.8)		21(65.6)	11(34.4)	

TUR-BT: Transurethral resection of bladder tumor; P < 0.05 was considered statistically significant; #: Pearson Chi-square test; *: Fisher's exact test; ^a P: low grade vs high grade; ^b P: Papilloma & PUNLMP vs BUC; ^c P: Papilloma & PUNLMP & low-grade vs high grade.

Table 1: Clinical and pathological characteristics correlate with the diagnostic sensitivity of tumor grade in biopsy and postoperative pathology.

In the stratified analysis of TUR-BT, tumor size was found to be responsible for the inaccuracy of the pathology based on postoperative samples, while tumor grade was statistically related to the sensitivity of biopsy pathology (P < 0.05) (Table 1). TUR-BT failed to grade 13.90% of BUT. In the cases receiving cystectomy, higher grade and larger size lowered the correction rate of biopsy pathology (Table 1). In the aspect of tumor stage, pretreatment interval longer than one month largely affected the finding of muscle infiltrating by the biopsy in total and cystectomy groups (P < 0.05) (Table 2).

Characteristics	Total patients						TUR-BT patients						Cystectomy patients		
	Biopsy pathology			Postoperative pathology			Biopsy pathology			Postoperative pathology			Biopsy pathology		
	Correct	Incorrect	P	Correct	Incorrect	P	Correct	Incorrect	P	Correct	Incorrect	P	Correct	Incorrect	P
Age															
≥ 60	23(34.3)	44(65.7)	0.255#	61(91.0)	6(9.0)	0.085*	11(42.3)	15(57.7)	0.033*	20(76.9)	6(23.1)	0.304*	12(29.3)	29(70.7)	0.874#
< 60	9(23.7)	29(76.3)		38(100.0)	0(0.0)		0(0.0)	9(100.0)		9(100.0)	0(0.0)		9(31.0)	20(69.0)	
Sex															
Male	29(33.3)	58(66.7)	0.162#	81(93.1)	6(6.9)	0.587*	11(40.7)	16(59.3)	0.037*	21(77.8)	6(22.2)	0.299*	18(30.0)	42(70.0)	1.000*
Female	3(16.7)	15(33.3)		18(100.0)	0(0)		0(0.0)	8(100.0)		8(100.0)	0(0.0)		3(30.0)	7(70.0)	
Pretreatment Interval															
≤ 1 month	22(40.7)	32(59.3)	0.019#	50(92.6)	4(7.4)	0.679*	7(63.6)	13(36.4)	0.721*	16(80.0)	4(20.0)	0.680*	15(44.1)	19(55.9)	0.012#
> 1 month	10(19.6)	41(80.4)		49(96.1)	2(3.9)		4(54.2)	11(45.8)		13(86.7)	2(13.3)		6(16.7)	30(83.3)	
Macroscopic Hematuria															
Yes	22(26.8)	60(73.2)	0.125#	78(95.1)	4(4.9)	0.610*	8(30.8)	18(69.2)	1.000*	22(84.6)	4(15.4)	0.635*	14(25.0)	42(75.0)	0.102*
No	10(43.5)	13(56.5)		21(91.3)	2(8.7)		3(33.3)	6(66.7)		7(77.8)	2(22.2)		7(50.0)	7(50.0)	
Tumor Diameter															
≥ 3 cm	21(30.9)	47(69.1)	0.902#	66(97.1)	2(2.9)	0.181*	6(37.5)	10(62.5)	0.478#	14(87.5)	2(12.5)	0.666*	15(28.8)	37(71.2)	0.720#
< 3 cm	11(29.7)	26(70.3)		33(89.2)	4(10.8)		5(26.3)	14(73.7)		15(78.9)	4(21.1)		6(33.3)	12(66.7)	
Tumor Number															
Single	20(32.3)	42(67.7)	0.634#	60(96.8)	2(3.2)	0.246*	4(21.1)	15(78.9)	0.150#	17(89.5)	2(10.5)	0.379*	16(37.2)	27(62.8)	0.097#
Multiple	12(27.9)	31(72.1)		39(90.7)	4(9.3)		7(43.8)	9(56.3)		12(75.0)	4(25.0)		5(18.5)	22(81.5)	
Operation Means															
TUR-BT	11(31.4)	24(68.6)	0.881#	29(82.9)	6(17.1)	0.001*	-	-	-	-	-	-	-	-	-

Cystectomy	21(30.0)	49(70.0)		70(100.0)	0(0.0)		-	-		-	-		-	-	
Grade															
Low Grade	3(13.6)	19(86.4)	0.054a#	21(95.5)	1(4.5)	1.000a*	1(14.3)	6(85.7)	0.392a*	6(85.7)	1(14.3)	1.000a*	2(13.3)	13(86.7)	0.202a*
High Grade	29(34.9)	54(65.1)		78(94.0)	5(6.0)		10(35.7)	18(64.3)		23(82.1)	5(17.9)		19(34.5)	36(65.5)	

TUR-BT: Transurethral resection of bladder tumor; P < 0.05 was considered statistically significant; #: Pearson Chi-square test; *: Fisher's exact test; a P: low grade vs high grade.

Table 2: Clinical and pathological characteristics correlate with the diagnostic sensitivity of muscle infiltrating in biopsy and postoperative pathology.

The detection rate of invasive muscle by the biopsy in TUR-BT group was lower in female and younger patients (P < 0.05) (Table 2). TUR-BT failed to detect 17.14% muscle infiltrating (Table 2). The statistically significant factors were recruited into the logistic regression models. The final result confirmed that biopsy largely lowered tumor grade (Table 3). Moreover, small tumor and TUR-BT were related factors for the success of the postoperative pathology (Table 3).

Variables	B	S.E.	Wald	df	Sig.	Exp(B)
Tumor Diameter ^{†a}	-0.389	0.255	2.318	1	0.128	0.678
Grade ^{†a}	-1.228	0.558	4.845	1	0.028	0.293
Constant ^{†a}	-0.313	0.19	2.731	1	0.098	0.731
Tumor Diameter ^{†b}	-0.184	0.274	0.451	1	0.502	0.832
Grade ^{†b}	0.868	0.273	10.068	1	0.002	2.381
Constant ^{†b}	-1.758	0.49	12.861	1	0	0.172
Tumor Diameter [*]	1.395	0.642	4.722	1	0.03	4.035
Operation Means [*]	1.623	0.765	4.5	1	0.034	5.067
Constant [*]	-4.601	0.832	30.592	1	0	0.01
Tumor Diameter ^{‡c}	-0.816	0.519	2.47	1	0.116	0.442
Grade ^{‡c}	-1.152	0.491	5.503	1	0.019	0.316
Constant ^{‡c}	0.123	0.276	0.198	1	0.656	1.13

†: Biopsy pathology in total patients; * Postoperative pathology in total patients; ‡: Biopsy pathology in cystectomy patients;
^aP: Papilloma & PUNLMP vs BUC; ^bP: Papilloma & PUNLMP & low-grade vs high grade; ^cP: low grade vs high grade.

Table 3: Variables in the equation of logistic regression analysis in pathology of patients with bladder urothelial tumor.

Discussion

BUC is one of the most common types of cancer worldwide [13] and approximately sixty percent are localized to the urothelium or lamina propria when diagnosed for the first time [14]. TUR-BT is the current standard treatment. BUC is always multifocal and

of high recurrence rate, and Proul, et al. found that 10%~30% of recurrent cases were higher than that of original tumor [15]. It makes follow-up a crucial component in postoperative management based on accurate pathology. Pathological results played a reliable role in monitoring prognosis. Unfortunately, histologic characteristics may have been altered secondary to the effect of operative coagulation. Over the past few years, investigators have committed in screening compensate methods. Besides low sensitivity in staging and grading, bladder biopsy is a painful, invasive, costly procedure and compels patients to take a humiliating position, which limits its role as a routine application. However, we determined that biopsy pathology was of pivotal implication in patching up postoperative pathology. In current study, we investigated the possible factors that undermined the assessment of postoperative pathology to further determine the situation in which biopsy was required. Muscle invasion was of special sense for tumor progression, and so was the accurate staging. It is widely accepted that TUR-BT may interfere with pathologic diagnosis [16,17].

However, the extent, to which TUR-BT spoils the operative tissue, is difficult to define as a result of lacking the trustworthy standard in patients undergoing TUR-BT. In our study, we took the advantage of biopsy pathology, which was supposed to be the gold standard for tumor diagnosis. Our findings demonstrated that cystectomy was sufficient enough to detect the status of muscle infiltrating, while TUR-BT bungled as many as 17.14% of tumor specimens. Local staging procedures before TUR-BT were suggested for bladder cancers [6]. Biopsy is one of recommended means. We then explored potential factors for the failing of staging. Pretreatment interval longer than one month was responsible for the meaningless results of biopsy pathology in total and cystectomy patients (P < 0.05). It was interesting that female and patients younger than sixty were impacting factors for biopsy staging in TUR-BT patients (P < 0.05). Satoh E et al reported that the combined application of probable characteristics efficiently predicted the possibility of muscle invasion [6]. In the case of pedunculated carcinoma and single papillary less than 1 cm, preoperative staging was not suggested, as a result of a rare possibility of muscle invasion. After all, we should pay attention to the role of biopsy as reserved pathology.

Simultaneously, we noticed that discrepancy of tumor grade between biopsy and postoperative pathology existed in a large bulk of patients. Many studies investigated methods to aid in distinguishing tumor stage [6], but few focused-on tumor grades. To achieve a better understanding of the situation for the necessary of cystoscopy biopsy, we performed the analyses of postoperative pathology. The sensitivity of postoperative pathology for tumor grade was 90.31% in total patients; while, 65.40% for biopsy pathology. The factors such as small tumor size and TUR-BT resulted in the mistakes of postoperative pathology ($P < 0.05$), which was further confirmed by logistic regression analysis as well. The majority of bladder tumors are superficial confined to the urothelial and lamina propria layers, which is suitable for TUR-BT. In the subgroup analysis of operation methods, TUR-BT bungled as many as 13.90% of tumor specimens for grading. Again, smaller tumor size leads to higher rate of false grade (14.5% and 17.3%) of postoperative pathology in total and TUR-BT patients respectively. Luckily, biopsy pathology functioned to remedy the postoperative pathology. However, the sensitivity of biopsy pathology was low, which estimated at 65.40%, 66.84% and 62.75% respectively in total, TUR-BT and cystectomy groups. The effect of biopsy pathology in letting down tumor grade would partly ascribe to larger tumor size (> 3 cm) ($P < 0.05$). Our results indicated that TUR-BT would significantly mistake postoperative grade of tumors whose diameter are less than 3 cm ($P = 0.024$). Therefore, biopsy pathology should be recommended for patients supposed for TUR-BT regardless of tumor size.

Recently, new means have been evaluated to supply preoperative pathology [7,8,18,19]. Optical coherence tomography(OCT), a real-time, noninvasive and microstructural imaging modality, is supposed to be an adjunct to fluorescence cystoscopy to enhance the efficiency of BUC detection [7,20,21]. However, the requirement of equipment's, fees and technique may limit its inclusive application, especially in most hospitals of small scale from developing countries. Markers, such as BTA stat, NMP22, HA, surviving, CD44v6 and VEGF, were examined for the clinical usage [8]. However, the value of a single marker was actually scant. A panel combining markers may serve as an alternative and credible method to determine the evidence. Some limitations in present study should be notified. First, this study was a retrospective, but not prospective study. Second, both biopsy and TUR-BT had the probability of damaging the specimens to affect the following pathologic diagnosis. Therefore, we could not exclude the trace possibility of the false pathology findings to lower tumor grade and stage of patients receiving TUR-BT.

Overall sensitivity of both biopsy and TUR-BT pathology for predicting the grade and/or stage of BUC is relatively low [16,17]. Postoperative pathology, especially from TUR-BT, should not be the only evidence [17]. Diagnostic bias of pathology

should be considered in the following clinical practice and medical studies. The combination of biopsy and TUR-BT pathology was proposed to achieve optimal accuracy of pathologic diagnosis. The retrieved findings of pathology may do great help to formulating postoperative therapy, predicting the disease prognosis and providing reliable basis for scientific research

Conclusions

Biopsy pathology contributes to the diagnosis of BUT. With a low sensitivity, it can still significantly rectify the inaccurate findings of postoperative pathology. We made a final conclusion based on concrete evidence in our series that biopsy should be suggested to perform routinely before tumor resection to properly grade and stage tumors, especially in patients supposed for TUR-BT and with small tumors.

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