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Original Article

Transurethral resection of bladder and radical cystectomy: Concordance of histology. Are we good enough?

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ABSTRACT

Objective: Urothelial carcinoma (UC) is heterogeneous, and variant histologies (VH) are more frequent than initially reported. Reporting VH is recommended by several guidelines because of prognostic and therapeutic implications. We evaluated the concordance of VH between the first transurethral resections of the bladder (TURBs) and the following radical cystectomy (RC). This paper is the first to compare VH with a central pathology review between TURB and RC.

Material and methods: In this retrospective study, we only included those patients who underwent TURB with VH and then RC between 01/2010 and 12/2013 at our institution. The presence of VH in both TURB and RC was assessed and compared according to the 2016 World Health Organization (WHO) classification by a central pathology review.

Results: Among 110 patients who had the initial TURB/RC, 54 (49.1%) were diagnosed with VH, 48 (43%) had a single pattern, and six had (5%) multiple histological patterns. Squamous differentiation was the most common single VH (31%). Twenty patients with UC (18%) showed discordance between TURB and RC, especially in micropapillary versus nested (n=3) cases. Concordant histology between TURB/RC was seen in 82% of the cases.

Conclusion: Discrepancies can be seen between TURB and RC when reporting VH, which can be problematic for selection of therapy and management. TURB alone might be insufficient to evaluate the presence of VH, especially in VH with heavy therapeutic implications, such as micropapillary carcinomas. Nevertheless, concordance with a central review by an experienced uropathologist when applying the WHO 2016 classification is 82%.

Keywords: Bladder cancer; bladder resection; cystectomy; histology, micropapillary carcinoma; urothelial carcinoma.

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Introduction

Urothelial carcinoma (UC) is a heterogeneous tumor and recent studies underscore this finding. Pathologists know that UCs frequently undergo various differentiation, resulting in a wide range of histological variants (VH). The WHO 2016 has updated the definitions of VH according to clinical and pathological criteria.

The identification of VH is important because some variants may be associated with poor clinical outcomes, which warrant different therapeutic approaches.[1] Some authors emphasize the importance of reporting VH, especially in non-muscle invasive carcinomas, as more aggressive treatment, including upfront radical cystectomy (RC), might be indicated for patients with aggressive VH.[2] Furthermore, the presence of VH may also affect the efficacy of neoadjuvant chemotherapy and immune checkpoint inhibitors.[3,4]

Several authors have concluded that VH is quite a frequent finding and with increasing evidence that the molecular characteristics of several VHs are distinct from conventional UC. Therefore, reporting of VH has increased. Nevertheless, the concordance of reporting VH on a morphological level is not always obvious even for experienced uropathologists. Some studies revealed a clear underreporting of VH, and others identified difficulties in reporting

VH whenever the morphological characteristics of the tumor were less typical.[5,6]

VH is probably not as rare as was suggested in initial reports, and it seems to be more frequent than first thought, as pathologists are more aware of it and as the ICCR (International Consultation on Cancer Reporting) has given recommendations about how to report VH.[7] In some recent reports, up to 31% VH has been reported in RCs.[6] The current recommendations emphasize reporting any UC variant.[8] Cut-offs have been suggested, but no common consensus exists from what percentage to call a variant as such.

Challenges exist when diagnosing and reporting VH in small samples, such as a biopsy or TURB when only a scant specimen is available. Some authors questioned whether TURB alone was sufficient to characterize a VH in UC in light of heterogeneity between the TURB and RC.[6] Nevertheless, it must be acknowledged that in most of these papers, the samples were not reviewed by a central uropathology review; therefore, it was difficult to give recommendations.

We aimed to evaluate the concordance between VH in TURB and RC after a central pathological review by an experienced uropathologist. Although bigger series exist, this is the first with a central pathology review allowing for precise evaluation and information about these carcinomas.

Material and methods

Patient population

In this retrospective, single-institution study, we included 110 patients with a diagnosis of UC on TURB, who underwent RC with a standard bilateral pelvic lymphadenectomy between 01/2010 and 12/2013. Informed consent was provided, and because this was a retrospective, completely anonymous study without any further impact on outcome and treatment of the patients, no ethical approval was necessary.

Main Points:

- The International Consultation on Cancer Reporting (www.ICCR-cancer.org) and the WHO 2016 require reporting of VH and their percentages in the pathology report.
- VHs have an impact on treatment and must be reported on the first TURB.
- Our study shows a high concordance of 82% between VH in a TURB and the findings on RC, as reviewed by an experienced uropathologist.
- The discrepancies between the findings on TURB and RC can be explained by the fact that bladder cancer is heterogeneous.

Relevant clinico-pathological parameters related to prognosis were collected: pathologic stage of the primary UC using the current 8th edition of the UICC (TNM) system.[9] We then retrieved the cases from our archives (TURB and RC). None of the selected patients had underwent neoadjuvant chemotherapy prior to the cystectomy.

Pathological evaluation

The VHs were evaluated on TURB and RC specimens by a senior pathologist (EC) and a junior pathologist (CN) according to the 2016 WHO classification of genito-urinary tumors, recognizing different patterns, which were reported.[10] Evaluation was done on the initial slides. All TURB slides for each patient were reevaluated. The same was done for all corresponding RC specimens. All available tumor slides were evaluated to detect any amount of variant histology. According to our grossing protocols in the department, we were able to analyze the whole tumor of the RC because we always include carcinomas totally in the RC. This allows a perfect overview of these heterogeneous carcinomas. In case of a discordance between the two pathologists, the case was reevaluated until a common consensus could be reached. We did not use a percentage of thresholds for variant histology as we considered that any VH should be reported. Descriptive statistical analysis was used in this study.

Results

Characteristics of patients

Among 110 patients who had undergone first a TURB and second a RC diagnosed with UC, the pT stages were as follows: 23 (20.9%) pT2 tumors, 24 (21.8%) pT3, and 63 (57.3%) pT4 (Table 1). Forty-four (40%) were found to have lymph node metastasis and 36 (32.7%) associated carcinoma in situ. The age range was between 47 and 83 years with a mean of 65 years. Among the 110 patients, 87 (79%) were male and 23 (21%) were female.

Pathologic findings on TURB

Among 110 patients, 54 (49.1%) patients presented with VH of UC in the TURB specimen. Among them, 43 were men (49% of men) and 11 were women (48% of women) who displayed

Table 1. Clinico-pathologic characteristics

Characteristics	Patients (%)
No. of patients	110 (100)
Pathologic stage	
pT2	23 (20.9)
pT3	63 (57.3)
pT4	24 (21.8)
N+	44 (40)

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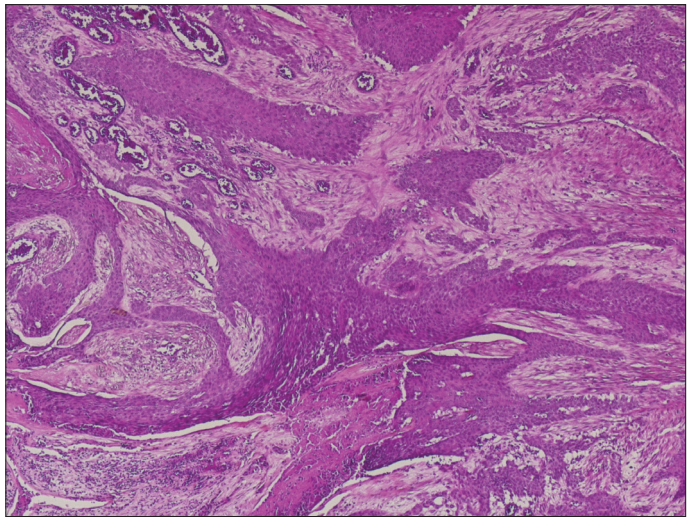

Figure 1. Squamous cell carcinoma of the bladder, with desmoplastic stroma (HPS × 10)

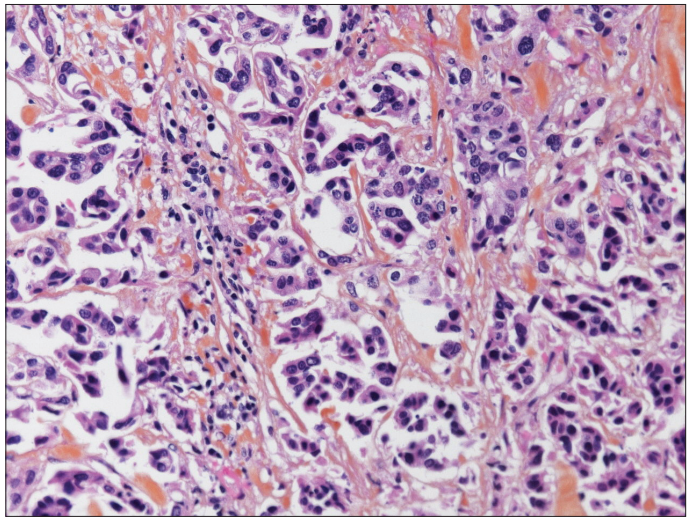

Figure 2. Typical micropapillary carcinoma (HPS/Hematein-Phloxin-Eosin Staining × 20) and retraction artefacts making it difficult to distinguish with lymphovascular invasion

VH, no predominant pattern according to sex was found. Squamous differentiation 19 (35.2%) sometimes with desmoplastic stroma (Figure 1), micropapillary 10 (18.5%) (Figure 2), and nested variants 7 (16.7%) were the most frequent VH. Forty-eight (89%) among the 54 patients showed a single VH, whereas the remaining six (11%) had multiple patterns (2 or 3 different VH) on the TURB specimens with mainly squamous differentiation in five cases. One case with predominantly plasmacytoid aspects was also in our series (Figure 3, Table 2). Any VH observed in our study always occupied at least 5% of the resection surface. According to pathology findings, each TURB and RC were evaluated for the whole amount of VH, and then these findings were compared.

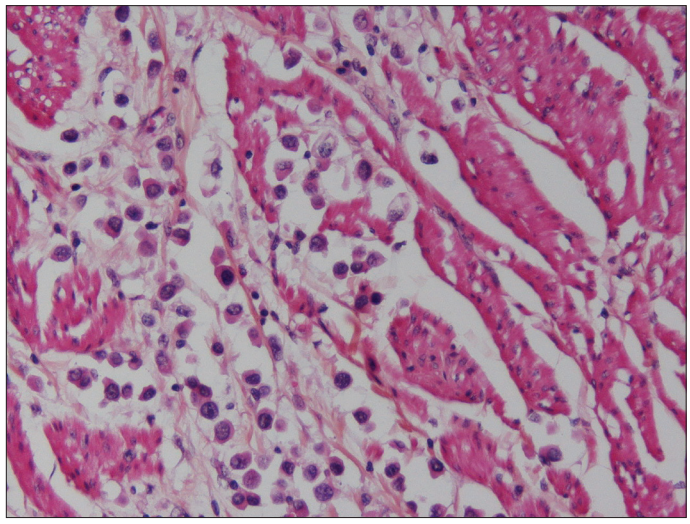

Figure 3. Plasmacytoid urothelial carcinoma, cells display discohesive features invading and destroying the detrusor muscle (HPS × 20)

Table 2. VH in TURB and matched RC

		TURB+/Cystectomy+
VH	**N° in TURB***	**n (%)**
Squamous	19	18 (94.7)
Micropapillary	10	7 (70.0)
Nested	7	5 (71.5)
Plasmacytoid/signet ring/diffuse	7	6 (86.0)
Poorly differentiated	6	6 (100)
Sarcomatoid	2	1 (50.0)
Microcystic	1	1 (100)
Glandular	1	0
Neuro-endocrine	1	1 (100)
Total	54	45 (82.3)

*The total number of TURB. The number of TURB with a diagnosis of VH on matched RC. VH: variant histologies; TURB: transurethral resections of the bladder; RC: radical cystectomy

Among the 54 patients with VH, 24 (44.4%) were diagnosed with lymph node metastasis. We did not control the VH in the lymph node metastasis as this was not the purpose of our study.

Evaluation of concordance between TURB and RC specimen

In total, we reported nine different patterns (Table 2). Finally, 82% of VH detected on TURB were equally found on the matched RC specimen (Table 2).

Of the 54 patients, 20 (37%) patients showed discordance between TURB and matched RC specimens (Table 3). Some did not display the same VH, whereas others had additional VH in the RC specimen.

Table 3. Differences between TURB and RC

Patient	VH in TURB	VH in RC
1	*Micropapillary*	–
2	*Squamous Sarcomatoid*	*Squamous*
3	*Squamous Nested*	*Squamous*
4	*Micropapillary*	–
5	*Sarcomatoid Plasmacytoid*	*Sarcomatoid*
6	*Microcystic*	Microcystic *Nested*
7	*Squamous*	Squamous *Sarcomatoid*
8	–	*Sarcomatoid Giant Cell*
9	–	*Squamous Micropapillary*
10	*Squamous*	Squamous *Micropapillary*
11	–	*Plasmacytoid*
12	*Squamous Glandular*	*Squamous Microcystic*
13	*Sarcomatoid*	*Squamous*
14	*Nested*	*Micropapillary Clear Cell*
15	*Nested*	*Micropapillary Sarcomatoid*
16	*Plasmacytoid Sarcomatoid Squamous*	*Plasmacytoid Sarcomatoid Micropapillary*
17	*Plasmacytoid*	*Sarcomatoid*
18	*Squamous Sarcomatoid*	*Squamous Plasmacytoid*
19	*Nested*	*Micropapillary*
20	*Micropapillary*	*Plasmacytoid*

Note. *In italic, changes in VH between TURB and matched cystectomy specimens*. VH: variant histologies; TURB: transurethral resections of the bladder; RC: radical cystectomy

In five patients (9%), uncommon VH detected on TURB was not found on the RC specimen: micropapillary (n=2), sarcomatoid (n=1), nested (n=1), and plasmacytoid (n=1).

In six patients, (11%) VH was found only on RC: sarcomatoid (n=3), nested (n=1), plasmacytoid (n=1), squamous (n=1), and micropapillary (n=1).

Nine patients (16%) were diagnosed with different variant histologic subtypes on TURB and matched RC.

Discussion

During the last few years, VHs have been at the center of interest in UC. Several authors have shown that some VHs are associated with adverse outcomes, and pathologists clearly play a key role in detecting patients with VHs and helping the management of patients with bladder cancer. Some studies reported differences in the patients' outcome in case of VHs and often a higher risk.[6] Furthermore, some authors emphasized that VH, especially the micropapillary carcinoma, which is known to have aggressive features, must be reported at any amount and probably be clinically managed more aggressively.[2] We also know that patients with some VHs such as squamous differentiation benefit more from neoadjuvant chemotherapies, although globally their outcome is poor.[3,11]

The key question is whether we can trust the initial pathology on a TURB. Therefore, several things must be taken into consideration, including how to report VH from a pathological standpoint.

In a consensus statement, the ICCR has recently underlined the importance of reporting any VH in percentages, and pathologists also have become more attentive in reporting VH. Both the WHO 2016 and the ICCR gave recommendations on how to report UC appropriately with divergent differentiation: "Reporting of UC that contains foci of squamous, glandular, or trophoblastic differentiation and/or other forms of differentiation that are not included in subsequent variant categories. These carcinomas are diagnosed as "UC with differentiation" and the percentage of the variant morphology reported." In case of classical UC and VH, the percentage of any VH should be given.[7]

Regarding whether initial histology on TURB is relevant, our study showed that the agreement between TURB and RC for detecting VH in UC was relatively high, with a concordance of 82%. One of the major problems in pathology is the dependence on sent material and consequent sampling issues. In particular, TURB specimens with only classical UC may lead to undetected VH, which is only discovered later when the RC is reviewed. The other problem is that of tumor heterogeneity. Larger tumors tend to display different VHs as compared with small tumors; the quasi entire tumor is resected during a TURB and can be completely evaluated in the first report. We did not have the clinical information on tumor size; therefore, we did not include this finding in our study. However, as we embedded the total amount of the tumor in RC, we ensured that we analyzed the total surface and all different histological aspects of the tumor.

Our study emphasized the high frequency of UC with 49% of the specimens displaying VH. VH displayed by men were similar to that of women (49% and 48%). Squamous differentiation was the most frequent variant detected in our study, consistent with other reports.[9,12,13] Concordance of TURB and RC to detect squamous differentiation was relatively high with a concordance of over 90%. This is critical in patient management after TURB and before RC. In patients with several VHs, squamous differentiation was still the most common. This is a very important finding in patients for whom the urologist/oncologist wants to administer neoadjuvant chemotherapy. In case of squamous differentiation, the clinician can confidently treat the squamous

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variant. From a pathological point of view, this kind of differentiation is relatively easy to recognize and must be reported in the pathology report.

In our study, the most important discrepancies were found between micropapillary and nested carcinomas (3/20 cases; 15%). The challenges associated with recognizing micropapillary carcinomas were already reported by Sangoi et al.[5] In their study they described that, in the case of classical micropapillary features, a concordance of 93% was observed, but as soon as the micropapillary aspects do not fit perfectly into the classical aspects, such as variations associated with extensive retraction or varying sizes of the tumor nests, the agreement is weak. When all the cases are considered together, the agreement in this study was moderate with a kappa=0.54. The differences in recognizing VH can also be explained by the fact that sometimes nested carcinomas can show retraction and mild vacuolization according to fixation artifacts. In contrast, micropapillary carcinomas, especially when not 100% typical, can form some kinds of compact nests with only very few retraction artifacts and can be mistaken as nested carcinomas. Therefore, discrepancies can be seen. Some clinicians claim that micropapillary carcinomas cT1N0M0 should be treated with an upfront cystectomy to guarantee the patient survival.[2] It is obvious that in these cases, the pathologist carries a heavy burden of responsibility.

In a recent paper, Moschini et al.[8] report poor agreement between TURB and RC with the micropapillary variant being especially challenging and obviously underreported with a Cohen kappa concordance of 0.1. For reporting any VH, the kappa was 0.27, which was also extremely low. Nevertheless, in their paper, they had considered patients from 1990 to 2013 because reporting of variants in earlier years was strictly not the same. The WHO 2016 classification has changed some of these categories as well as added newly recognized VH. Some variants like the micropapillary carcinoma have only been described in 1994.[8,14] Therefore, reports before 2004 without a central review and diagnosis should be looked at with caution. Although we had a discordance in reporting micropapillary carcinoma, it was minor because the central uropathology review was done according to the latest WHO 2016 classification.[7]

The second most important difference in our study was between squamous and sarcomatoid VH. This can be explained by the fact that several squamous carcinomas have a tendency to develop sarcomatoid features, and the ascertaining the difference between both can be challenging (Figure 1). However, according to the literature, they seem to have quite close outcomes and mixed features might be more common than expected.[15]

Only a few studies have evaluated the concordance of VH between TURB and RC. A recent paper of Soave et al.[16] showed that the extent of VH plays a role in patients' outcome when treated with RC. Therefore, sampling and reporting these carcinomas in a precise manner is of major importance. According to the ICCR recommendations, any amount of VH has to be reported. Our study is limited by the relatively small number of cases; however, it is the only study with a central pathology review and a review according to the latest WHO 2016 classification.[11]

Reporting VH in urothelial bladder carcinoma is important for the clinical management of patients, and globally recognized organizations like the ICCR have underlined this point. They have also underlined the necessity to report any VH in a bladder cancer because no global recommendation exists about the cut-offs on reporting a variant. Although we know that the UCs are heterogeneous tumors, we must be aware that TURB alone might be insufficient to characterize all the VHs in a UC, but in most cases, as highlighted by our study, the difference between TURB and RC remains acceptable.

Ethics Committee Approval: According to the set up of the study no approval was required in France.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.C.; Design – E.C., O.C.; Supervision – E.C.; Resources – E.C., O.C.; Materials – C.N., E.C.; Data Collection and/or Processing – C.N., E.C.; Analysis and/or Interpretation – C.N., E.C., O.C.; Literature Search – C.N., E.C.; Writing Manuscript – C.N., E.C.; Critical Review – O.C.

Conflict of Interest: The authors have no conflicts of interest to declare.

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