

Bladder cancer histological variants: which parameters could predict the concordance between transurethral resection of bladder tumor and radical cystectomy specimens?

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Introduction The concordance rate of bladder cancer (BCa) histological variants (HV) between transurethral resection of bladder tumor (TURBT) and radical cystectomy (RC) is sub-optimal and is unclear which factors may influence it. The aim of this study was to identify factors that may be correlated to a higher TURBT-RC concordance rate.

Material and methods Consecutive patients who had undergone RC between 2000 and 2019 at a single Institution with pathological evidence of HV were included. Patients with diagnosis of HV both at RC and at the previous TURBT were enlisted in the TURBT-RC Concordance Group (CG), whereas patients with only evidence of HV at RC in the TURBT-RC Non-Concordance Group (NCG). Surgical factors evaluated were the source of energy (mono- vs bipolar), surgeon's experience ($</\geq 100$), execution of re-TURBT, number and size of specimens at TURBT.

Results A total of 81 patients were included, 49 (60.5%) in the CG and 32 (39.5%) in the NCG. Among the surgical factors, maximal core length (MCL) was significantly higher in the CG (12.5 vs. 10 mm, $p = 0.014$) (Table 1). At uni- and multivariable analyses, MCL > 10 mm represented an independent predictor of concordance [OR 2.95; CI (1.01–8.61); $p = 0.048$]. Tumor recurrence, focality and dimension, source of energy, surgeon's experience, performance of re-TURBT and total number of specimens at TURBT did not significantly predict the concordance.

Conclusions Longer specimens at TURBT yield a higher chance to detect HV before RC. In this light, improving the quality of bladder resection means improving the management of BCa.

Key Words: bladder cancer \leftrightarrow histological variants \leftrightarrow mixed variants
 \leftrightarrow radical cystectomy \leftrightarrow urothelial bladder cancer

INTRODUCTION

Bladder cancer (BCa) is one of the most common urological cancers and often requires multiple surgical treatments as well other radical and invasive therapies [1, 2]. Histology is a factor of paramount importance determining the prognosis of BCa pa-

tients and the presence of histological variants (HV) may impact disease-specific survival as compared to pure transitional cell carcinoma (TCC) of the bladder [3, 4]. HV are actually not that rare, their presence being estimated in about 14% to 25% of all BCa diagnoses [5, 6, 7]. Furthermore, HV identification at the time of transurethral resection of the bladder

Table 1. Baseline characteristics

	Total 81	Concordance Group 49 (60.5)	No Concordance Group 32 (39.5)	p
CLINICAL FACTORS	Gender, n (%)			
	Male	60 (74.1)	25 (78.1)	0.679
	Female	21 (25.9)	7 (21.9)	
	Age, median (IQR)	73 (66–78)	73.5 (64–78.8)	0.254
	TURBT [†] histopathology, n (%)			
	TCC only	/	32 (39.5)	/
	TCC + Squamous	27 (33.3)	/	
	TCC + Nested	2 (2.5)	/	
	TCC + NEE	1 (1.2)	/	
	TCC + Sarcomatoid	5 (6.2)	/	
	TCC + Glandular	5 (6.2)	/	
	TCC + more than 1 variant (including giant cells and signet ring)	9 (11.1)	/	
	pT TURBT [†] , n (%)			
	T1	9 (11.1)	4 (12.5)	0.384
	≥T2	67 (82.7)	25 (78.1)	
	Cis	5 (6.2)	3 (9.4)	
	pT RC, n (%)			
	Ta	1	0	0.472
	T1	4	1	
	T2	27	13	
	T3a	16	6	
	T3b	17	9	
	T4a	13	3	
	T4b	0	0	
	Dmax, mm median (IQR)	30 (24–46.5)	25 (20–40)	0.172
	BCa recurrence, n (%)			
	Primary	68 (84)	24 (75)	0.143
	Recurrent	13 (16)	8 (25)	
	Tumor focality, n (%)			
	Single	66 (81.5)	23 (71.9)	0.132
	Multiple	15 (18.5)	9 (28.1)	
	RC histopathology, n (%)			
	TCC + Squamous	41 (50.6)	16 (19.8)	0.153
	TCC + Nested	4 (4.9)	3 (3.7)	
	TCC + NEE	1 (1.2)	0 (0.0)	
	TCC + Sarcomatoid	11 (13.6)	5 (6.2)	
	TCC + Glandular	4 (5.0)	2 (2.5)	
	TCC + more than 1 variant (including giant cells and signet ring)	20 (24.7)	6 (7.1)	
SURGICAL FACTORS	Number of specimens, n (%)			
	≤50	34 (42)	20 (62.5)	0.313
	51–200	35 (43.2)	10 (31.3)	
	≥200	12 (14.8)	2 (6.2)	
	MCL, n (%)			
	<10 mm	47 (58)	24 (75)	0.012
	≥10 mm	34 (42)	8 (25)	
	MCL, mm median (IQR) (continuous)	10 (8–12)	10 (7–10)	0.014
	Execution of reTURBT, n (%)			
	Yes	16 (19.8)	6 (18.8)	0.919
	No	65 (80.2)	26 (81.2)	
	[§] histological variant detection at, n (%)			
	Only TURBT	6 (60)	/	/
	Only reTURBT	1 (10)	/	
	Both	3 (30)	/	
	Source of energy, n (%)			
	Monopolar	60 (74.1)	25 (78.1)	0.680
	Bipolar	21 (25.9)	7 (21.9)	
	Fragmentation rate, median (IQR)	0.48 (0.24–0.75)	0.63 (0.36–0.84)	0.547
	Surgeons experience*, n (%)			
	<100 cases	36 (44.4)	16 (38.1)	0.332
	≥100 cases	45 (55.6)	26 (61.9)	

n – number; IQR – interquartile range; BCa – bladder cancer; TURBT – transurethral resection of bladder tumor; TCC – transitional cell carcinoma; NEE – neuroendocrine; Dmax – maximal bidimensional diameter of bladder tumor at preoperative imaging (computed tomography scan and/or ultrasonography); MCL – maximal core length; RC – radical cystectomy; fragmentation rate – Dmax / number of specimens

[†]The TURBT is meant as the worst pre-RC TURBT (either first TURBT or reTURBT). Worst is meant as the higher pT stage or the presence of histologic variant or both

*In case of re-TURBT, the re-TURBT and the corresponding previous TURBT were performed by the same surgeon

tumor (TURBT) is of utmost importance for the planning of the best multimodal approach. However, the histological concordance between TURBT and radical cystectomy (RC) in detecting HV is sub-optimal [5, 8, 9]. Although it is not established whether the experience of the pathologist correlates with the TURBT-RC agreement [8], several factors may influence pathological diagnosis accuracy in the first place, including cautery and other artifacts. However, these factors have not been evaluated in detail for this purpose.

We hypothesized that surgical factors may have an impact on identification of HV at TURBT. In this light, the aim of the study was to evaluate if any surgical or clinical factor may be correlated to TURBT-RC concordance.

MATERIAL AND METHODS

Study design and patient population

Between 2000 and 2019 all consecutive patients treated at a single tertiary referral center with RC and pathological evidence of HV were identified. Indications for RC included muscle-invasive BCa, non-muscle-invasive (high grade pT1) BCa and diffuse carcinoma in situ (CIS) refractory to intravesical therapy.

All RC were performed by experienced surgeons with an open approach, while TURBT were performed both by experienced and non-experienced surgeons (≤ 100 previous procedures). Each re-TURBT was performed by the same surgeon of the corresponding previous TURBT. All patients received a conventional TURBT (no en bloc resections) either with monopolar or bipolar source of energy and without the use of enhanced view technologies such as narrow-band imaging or blue light cystoscopy [10].

The histological type of the RC specimens was compared to the histological findings at the corresponding TURBT.

Patients with diagnosis of BCa-HV both at RC and at the correspondent previous TURBT were enlisted in the TURBT-RC Concordance Group (CG), whereas patients with only evidence of BCa-HV at RC in the TURBT-RC Non-Concordance Group (NCG). Both procedures were performed at the same institution. Patients with diagnosis of HV at TURBT and no evidence of residual tumor (pT0, $n = 3$) at the final pathology were excluded from the analysis.

Bidimensional maximal tumor size (Dmax) was defined as the major diameter at the preoperative imaging [either computed tomography (CT) scan or sonography]. Demographic and clinicopathologic data (age, gender, histology at TURBT and RC, pTNM

at TURBT, Dmax, number of lesions at TURBT and recurrence of BCa) were considered as clinical factors. Through the comparison between TURBT and corresponding RC pathology reports, the upstaging rate was also assessed in both groups, looking at a potential role played by the TURBT / RC concordance regarding this aspect.

Surgical factors were the source of energy, surgeon's experience of TURBT, execution of re-TURBT, number and size of specimens (maximal core length, MCL) at TURBT. A ratio between Dmax and the number of specimens at TURBT was calculated as a sort of normalization variable, in order to make differently sized tumors directly comparable in terms of fragmentation rate at TURBT [11]. Patients with incomplete information were excluded from the analysis. Patients who had undergone preoperative sonography instead of CT scan were included only if the imaging was performed at the same institution.

Specimen sampling and pathological examination

During TURBT, the specimens were carefully retrieved by flushing them out of the bladder either using the Ellik evacuator or with a sheet-compatible Toomey syringe. In case of multifocal tumors, the specimens of each lesion were carefully retrieved immediately after completing the resection and subsequently transferred to the pathology department in separate containers, each one with the detailed vesical site of origin. Specimens of TURBT were routinely fixed overnight in 10% formalin solution, totally submitted for histological examination and processed using an automated tissue processor and paraffin embedded. Histological sections were cut at 4 micrometer thickness and routinely stained using hematoxylin and eosin (H&E) and, if necessary, immunohistochemical stain. All the specimens were measured and analyzed by dedicated uro-pathologists of the same pathology department. Diagnosis of urothelial bladder carcinoma with rare variants' differentiation was based on the identification of specific histological features according to the World Health Organization classification in use at the time of diagnosis [12, 13]. Pathologic staging was established using the American Joint Committee on Cancer (TNM) system [14].

Statistical analysis

Data were entered into an anonymized database and transferred to SPSS 26.0 for Windows (SPSS, Inc., Chicago, IL, 2011). Continuous variables were presented as medians with interquartile ranges (IQRs). For comparison of variables between CG and NCG,

Student's t-test and Chi-squared test were used for continuous and categorical variables, respectively. Moreover, uni- and multivariable logistic regression analyses were used to test the role of factors of interest in predicting concordance between TURBT and RC, including in the multivariate model also variables showing a trend to significance at the univariate analysis.

RESULTS

Among the entire caseload of 384 cystectomies performed for bladder malignancy, a total of 81 (21.1%) consecutive patients with diagnosis of BCa and at least one HV at RC pathology were included. Of them, 60 (74.1%) were men and 21 (25.9%) were women. The median age was 73 years (IQR 66–78) (Table 1).

Fourteen patients (17.3%) underwent RC for a non-muscle invasive BCa at TURBT (T1 and/or CIS). Sixty-eight patients (84%) were treated with RC after having received a first diagnosis of BCa, the other 13 patients (16%) after an umpteenth relapse. The source of energy used during the TURBT was monopolar in 60 cases (74.1%) and bipolar in 21 (25.9%). The number of the specimens at TURBT was <50 in 34 patients (42%), 51–200 in 35 (43.2%) and >200 in 12 patients (14.8%). For 47 patients (58%) the MCL was <10 mm and in 34 (42%) it was ≥ 10 mm. The median fragmentation rate was 0.48 overall (IQR 0.24–0.75), 0.40 in CG (IQR 0.17–0.65) and 0.63 in NCG (0.36–0.84). Thirty-two patients (39.5%) had pure TCC at TURBT (NCG), while 40 and 9 patients (49 taken together, 60.5%) had respectively one and more than one HV at TURBT (CG), yielding a concordance rate of 60.5%. In particular, the distribution of histotypes at TURBT was TCC (39.5%), squamous (33.3%), sarcomatoid (6.2%), glandular (6.2%), NESTED (2.5%), neuroendocrine (NEE) (1.2%) and more than 1 variant (11.1%). The RC pathology revealed the following distribution of histotypes: squamous (50.6%), sarcomatoid (13.6%), glandular (5%), NESTED (4.9%), NEE (1.2%) and more than one HV (24.7%). The median size of the tumor (Dmax) at pre-TURBT imaging was 30 mm (IQR 24–46.5). Sixty-six tumors were monofocal (81.5%) while the remaining 15 (18.5%) were multifocal.

No differences between the two groups (CG vs. NCG) were found in terms of age ($p = 0.254$), sex ($p = 0.679$), Dmax ($p = 0.172$), tumor focality ($p = 0.132$), histotype found at RC ($p = 0.153$), pTNM at TURBT ($p = 0.384$) and BCa recurrence ($p = 0.143$).

In addition, we compared the TURBT and the RC final pathology reports of each patient and we observed an upstaging rate of 65.3% and 81.3% for the

CG and the NCG respectively ($p = 0.094$); although, no significant relationship was detected between TURBT/RC concordance and pathologic upstaging ($p = 0.472$).

Among surgical factors, longer specimens (MCL) were found in the CG both as a continuous variable and using 10 mm as a cut-off ($p = 0.014$ and $p = 0.012$, respectively) while no differences were noted between mono- and bi-polar resection ($p = 0.680$), surgeons' experience ($p = 0.332$), execution of reTURBT ($p = 0.919$), number of specimens at TURBT ($p = 0.313$) and fragmentation rate ($p = 0.547$) (Table 1).

At uni- and multivariable analyses, after adjusting for BCa recurrence, tumor focality and fragmentation rate, MCL represented an independent predictor of higher concordance [multivariable analyses: OR 2.95 (1.01–8.61); $p = 0.048$, univariable analyses: OR 3.39 (1.28–9.02); $p = 0.014$] (Tables 2, 3).

DISCUSSION

Bladder cancer may present with foci of rare histologies that differ from the common urothelial aspects and it is established that the presence of HV is associated with a decrease in survival and patients'

Table 2. Univariate analysis

	OR, CI 95%	p
MCL		
<10 mm	Ref.	
≥10 mm	3.39 (1.28–9.019)	0.014
MCL (continuous variable)	1.15 (1.02–0.29)	0.021
Dmax	1.02 (0.99–1.05)	0.139
BCa recurrence		
Primary	Ref.	
Recurrent	2.93 (0.86–9.97)	0.085
Tumor focality		
Single	Ref.	
Multiple	2.80 (0.89–8.86)	0.079
Source of energy		
Monopolar	Ref.	
Bipolar	1.43 (0.50–4.05)	0.502
Number of specimens (continuous)	1.01 (1.00–1.01)	0.508
Fragmentation rate (continuous)	0.40 (0.16–1.01)	0.052
Surgeons' experience		
<100	Ref.	
≥100	1.24 (0.98–1.41)	0.117
Performance of reTURBT		
No	Ref.	
Yes	0.94 (0.81–1.12)	0.386

MCL – maximal core length; OR – odds ratio; CI – confidence interval;

Dmax – maximal bidimensional diameter of bladder tumor at preoperative imaging (computed tomography scan and/or ultrasonography); BCa – bladder cancer; TURBT – transurethral resection of bladder tumor

UVA (dependent variable = concordance yes)

Table 3. Multivariate analysis

	OR, CI 95%	p
MCL		
<1 cm	Ref.	
≥1 cm	2.95 (1.01–8.61)	0.048
Fragmentation rate (continuous variable)	0.56 (0.22–1.42)	0.221
BCa recurrence		
Primary	Ref.	
Recurrent	2.67 (0.63–11.32)	0.181
Tumor focality		
Single	Ref.	
Multiple	1.97 (0.53–7.43)	0.314

MCL – maximal core length; OR – odds ratio; CI – confidence interval;

BCa – bladder cancer

MVA (dependent variable = concordance yes)

prognosis [15–18]. Several retrospective studies suggested that HV portends worse clinical outcomes. Kim and colleagues reported 186 patients with diagnosis of HV (mainly squamous and glandular variants) at final pathology among a caseload of 1031 RC and found out that the presence of HV was associated with increased prevalence of extravesical disease (pT3–T4 tumors 70% vs. 38%, $p < 0.001$) and lymph node metastasis (20% vs 15%, $p = 0.05$) [19].

A correct diagnosis is crucial for the urologists in order to properly manage the patients diagnosed with BCa and finding a variant histotype at TURBT is determining while offering multimodal therapies. [20]

However, the diagnosis of a HV is challenging for the pathologist, at TURBT particularly, which has been reported to detect only 39% of variant cancers that present within the bladder [21]. Up to 44% of cases of HV are not recognized by community pathologists, further leading to mismanaging the patients [15]. Indeed, the tissue to analyze may be very small and many artefacts may be present due to repeated coagulation during an often piecemeal resection [22]. For this reason, over the last years the interest in en bloc resection of bladder tumour (ERBT) is constantly increasing [23]. ERBT seems to provide an oncologically non-inferior alternative to TURBT with better histology specimens and its use is constantly increasing in many urological departments [24]. Similarly, increasing interest in better sampling with larger specimens is currently ongoing for other endoscopically managed non-urolological tumors [25].

Over the last years the identification of HV at TURBT has been a topic of interest and the histological concordance rate between TURBT and RC is estimated about 45–50% [5, 8]. However, the possible reasons for this poor concordance have not been properly investigated and to date there are no certain elements on how to improve the TURBT-RC agreement [9].

Our results show that a longer specimen at the TURBT yields a higher chance to detect a variant histology before RC, with subsequent higher concordance rates between TURBT and RC. In particular, when the maximal length of the specimens is over 10 mm the concordance rate is 3.4 times higher. This finding leads to the simple but reasonable hypothesis that rare foci of histological variants, often present in minimal quantities in the presence of a urothelial tumor, may be considerably affected by multiple electrocoagulation artifacts made by a piecemeal TURBT. The quality of the tissues given to the pathologist must be as high as possible in order to enable the best diagnostic precision. Adequate specimen preservation, cold blade dissections and minimal tissue manipulation are mandatory for that purpose. Similarly, the best surgical quality of resection is of paramount importance in order to provide the pathologist with the highest quality of the tissue.

Hypothetically, considering our results, among the possible benefits not yet investigated of the ERBT there could also be an increase in TURBT-RC agreement as regards the presence of rare variants. In this light, our data give support towards en bloc resection when feasible.

A crucial implication of our work stems in the possibility that the identification of HV at the time of TURBT may influence the entire treatment algorithm; since rates of occult metastatic disease have also been reported as high as 27% to 44% among non-muscle invasive (NMI) BCa variant tumors, a more aggressive treatment strategy is warranted even in the setting of NMI disease. In particular, for sarcomatoid, plasmacytoid and micropapillary NMI-BCa early cystectomy should be considered. The same goes for small cell NMI-BCa, in case of whom a neoadjuvant chemotherapy regimen based on cisplatin is recommended since it has been demonstrated to dramatically improve overall survival (159.5 vs 18.3 months; $p < .001$) and disease-specific survival (5-year 79% vs 20%; $p < .001$) [26]. In case of squamous, glandular or nested differentiated NMI-BCa, a pT1 stage at the reTURBT represents indication for early cystectomy, as the role of intravesical treatment with Bacillus Calmette-Guerin (BCG) appears to be controversial.

Also in case of cT2–cT4a N0M0 BCa the detection of HV potentially may influence the management of the malignancy. A neoadjuvant chemotherapy based on cisplatin, when allowed by the performance status of the patient, must be considered in case of squamous, sarcomatoid, plasmacytoid, micropapillary and small cell BCa. On the contrary, pure squamous cell carcinoma seems to benefit from neoadju-

vant 50 Gy radiation therapy but the available data in this field are still limited and scarce.

We acknowledge the limitations of the study. Firstly, the size of the sample is limited. However, since these are rare variants and a single center, the number of patients is relatively large. This does not make it possible to evaluate the possible TURBT/RC agreement rate for the different types of histological variants, which would likely require a large multi-center study. Secondly, since it is a retrospective evaluation of the sample, it is not possible to know for certain some technical details concerning the TURBT, such as for example any different electro-resection settings used for certain patients. However, this is a limitation existing in all previously published similar studies and inevitable to obtain a discrete sample that can be analyzed in a single center. Third, all patients were managed at a tertiary center with a dedicated urological pathology department and therefore our findings may

not be fully reproducible in non-institutional centers where histological variants have been found to be underestimated [27].

CONCLUSIONS

Our results show that a longer specimen (≥ 10 mm) at TURBT yields a higher chance to detect a variant histology before RC, with subsequent higher concordance rates between TURBT and RC. In this light, our data give support towards en bloc resection, in order to provide better specimens to the pathologist and possibly increase the detection of HV. Multicentric studies are required to evaluate these findings on larger populations and the possible impact on TURBT/RC agreement rate for the different types of histological variants.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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