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ORIGINAL PAPER

Effect of variant histology presence and squamous differentiation on oncological results and patient's survival after radical cystectomy

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Summary ***Objective: To evaluate the effect of variant histology on pathological and survival findings in patients undergoing radical cystectomy due to muscle invasive bladder cancer.***

Materials and methods: Data from 146 patients with radical cystectomy performed due to muscle-invasive urothelial carcinoma between January 2006 to November 2016 at our clinic were investigated. The preoperative and postoperative data of patients with variant histology were compared with nonvariant urothelial carcinoma patients. Then of patients with variant histology only those with squamous differentiation (SqD) were compared with nonvariant urothelial carcinoma patients in terms of preoperative, postoperative and survival data.

Results: Of the 146 patients, 23 had carcinoma with variant histology. Of these, 17 had SqD, 4 had glandular differentiation, 1 patient had plasmocytoid variant and 1 patient had sarcomatoid variant. In patients with variant histology, postoperative T stage and upstaging was higher, with no difference observed in terms of overall and cancer-specific survival compared with nonvariant urothelial cancer patients. SqD patients were observed to have higher postoperative T stage compared to nonvariant urothelial cancer patients, with no significant difference observed in terms of survival.

Conclusions: In cystectomy pathologies, patients with variant histology (especially SqD patients) were observed to have proportionally higher T stage compared to nonvariant urothelial carcinoma; however there were no significant differences for overall survival and cancer-specific survival.

KEY WORDS: Bladder cancer; Radical cystectomy; Squamous differentiation; Variant histology; Survival.

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INTRODUCTION

The most common histologic type observed in bladder cancers is urothelial carcinoma. Urothelial carcinoma is known to sometimes display extraordinary characteristics (variants) differentiated from normal morphology (1). The histologic variant differentiation rate for bladder urothelial carcinoma is reported as 7-81% in radical cystectomy series (2). There are some studies stating that oncologic results and especially survival results are worse for bladder cancers with variant histology (3, 4). The most commonly observed among histologic variants of urothelial carcinoma is *squamous differentiation* (SqD), though other non-SqD variants may be observed (5). There are studies reporting that the survival for non-SqD histologic variants is lower (6).

In our study in patients with radical cystectomy performed due to muscle-invasive bladder cancer, firstly we aimed to assess the effect of the presence of variant histology on oncologic results and survival results, and secondly we aimed to compare oncologic data and survival data between the most commonly observed histologic variant of SqD with nonvariant urothelial carcinoma.

MATERIALS AND METHODS

The data belonging to 178 patients with radical cystectomy performed for bladder tumors from January 2006 to November 2016 at our clinic were retrospectively investigated. Patients who undergone radical cystectomy due to high risk non-muscle-invasive bladder, patients with non-urothelial carcinoma pathology and patients who had missed data were excluded from the study. Finally the study included 146 patients who undergone radical cystectomy operation due to muscle-invasive urothelial bladder carcinoma. Pathologic staging of patients was performed according to the 2002 *Union for International Cancer Control* (UICC) TNM staging system. All patients provided informed consent before the procedure. Before radical cystectomy, patients had preoperative clinical staging with examination, *transurethral resection* (TUR) and computed tomography.

The age, gender, preoperative data (presence of hydronephrosis, clinical stage and tumor grade and presence of *carcinoma in situ* (CIS) in TUR pathology data, postoperative data (postoperative T stage, tumor grade, surgical margin positivity, lymph node metastasis, presence of prostate and urethra invasion and lymphovascular invasion), upstaging and overall and cancer-specific survival data were assessed.

Additionally patients with variant histology on radical cystectomy pathology and the histologic type of this variant were noted. Patients with variant histology observed were called Group 1, with patients with nonvariant histology called Group 2. Patients in Group 1 with SqD were separately assessed.

No conflict of interest declared.

Statistical analysis

Patient data was first compared between Group 1 and Group 2 and then between patients with SqD and Group 2 using the Mann-Whitney U test and the Pearson X^2 test. The cancer-specific survival and overall survival times in the groups were assessed with the Kaplan-Maier survival analysis. Statistical analysis was completed using the Statistical Package for the Social Sciences (SPSS) Version 20.0 (*SPSS, Chicago, Illinois, USA*). Data are presented as mean and standard deviation, with statistical analysis calculated on the median values. The analysis results with p value < 0.05 were accepted as significant.

Results

There were 13 females and 133 males with radical cystectomy performed due to muscle-invasive bladder cancer. The mean age of all patients was 64.4 ± 9 years.
The mean follow-up time was 31.7 ± 31.8 months.

A total of 23 patients had variant histology; 17 had SqD, 4 had glandular differentiation, 1 patient had plasmocytoid variant and 1 patient had sarcomatoid variant.
The preoperative, postoperative and survival data and comparison between Group 1 (n = 23) and Group 2 (n = 123) are given in Table 1. When the comparison results are investigated, in the preoperative data, age, gender and clinical T stage and TUR pathology tumor grade and CIS presence were similar in Group 1 and Group 2.
In the postoperative data, tumor grade, surgical margin positivity, prostate invasion, urethral invasion and presence of lymphovascular invasion were similar in both groups. However, the postoperative pathologic T stage and pathologic upstaging were significantly higher in Group 1. There were no significant differences observed between the groups in terms of overall and cancer-specific survival.
Data for patients with urothelial carcinoma with the most commonly observed variant histology of SqD along with Group 2 patient data were compared and results are given in Table 2. Patients with SqD had significantly higher rates of preoperative tumor grade (p = 0.020) and postoperative pathologic T stage (p = 0.040) compared with Group 2. When survival data were examined, though patients with SqD had lower overall survival (52.3 ± 4.7 and 49.6 ± 10.4 months, respectively) and cancer-specific survival times (64.7 ± 5.3 and 58.4 ± 10.7 months, respectively) compared to Group 2, no statistically significant difference was found between the two groups.

Table 1.
Preoperative and postoperative patient characteristics and survival results for Group 1 and Group 2.

		Variant histology (+) n: 23	Variant histology (-) n: 123	P*
Age		63.7 ± 10.4	64.5 ± 8.7	0.119
Gender	Female	4	9	0.136
	Male	19	114	
Preoperative hydronephrosis	Positive	11	40	0.158
	Negative	12	83	
Preoperative T stage	T2	23	118	0.325
	T3	0	5	
Preoperative tumor grade	Grade 1	1	0	0.065
	Grade 2	1	4	
	Grade 3	21	119	
CIS	Positive	5	37	0.380
	Negative	18	83	
Postoperative T stage	≤ T1	0	19	0.035
	T2	10	61	
	T3	10	17	
	T4	3	26	
Postoperative tumor grade	1	1	4	0.967
	2	1	4	
	3	21	104	
Surgical margin	Positive	3	25	0.416
	Negative	20	98	
Lymph node metastasis	Positive	7	23	0.160
	Negative	16	93	
Invasion of prostate	Positive	2	15	0.606
	Negative	20	100	
Invasion of urethra	Positive	2	8	0.760
	Negative	21	108	
Lymphovasculer invasion	Positive	7	18	0.081
	Negative	16	100	
Perineural invasion	Positive	3	17	0.864
	Negative	17	101	
Upstaging	Positive	14	45	0.029
	Negative	9	78	
Overall survival	47.1 ± 8.6	52.3 ± 4.70	0.816	
Cancer spesific survival	52.8 ± 4.8	64.8 ± 5.3	0.824	

**Mann-Whitney U test CIS:carcinoma in situ.*

Discussion

In our study, the rate of patients with variant histology on radical cystectomy pathology was 16%, while the SqD rate was 12%. In the literature, different studies show different rates for variant histology, with these rates reported between 7 and 81% (2).
This large difference in variant histology rates may be explained by not using defined criteria for evaluation. SqD is reported to be most common among observed histologic variants, in fact in our study the rate of SqD among all histologic variants is 74% (17/23). Though SqD is characterized by histologic intercellular bridges and keratinization, the *World Health Organization* (WHO) defines it is a urothelial carcinoma variant (7). Among non-urothelial bladder cancers, squamous cell carcinoma and adenocarcinoma are known for their aggressive nature and low survival rates (8). However there is no consensus on the prognostic importance of histologic

Table 2.
Patient characteristics and survival results of urothelial carcinoma with squamous differentiation and nonvariant urothelial cancer patients.

		Squamous differantiation n: 17	Nonvariant urothelial cancer n: 123	P*
Age		66.9 ± 10	64.5 ± 8.8	0.219
Gender	Female	3	9	0.154
	Male	14	114	
Preoperative hydronephrosis	Positive	7	40	0.479
	Negative	10	83	
Preoperative T stage	T2	17	118	0.397
	T3	0	5	
Preoperative tumor grade	Grade 1	1	0	0.020
	Grade 2	0	4	
	Grade 3	16	119	
CIS	Positive	4	37	0.538
	Negative	13	83	
Postoperative T stage	≤ T1	0	19	0.040
	T2	8	61	
	T3	6	17	
	T4	3	26	
Postoperative tumor grade	1	1	4	0.802
	2	1	4	
	3	15	104	
Surgical margin	Positive	3	25	0.796
	Negative	14	98	
Lymph node metastasis	Positive	4	23	0.723
	Negative	13	93	
Upstaging	Positive	10	45	0.078
	Negative	7	78	
Overall survival		49.6 ± 10.4	52.3 ± 4.7	0.626
Cancer specific survival		58.4 ± 10.7	64.7 ± 5.3	0.743

variants of urothelial carcinoma. Studies of variant histologies and their clinical importance are examined, have generally heterogeneous populations and small scale.
A study by *Monn et al.* observed that generally patients with variant histology have high pathologic T stage.
When subtypes are investigated, while plasmocytoid and micropapillary variants have high mortality, SqD and sarcomatoid variants were identified to have similar survival to nonvariant urothelial carcinoma (9).
In our study, patients with variant histology had higher postoperative pathologic T stage and upstaging rate compared to nonvariant urothelial carcinoma patients, while survival rates were similar in accordance with the literature.
There are studies showing that bladder cancers with variant histology forms are aggressive tumors with high tumor stage and high lymph node metastasis rates (10-12). *Xylinas et al.* reported that patients with variant histology on radical cystectomy pathology were correlated with high tumor stage, high lymph node metastasis, *lymphovascular invasion* (LVI) presence, high recurrence risk and increased cancer-specific mortality.
Furthermore, they stated the patients with non-squamous differentiation were the worst prognostic group. In spite of this, they reported that variant histology was not an independent risk factor in terms of prognosis (13).
In the present study, though the preoperative tumor grade and postoperative tumor stage were high among patients with SqD, the overall survival and cancer-specific survival were similar to nonvariant urothelial carcinoma. Our findings support the report of *Moschini et al.* who assessed 1067 radical cystectomy cases, observing SqD in 10.2% of patients with no effect of SqD on survival (14).
Our study has some limitations.
The most important of these are that it is a retrospective study and the low number of patients.

Conclusions

Patients with variant histology on cystectomy pathology were observed to have high T stage compared to those with nonvariant urothelial cancer; however there were no significant differences in overall survival and cancer-specific survival.
When the most commonly observed histologic variant of SqD is investigated, though there was higher stage disease compared to nonvariant urothelial cancers, there was no effect shown on overall survival and cancer-specific survival.

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