ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

Is transurethral resection alone enough for the diagnosis of histological variants? A single-center study

Marco Moschini, M.D.[a,b,*], Shahrokh F. Shariat, M.D.[c], Massimo Freschi, M.D.[d], Francesco Soria, M.D.[c], David D'Andrea, M.D.[c], Mohammad Abufaraj, M.D.[c], Beat Foerster, M.D.[c], Paolo Dell'Oglio, M.D.[a], Emanuele Zaffuto, M.D.[a], Agostino Mattei, M.D.[b], Andrea Salonia, M.D., Ph.D[a], Francesco Montorsi, M.D.[a], Alberto Briganti, M.D., Ph.D[a], Andrea Gallina, M.D.[a], Renzo Colombo, M.D.[a]

[a] *Unit of Urology/Division of Oncology, IRCCS Ospedale San Raffaele, Urological Research Institute, Milan, Italy*
[b] *Department of Urology, Klinik für Urologie, Luzerner Kantonsspital, Lucerne, Switzerland*
[c] *Department of Urology, Medical University of Vienna, Vienna, Austria*
[d] *Department of Pathology, Ospedale San Raffaele, Milan, Italy*

Received 23 December 2016; received in revised form 23 February 2017; accepted 21 March 2017

Abstract

Introduction: To evaluate incidence of histological variants and grade agreement between transurethral resection (TUR) and radical cystectomy (RC) in patients with bladder cancer.

Methods: A total of 779 patients treated with TUR and subsequently with RC between 1990 and 2013 at a single center were analyzed retrospectively. Variant histology classifications used in our analyses were sarcomatoid, small cell, squamous, or micropapillary. Grade agreement was calculated using the Cohen kappa coefficient. Logistic regression analyses were built to predict adverse pathologic features from histological variants at TUR.

Results: Considering TUR, 213 (27.3%) patients were diagnosed with histological variants. Of these, 2.1% ($n = 16$) were found with sarcomatoid variant, 1.7% ($n = 13$) with small cell, 7.1% ($n = 55$) with squamous, 12.5% ($n = 97$) with micropapillary. Considering RC, 212 (27.2%) patients were diagnosed with histological variants. Poor agreement was found considering micropapillary variant and the presence of a histological variant in general (0.11 and 0.27, respectively). Intermediate agreement was found analyzing the presence of sarcomatoid, small cell, and squamous variants (0.43, 0.61, and 0.61, respectively). Small cell carcinoma at TUR was found associated with an increased risk of harboring positive soft tissue surgical margin (odds ratio = 2.08; CI: 1.27–3.41; $P = 0.03$).

Conclusions: One out of our patients with bladder cancer was diagnosed with a histological variant either at TUR and RC. We found poor agreement between TUR and RC. Our findings highlight that TUR alone is not sufficient to accurately evaluate the presence of histological variants that may have an effect on treatment and survival outcomes.

Keywords: Bladder cancer; Radical cystectomy; Histological variants; Transurethral resection

1. Introduction

Urothelial carcinoma of the bladder presents often morphological features that differ from the urothelial common aspect. The recent WHO 2016 [1,2] consensus highlighted the importance of a careful morphological description of bladder pathologic specimens as the presence of histological variants may drive management of disease and change survival expectations [3–7]. In this perspective, the correct diagnosis of histological variants at the time of transurethral resection (TUR) and radical cystectomy (RC) is pivotal to optimize therapeutic strategies (Fig.)

Marco Moschini is supported by the EUSP Scholarship—European Association of Urology.

* Corresponding author. Tel.: +39-02-0643-5664; fax: +39-02-2643-5659.
E-mail addresses: marco.moschini87@gmail.com, marco.moschini@luks.ch (M.-A. Moschini).

http://dx.doi.org/10.1016/j.urolonc.2017.03.024
1078-1439/

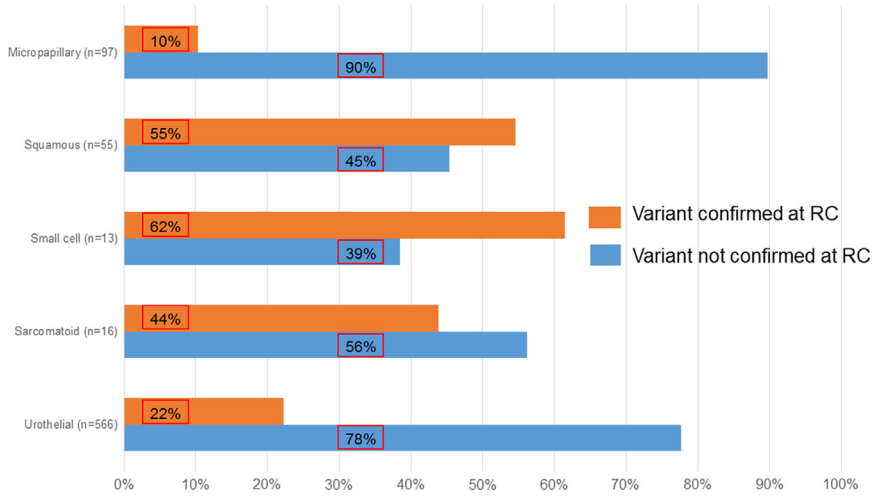

Fig. Histological variant diagnosed at transurethral resection confirmed in the radical cystectomy specimen. (Color version of figure is available online.)

However, the correct diagnosis of histological variants has several difficulties. In perspective, a higher incidence of histological variants has been reported when high-trained uropathologists working in referral centers were asked to evaluate this aspect [7]. Considering TUR in fact, the diagnosis can be challenging considering the small amount of the specimen that can be eventually damaged by the resection itself [1,2]. However, at the time data about concordance between TUR and RC in respect of histological variants diagnosis are lacking. Assessing this can be of paramount importance to fully understand a phenomenon that can influence severely patients' treatment. Moreover, finding poor concordance between TUR and RC may represent a strong argument in favor of an increased diagnostic awareness at the time of TUR suggesting the introduction of new biomarkers and therefore testing new techniques that can potentially avoid misdiagnosis.

The aim of our study is to evaluate the incidence of histological variants at TUR submitted subsequently to RC in a single tertiary referral center. Moreover, we evaluated the concordance of these findings using RC as reference in a selection of patients treated without neoadjuvant chemotherapy (NAC) to minimize confounding effects.

2. Materials and methods

A total of 779 patients treated with TUR and subsequently with RC and pelvic lymph node dissection between 1990 and 2013 at a single tertiary referral center were retrospectively evaluated. The procedures were approved by the institutional review board (Vescica/2010). Patients treated with NAC and pT0 at RC were excluded from the cohort due to the aim of this study. Pathological stages were classified according to the 2009 TNM classification [8]. Adverse pathologic stage was defined as pT3–T4 disease. Positive soft tissue surgical margin (STSM) was defined as the presence of tumor at inked areas of soft tissue on the RC specimen. Tumor grade was assessed according to 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification [9]. Dedicated uropathologists evaluated the presence of histological variants. Specifically, we stratified variant histology as follows: sarcomatoid, small cell, squamous, or micropapillary. Glandular, nested, lymphoepithelial, adenocarcinoma, or plasmacytoid variants were included in a group defined "others" as a consequence of the rarity of these findings in our series. We did not use a percentage of thresholds for variant histology, as we assumed in conformity with previous findings that any component of variant histology would drive outcomes [6].

2.1. Outcomes definitions

The primary end was to evaluate concordance between last TUR before RC and RC findings regarding histological variants. The secondary end point is to evaluate the incidence of histological variants at TUR and RC.

2.2. Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges were reported for continuously coded variables. The Mann-Whitney test and chi-square test were used to compare the statistical significance of differences in medians and proportions, respectively. Grade agreement was calculated using the Cohen kappa coefficient. Absolute value ranges between 0 and 1, where 0 represents pure chance agreement, and 0.1 to 0.4, 0.4 to 0.75, and 0.75 to 1.0, respectively, represent poor, intermediate, and good agreement. Multivariable logistic regression tested the effect of histological variants at the time of TUR and the subsequent risk of harboring adverse pathologic stage, node metastasis, or positive STSM at RC. Statistical significance was considered at $P < 0.05$. Statistical analyses were performed using SPSS v.22.0 (IBM Corp., Armonk, NY, USA) and STATA 13 (Stata Corp., College Station, TX, USA).