Clinical outcomes of patients with T1 nested variant of urothelial carcinoma compared to pure urothelial carcinoma of the bladder

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Abstract

Purpose—Evaluate oncologic outcomes of patients with cT1 nested variant of urothelial carcinoma and compare to cases of pure urothelial carcinoma of the bladder.

Materials and Methods—We retrospectively identified 30 patients with nested variant who, between 1997 and 2012, underwent transurethral resection with T1 tumor stage, followed by restaging transurethral resection within 3 months confirming non-muscle invasive disease. Radical cystectomy within 3 months of restaging transurethral resection was considered “early” treatment. We matched 3 pure urothelial carcinoma patients to each nested patient.

Results—Median follow-up for survivors was 4.3 yr from T1-staged transurethral resection. Nested variant patients had no statistically significant difference in metastasis-free survival ($p=0.2$) and cancer-specific survival ($p=0.2$) compared with patients to patients with pure urothelial carcinoma. However, it is concerning that the rate of upstaging to bladder and/or lymph nodes was 54% in nested variant patients who underwent early radical cystectomy, even after rigorous restaging.

Conclusions—While NV UC may be diagnosed at a higher stage, when stage matched we have not seen any statistical evidence that it is more aggressive than typical UC. Since NV UC patients who are cT1 on restaging TUR appear to have a higher propensity to develop nodal metastatic disease and a higher rate of upstaging, patients with cT1 NV UC on restaging biopsy may benefit from “early” RC, while patients with <cT1 on restaging may be considered for conservative management.

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CONFLICT OF INTEREST:
None declared

Keywords

Bladder cancer; Nested histology; Nested variant; non-muscle invasive; Urothelial carcinoma; Clinical outcomes

1. Introduction

Nested variant (NV) of urothelial carcinoma (UC) was first reported in 1979 (1) and incorporated into the World Health Organization classification in 2004 (2). It is a variant of UC that is both rare and underreported, with a reported incidence of 0.3% of invasive bladder tumors (3). While this variant has a deceptively benign appearance (4), it has been historically viewed as being very aggressive with high rates of muscle invasion at transurethral resection (TUR), extravesical disease, and metastatic disease (5–8). The current literature is limited to a few case series with small patient numbers, possible understaging, and combined patient cohorts that included different disease stages and different treatment modalities. In particular, there have been no reports in the literature focused on NV non-muscle-invasive bladder cancer (NMIBC). This is attributed to not only the rarity of NV, but also the low incidence of NV with NMIBC. With conventional UC, NMIBC accounts for 70% of cases, but only about 30% of NV cases are non-muscle-invasive at the time of diagnosis (5). However, the true incidence of NV NMIBC is likely lower since no study to date has limited their cohort to patients who underwent a restaging TUR. The incidence and optimal management of NV cT1 UC is not known.

To better understand the natural history of cT1 UC with NV histology, and to determine an appropriate treatment strategy, we retrospectively reviewed our institution's clinical experience. We analyzed the outcomes of restaged NMIBC with NV histology, compared to outcomes of pure UC of the bladder.

We had two primary objectives. First, to assess whether there is a difference in progression-free survival (PFS), metastasis-free survival (MFS), or cancer-specific survival (CSS) between patients with cT1 disease with NV features compared to patients with typical UC. Second, whether there is a difference in MFS or CSS among NV patients receiving early cystectomy (within 3 mo of restaging TUR) compared to those undergoing any other treatment ("conservative treatment").

2. Materials and Methods

After receiving institutional review board approval, we queried our prospectively maintained institutional database for patients between 1997 and 2012 with bladder cancer with nested features. We identified 203 patients with NV of UC of the bladder (all stages). In this cohort, 71 patients had NMIBC at the time of the NV diagnosis. We then limited our final cohort to those who had had (1) cT1 diagnosis based on imaging, bimanual exam, and TUR with a T1 tumor stage; (2) restaging TUR within 3 mo confirming NMIBC; (3) nested features found on either the diagnostic or restaging TUR; and (4) follow-up data. One patient included in the nested group was found to have nested features 3 mo and 1 wk after initial T1-staged TUR. Patients excluded from our cohort included 32 who were upstaged on restaging TUR

or imaging, 6 who did not undergo a restaging TUR within 3 mo, and 3 without any follow-up after their restaging TUR. Our final group of NV NMIBC patients was 30 patients. We then matched 3 pure UC patients for every NV patient; matched patients likewise had undergone TUR resulting in a T1-staged tumor and had been confirmed as non-muscle-invasive by a restaging TUR within 3 mo. To ensure similar follow-up time between the two groups, the pure UC patients selected had undergone their T1-staged TUR within 4 mo of their nested counterpart's T1-staged TUR. To ensure accurate ascertainment of outcomes, full medical chart review for both NV cases (n=30) and matched controls with pure UC (n=90) was completed by urologists ADM or GD, or both. Treatment management was classified as aggressive treatment ("early" radical cystectomy [RC]) or conservative treatment (any treatment other than "early" RC, including deferred RC [RC more than 3 mo after restaging TUR]).

To determine whether there were differences in demographics and T1-staged TUR tumor characteristics between patients with nested features and patients with pure UC, group comparisons were made using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. We used the Kaplan-Meier method to estimate MFS and CSS and the log-rank test to assess whether there are differences between NMIBC patients with pure UC and those with nested features. Among patients undergoing conservative treatment, we estimated PFS using Kaplan-Meier methods, censoring patients who had not progressed at the date of their RC or the date of their last follow-up if they did not undergo surgery. Progression was defined as upstaging to muscle-invasive bladder cancer, developing node-positive disease, or developing distant metastases. The log-rank test was used to assess difference based on histology. Our analysis assessing PFS excluded patients who received "early" RC since they were no longer at risk of progression after surgery. Among patients undergoing conservative treatment, we evaluated how many proceeded to deferred cystectomy, censoring patients who had not undergone surgery by the date of their last follow-up. Finally, among the group of patients with nested features, we used the Kaplan-Meier method to estimate MFS and CSS and the log-rank test to assess differences based on treatment management. All statistical analyses were conducted using STATA 13.0 (StataCorp, College Station, TX).

3. Results

Characteristics of the full cohort of 120 patients are shown in Table 1. The median age of nested patients at their T1-staged TUR was 65 and approximately three-quarters of both the nested and the pure UC groups were male. Patients with nested features had higher stage disease at their restaging TUR ($p=0.0002$). A larger proportion of nested patients underwent aggressive treatment (difference: 28%; 95% CI 8.5–47%; $p=0.004$) compared to patients with pure UC histology, likely in part influenced by the restaging TUR results.

Among the 30 patients with NV UC, 3 progressed to metastatic disease and died of their disease; median follow-up for survivors was 3.4 yr from T1-staged TUR. Among the 90 patients with pure UC, 5 patients progressed to metastatic disease, 4 of whom later died of their disease; median follow-up for survivors was 4.9 yr from T1-staged TUR. Kaplan-Meier estimated MFS and CSS curves based on histology were analyzed; we found no statistical

difference in MFS ($p=0.2$) and CSS ($p=0.2$) between patients with nested features and patients with pure UC.

Table 2 shows the characteristics of our subcohort of 30 nested patients by treatment management; 13 (43%) patients underwent “early” RC (within 3 mo of restaging TUR) and 17 (57%) underwent conservative treatment. Conservative treatment for both NV and typical UC was defined as anyone who did not undergo RC within 3 months of restaging TUR. Of the 3 NV patients who developed metastases and later died due to their disease, 1 had been conservatively treated.

Table 3 shows the outcomes for the 13 patients with nested histology who underwent “early” RC. In these patients, the rate of upstaging to bladder and/or lymph nodes was 54% (7/13), even after rigorous restaging. This included 4 patients (31%) with node-positive disease, and 5 patients (38%) who were upstaged in the bladder. By comparison, in the 14 patients with pure UC who underwent “early” RC, only 2 (14%) were upstaged in the bladder and none had node-positive disease.

Within the group of 93 patients (76 pure UC, 17 NV) who received conservative treatment, 1 NV patient and 12 pure UC patients progressed. Median follow-up for survivors was 3.9 yr from T1-stage diagnosis. There was no significant difference in PFS ($p=0.5$) based on histology. Our patients with NV NMIBC treated conservatively had metastasis and progression rates at 5 yr of 14% (95% CI 2–67%) and 17% (95% CI 3–73%), respectively, with a median follow-up of 3.5 yr in overall survivors. Table 4 lists treatments and outcomes in patients managed conservatively. Only 1 NV patient who underwent conservative treatment progressed. The progression was 4.6 yr after initial diagnosis of NV features; at that time the patient underwent neoadjuvant chemotherapy and the cystectomy was aborted due to progression to metastatic disease. Three patients in the nested cohort who were managed conservatively underwent a deferred RC, and 2 underwent partial cystectomy; in each of those instances, the decision to proceed to RC was due to recurrent T1 disease and the cystectomy pathology revealing non-muscle-invasive disease. The median follow-up for nested patients not having undergone cystectomy was 3.5yr from T1-staged TUR. Among the 76 pure UC patients who underwent conservative treatment, 16 patients had deferred RC, 4 of whom did so due to progression to T2 disease. The median follow-up for pure UC patients not having undergone deferred RC was 5.2yr from T1-staged TUR. Among pure UC and nested patients undergoing conservative treatment, there was no significant difference in persisting on the conservative treatment path ($p=0.3$) based on histology.

4. Discussion

To our knowledge, this is the only series focused on cT1 with NV UC at diagnosis. The incidence of NMIBC with NV UC frequently reported in the literature is derived from a series with 30 cases, of whom 9 (31%) patients had NMIBC (5). The total incidence of NV UC in our database was 203 patients, with our initial incidence of NMIBC with NV histology 35% (71/203). However, after a rigorous restaging biopsy, the true incidence of NV NMIBC was 15% (30/203). It is important to note that no study to date has required a restaging biopsy to confirm the accuracy of the staging. Even the largest case series on NV

UC, derived from 10 institutions across Europe reviewing cases over a 9-yr period, found only 9 cases (16%) of NV NMIBC (9). These patients were not restaged to confirm NMIBC status. Therefore, along with the rarity of patients with NV NMIBC, these studies represent an inadequately staged cohort. The low incidence of NMIBC with NV histology is in stark contrast to the 70% NMIBC incidence seen with pure UC.

Besides being associated with muscle invasion at presentation, it has been reported that NV is associated with a higher incidence of extravesical disease at cystectomy (33% vs 83%; $p<0.0001$) and metastatic disease (19% versus 67%; $p<0.0001$) compared with pure UC (5). Based on the largest series on NV to date, most patients were either alive with metastatic disease or had died of disease within 2 years of treatment (9). The concern is that NV is inherently more aggressive and that conservative management for patients with NV NMIBC may be deleterious. However, while NV UC may be diagnosed at a higher stage, when stage matched it may not necessarily be more aggressive than typical UC. Linder et al. have shown that nested patients do not have a worse prognosis following RC compared to typical UC after accounting for stage (10). Though, as only 1 patient in their cohort had NMIBC, it is still unknown how best to manage the NV NMIBC population.

We wanted to ascertain if patients with NV NMIBC were at increased risk of progression. Currently, early RC for NMIBC is indicated in patients with unfavorable prognostic factors such as high-grade disease, tumors 3 cm or greater, or carcinoma in situ, as well as patients with recurrent/persistent T1 disease after bacillus Calmette-Guerin, micropapillary UC, vascular invasion, and T1b (versus T1a) (11,12).

In our series, the rate of upstaging to bladder and/or lymph nodes in NV patients who underwent “early” RC, even after rigorous restaging, was 54%. This included 31% with node-positive disease (versus 0% in the pure UC cohort), and 38% who were upstaged in the bladder (versus 14% in pure UC cohort). It appears NV histology has a high propensity for early metastasis to the lymph nodes, even in patients with NMIBC on RC pathology. The high rate of both muscle-invasive disease and lymph node involvement in the “early” RC cohort is worrisome. However, the “early” RC cohort was at higher risk of progression, independent of the nested histology, since 92% of the patients in the “early” cystectomy cohort had cT1 upon restaging. But the rate of upstaging in bladder and/or lymph nodes is still out of proportion to what would be expected. Furthermore, even pT1 patients had a higher rate of nodal involvement (2 of 8).

We have previously shown the rate of upstaging on RC pathology for patients who had persistent cT1 at restaging TUR and who underwent “early” RC to be 24% (13). So the 38% upstaging in the bladder in our NV cohort could be due to both nested histology along with restaging TUR confirming cT1. Furthermore, the rate of lymph node metastases in patients with non-muscle-invasive pure UC is 1% (personal communication). In our pure UC cohort, it was 0%. Yet the rate of lymph node metastasis was 31% in our “early” RC cohort and half of the patients with lymph node metastasis had pT1 disease.

We did not find a significant difference in outcomes based on treatment management. It should be noted, though, that NV patients who had cT1 on restaging TUR were more likely

to undergo “early” RC. By conducting earlier treatment in a potentially more aggressive cohort, we may have mitigated the survival difference between the nested and the pure UC cohorts.

The limitations of our study include retrospective analysis and that our results may have been affected by the treating clinicians’ selection bias toward “early” RC for patients with cT1 nested variant. Treating patients with nested histology more aggressively could therefore minimize any survival difference between the nested and pure UC cohorts. Furthermore, the small sample size may be insufficient to detect survival differences between groups. However, to the best of our knowledge, it is the largest series to date on NMIBC with NV histology, and is the only study to date to include restaging TUR to confirm NMIBC.

Risk stratification is essential to proper management of patients with cT1 NMIBC, which is a heterogeneous disease. In our cohort of restaged cT1 NV UC, there was no statistical difference in CSS and metastatic disease compared to pure UC in properly selected patients. For example, the difference in the Kaplan-Meier CSS curves 3 years after T1-stage diagnosis is 6.7% (95% CI - 4.3–17.7%). Although these results are not statistically significant, the confidence intervals around the estimates do not exclude important differences in survival between patients with nested histology and patients with typical UC. It is possible there was a clinically significant difference that was not detected because either our cohort was underpowered or because “early” cystectomy minimized a survival difference. While NV UC may be diagnosed at a higher stage, when stage matched it may not necessarily be more aggressive than typical UC. Since NV UC patients who are cT1 on restaging TUR appear to have a higher propensity to develop nodal metastatic disease and a higher rate of upstaging, patients with cT1 NV UC on restaging biopsy may benefit from “early” RC, while patients with <cT1 on restaging may be considered for conservative management.

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Table 1

Patient characteristics

	Pure urothelial carcinoma patients (N=90)	Patients with nested variant ¹ (N=30)	<i>p</i> value
Age, yr, median (IQR) ²	68 (61–74)	65 (58–73)	0.3
Male, n (%)	71 (79)	23 (77)	0.8
Carcinoma in situ, n (%) ²	32 (36)	7 (23)	0.3
Multifocal, n (%) ²	44 (49)	18 (60)	0.4
Category at restaging TUR, n (%) ³			
<T1	64 (71)	9 (30)	0.0002
T1	26 (29)	21 (70)	
“early” radical cystectomy, n (%)	14 (16)	13 (43)	0.004

¹This includes two patients who were found to have nested features on restaging TUR, but not on initial TUR.

²At the time of the initial T1-staged TUR.

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IQR = interquartile range; TUR = transurethral resection.

Table 2

Characteristics of nested patients, comparing those who received “early” RC versus conservative treatment

	Conservative treatment (N=17)	“early” RC (N=13)	<i>p</i> value
Age, yr, median (IQR) *	67 (58–73)	65 (60–72)	0.7
Male, n (%)	12 (71)	11 (85)	0.4
Carcinoma in situ, n (%) *	2 (12)	5 (38)	0.2
Difficult location, n (%) *	2 (12)	2 (15)	>0.9
Multifocal, n (%) *	8 (47)	10 (77)	0.14
Stage at restaging TUR, n (%)			
<T1	8 (47)	1 (7.7)	0.042
T1	9 (53)	12 (92)	

* At the time of the initial T1-staged TUR.

RC = radical cystectomy; TUR = transurethral resection; IQR = interquartile range.

Table 3

Treatment and clinical outcomes for 13 patients with nested variant NMIBC who received “early” RC

Stage at restaging TUR	Stage at cystectomy	Intravesical therapy	Systemic chemo-therapy	Follow-up after T1-stage diagnosis, yr	Distant metastases	Living status at final follow-up
<T1	Tis N0	Yes	No	3.3	No	Alive
T1	T0 N0	No	No	3.6	No	Alive
T1	T0 N0	No	No	1.1	No	Alive
T1	Tis N1	No	No	2.1	No	Alive
T1	Tis N0	Yes	No	2.1	No	Died of other cause
T1	T1 N0	No	No	2.8	No	Alive
T1	T1 N0	No	Yes	2.7	Yes	Died of bladder cancer
T1	T1 N1	No	Yes	4.6	No	Alive
T1	T2 N0	No	No	16.8	No	Alive
T1	T2 N0	Yes	No	1.0	No	Alive
T1	T2 N1	No	No	3.3	No	Died of other cause
T1	T2 N0	No	No	12.4	No	Alive
T1	T3 N1	Yes	Yes	1.6	Yes	Died of bladder cancer

NMIBC = non-muscle-invasive bladder cancer; RC = radical cystectomy; TUR = transurethral resection.

Table 4

Treatment and clinical outcomes for 17 patients with nested variant NMIBC who received conservative treatment

Repeat TUR stage	Treatment	Followup after T1-stage diagnosis, yr	Distant metastases	Living status at final follow-up
<T1	Surveillance	1.6	No	Alive
<T1	Surveillance	7.5	No	Alive
<T1	Surveillance, deferred RC	9.9	No	Alive
<T1	Intravesical	3.4	No	Alive
<T1	Intravesical	3.5	No	Alive
<T1	Intravesical	3.6	No	Alive
<T1	Intravesical	7.2	No	Alive
<T1	Intravesical	8.1	No	Alive
T1	Intravesical	3.0	No	Died of other cause
T1	Intravesical	3.3	No	Alive
T1	Intravesical	3.3	No	Alive
T1	Intravesical	7.7	No	Alive
T1	Intravesical, neoadjuvant chemotherapy, aborted RC *	4.6	Yes	Died of bladder cancer
T1	Surveillance, partial cystectomy	5.4	No	Alive
T1	Intravesical, partial cystectomy	3.6	No	Alive
T1	Surveillance, deferred RC	3.2	No	Died of other cause
T1	Intravesical, deferred RC	0.8	No	Alive

* This patient's RC was aborted due to progression to metastatic disease.

NMIBC = non-muscle-invasive bladder cancer; TUR = transurethral resection; RC = radical cystectomy.