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Comparative Outcomes of Pure Squamous Cell Carcinoma and Urothelial Carcinoma With Squamous Differentiation in Patients Treated With Radical Cystectomy

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Abstract

Purpose—We compared clinical outcomes, and identified predictors of cancer specific and overall survival after radical cystectomy in patients with urothelial carcinoma with squamous differentiation and those with pure squamous cell carcinoma.

Materials and Methods—We reviewed data on 2,031 patients treated with radical cystectomy and pelvic lymph node dissection at a single high volume referral center. Of these patients 78 had squamous cell carcinoma and 67 had squamous differentiation. Survival estimates by histological subtype were described using Kaplan-Meier methods. Within histological subtypes pathological stage, nodal invasion, soft tissue margins, age and gender were evaluated as predictors of cancer specific survival and overall survival using univariate Cox regression.

Results—Median followup was 44 months. Of 104 patient deaths 60 died of their disease. We did not find a statistically significant difference between survival curves of patients with squamous cell carcinoma and squamous differentiation (log rank overall survival $p = 0.6$, cancer specific survival $p = 0.17$). Positive soft tissue margins were associated with worse cancer specific survival (HR 6.92, 95% CI 2.98–16.10, $p = 0.0005$) and overall survival (HR 3.68, 95% CI 1.84–7.35, $p = 0.0005$) in patients with pure squamous cell carcinoma. Among patients with squamous differentiation, pelvic lymphadenopathy was associated with decreased overall survival (HR 2.52, 95% CI 1.33–4.77, $p = 0.004$) and cancer specific survival (HR 3.23, 95% CI 1.57–6.67, $p = 0.002$).

Conclusions—There appears to be no evidence of a difference in cancer specific survival or overall survival between patients with squamous cell carcinoma and those with squamous differentiation treated with radical cystectomy and pelvic lymph node dissection. Patients with squamous differentiation and tumor metastases to pelvic lymph nodes should be followed more closely, and adjuvant treatment should be considered to improve survival. Wide surgical resection is critical to achieve local tumor control and improve survival in patients with squamous cell carcinoma.

Keywords

urinary bladder neoplasms; treatment outcome; histology; carcinoma; squamous cell; cystectomy

Bladder cancer is the seventh most prevalent cancer worldwide, accounting for 3.2% of all malignancies.¹ Bladder cancer encompasses a broad spectrum of histological subtypes. Urothelial carcinoma represents 90% of these tumors. Alternatively, pure squamous cell carcinoma represents 2.7% of all bladder tumors.² In the Western hemisphere SCC of the bladder arises in patients with chronic inflammation, keratinizing squamous metaplasia and bladder stones. The histogenesis of bladder SCC involves the conversion of transitional cells to stratified squamous epithelium.

Urothelial carcinoma with SqD occurs along a similar molecular pathway, and is histologically characterized by intercellular bridges and keratinization.^{3–5} Compared to conventional urothelial carcinoma, SqD is an adverse pathological feature associated with worse recurrence-free and cancer specific survival.^{6,7} Similarly, compared to conventional urothelial carcinoma, SCC has been associated with adverse oncologic outcomes after adjusting for the effects of stage and common prognostic factors.⁸

To our knowledge no study has compared the clinical outcomes of patients with SCC to the outcomes of those with SqD. We compared the cancer specific survival and overall survival of patients with SCC and SqD, and identified prognostic factors in those treated with radical cystectomy for each histological variant.

MATERIALS AND METHODS

Patient Population

Between February 1990 and July 2009, 2,031 patients were treated with RCPLND at our institution. Of these cases 145 were pathologically confirmed on the radical cystectomy specimen as having SCC or SqD of the bladder. Institutional review board approval was obtained before the study commenced. Clinical and pathological information was retrospectively obtained from patient charts and electronic medical records. Patients were included in the study if radical cystectomy was successfully completed, and all clinical, pathological and followup data were available.

The indications for radical cystectomy were tumor invasion into the muscularis propria or prostatic stroma, nonmuscle invasive tumors (such as Ta or T1), or carcinoma in situ refractory to transurethral resection of the bladder tumor with intravesical chemotherapy and/or immunotherapy. Neoadjuvant chemotherapy was offered to most patients with adequate renal function who had muscle invasive disease diagnosed at transurethral bladder resection starting in approximately 2003. In patients with SCC the chemotherapy regimens were heterogeneous, and included treatment in clinical trials and for advanced tumors (T4).

Final pathological staging was defined as the higher of the preoperative clinical and pathological stages. A positive soft tissue margin was defined by the presence of tumor at the margin of perivesical soft tissue or urethra on the cystectomy specimen on final pathology.

All patients underwent radical cystectomy and bilateral pelvic lymphadenectomy with urinary diversion. The individual surgeon determined the surgical technique. Limits of the nodal resection varied by surgeon but were bounded at a minimum by the genitofemoral nerve (lateral), bladder (medial), bifurcation of common iliac vessels (cephalad), femoral

canal (caudal) and hypogastric vessels (posterior).⁹ Beginning in 2001 some surgeons implemented extended lymph node dissection as a standard, which includes the traditional dissection plus the common iliac and aortic bifurcation lymph nodes.

For histopathological evaluation the specimens were processed routinely using standard pathology techniques and were reviewed by staff pathologists. The 1997 American Joint Committee on Cancer TNM classification system was used for pathological staging and patients who underwent surgery before 1997 had pathological stage updated.^{10,11} The definition of SCC of the bladder was limited to those exhibiting pure lesions, ie no urothelial component in the radical cystectomy specimen. Urothelial tumors with mixed histological components comprised of keratinization and/or intercellular bridges were defined as SqD.

Followup

At a minimum postoperative followup consisted of a history and physical examination, chest x-ray, blood chemistry assessment and abdominal/pelvic imaging (computerized tomography or magnetic resonance) every 6 months during the first 2 years after surgery. Further evaluation and/or followup were determined on a case by case basis by the treating physician. The cause of death was determined by the treating physician using chart review and death certificates, family death report or by death certificate alone. The majority of patients identified as having died of bladder cancer had progressive, widely disseminated disease and often highly symptomatic metastases at the time of death.

Statistical Analysis

Differences in patient characteristics were tested for using the Mann-Whitney test (continuous variables) and Fisher's exact test (categorical variables). Overall and cancer specific survival were estimated using Kaplan-Meier methods stratified by histological subtype, and curves were compared using a log rank test of equality. Although proportionally there was a large number of deaths in this cohort, we chose to use Cox regression rather than competing risks methods because it is implausible that rates of death from other causes would differ importantly by histological type. Death from causes other than bladder cancer was censored in the disease specific analysis. Pathological stage (localized defined as T2 or less and extravesical defined as greater than T2), positive nodes, soft tissue margins, age and gender were evaluated as predictors of OS and CSS using univariate Cox regression models separately for each histological subtype. Using multivariable methods including interaction terms, we determined whether the relationship between soft tissue margins and survival, and positive lymph nodes and survival differed by histological subtype. All statistical analyses were conducted using STATA[®] 11.0.

RESULTS

Of 2,031 patients who underwent radical cystectomy 78 had SCC and 67 had SqD. Patient characteristics by histology are given in table 1. There were no important differences in age, race, positive lymph nodes and neoadjuvant chemotherapy between the groups. However, patients with SqD were more likely to be male (70% vs 42%, $p < 0.001$). In 7 cases the tumor exhibited areas of divergent differentiation other than SqD including glandular (3 cases), sarcomatoid (2), spindle cell (2) and neuroendocrine (1). Extended pelvic lymph node dissection was performed in 8 (10%) patients with SCC and 10 (15%) with SqD.

Of the 145 patients with SqD or SCC 25 (17%) received neoadjuvant chemotherapy, including 13 treated with gemcitabine and cisplatin, 3 who received taxane based chemotherapy, and 1 who received methotrexate, vinblastine, doxorubicin and cisplatin.

Eight patients received experimental chemotherapy regimens as part of ongoing clinical trials.

Overall there were 104 deaths among patients with SCC and SqD, and 60 died of their disease. Survivors were followed for a median of 3.7 years. Median followup was 1.8 and 3.9 years for survivors with SqD and SCC, respectively. Compared to patients with conventional urothelial carcinoma, overall and disease specific survival were significantly worse for those with SCC (log rank OS $p < 0.001$, CSS $p < 0.001$) and SqD (log rank OS $p < 0.001$, CSS $p < 0.001$).

The Kaplan-Meier probability of OS at 5 years was 40% (95% CI 28–51) for those with SCC and 31% (95% CI 19–43) for those with SqD (part A of figure). The probability of CSS at 5 years was 58% (95% CI 44–70) for those with SCC and 39% (95% CI 26–53) for those with SqD (part B of figure). We did not see a significant survival difference between patients with SCC and those with SqD (log rank OS $p = 0.6$, CSS $p = 0.17$).

In patients with SCC a positive soft tissue margin was the only predictor significantly associated with worse OS (HR 3.68, 95% CI 1.84–7.35, $p = 0.0005$) and CSS (HR 6.92, 95% CI 2.98–16.10, $p = 0.0005$), which was not the case in those with SqD (overall death $p = 0.8$, cancer specific death $p = 0.7$, table 2). In patients with SqD positive nodes were significantly associated with reduced OS (HR 2.52, 95% CI 1.33–4.77, $p = 0.004$) and CSS (HR 3.23, 95% CI 1.57–6.67, $p = 0.002$).

To further investigate this relationship we performed interaction analyses. When looking at the cohort as a whole, there was evidence of interactions between histological subtype and soft tissue margins (interaction term, OS $p = 0.008$, CSS $p = 0.007$), and some evidence of an interaction between histological subtype and positive nodes (interaction term, OS $p = 0.07$, CSS $p = 0.16$). While the interaction between subtype and positive nodes did not meet conventional levels of statistical significance, interaction analyses are typically underpowered. This finding suggests that patients with positive soft tissue margins and SCC have significantly worse survival than those with positive margins and SqD, and patients with positive nodes and SqD are at higher risk than those with positive nodes and SCC.

DISCUSSION

We observed no difference in cancer specific and overall survival between patients diagnosed with SCC and those with SqD after treatment with radical cystectomy. However, compared to patients with conventional urothelial carcinoma, overall and disease specific survival were significantly worse for patients with SCC and SqD.

Differences in pathological factors were associated with survival in each histological variant. In SCC, positive soft tissue margins were associated with adverse oncologic outcomes. These results support previous studies and emphasize the importance of wide surgical resection because of the high likelihood of local failure as the leading presentation of disease recurrence.¹² In SqD, positive lymph nodes were associated with reduced CSS and OS. In these patients the success of treatment may rely on early detection and adequate lymphadenectomy for accurate stage classification and appropriate adjuvant treatment.

Bladder cancer comprises a spectrum of epithelial tumors, the most common of which is urothelial, but also includes SCC, adenocarcinoma and small cell tumors. Additionally, urothelial carcinoma has a propensity for divergent differentiation and the spectrum of microscopic forms of urothelial carcinoma has expanded to include several histological variants, including SqD.¹³ Our results validate previous studies that suggest SqD, compared to conventional urothelial carcinoma, is an adverse pathological feature associated with

worse CSS and OS.^{6,7} The incidence of SqD varies considerably among published series because no strict pathological criteria have been defined.^{7,14,15} Histologically SqD is characterized by the presence of intercellular bridges or keratinization. The WHO recommended classifying SqD as a urothelial carcinoma and reserving the diagnosis of SCC for tumors composed of pure squamous cell carcinoma.¹¹

Consistent with previous comparative studies with conventional urothelial carcinoma, our patients with SCC of the bladder experienced worse CSS and OS.⁸ SqD and SCC may share similar genetic alterations and molecular pathways of dedifferentiation, which may explain why our results suggest comparable outcomes.³⁻⁵ We found that patients with positive lymph nodes and SqD fared worse than those with positive lymph nodes and SCC. This finding may represent a preferential pattern of lymphovascular metastasis attributable to urothelial carcinoma (compared to SCC, which is characterized by pelvic recurrence).¹² In addition, studies have shown that lymphovascular invasion is a strong predictor of outcomes in patients with urothelial carcinoma.¹⁶ Importantly the natural history of disease progression after lymph node metastasis appears to be affected by histology. This is an interesting finding that requires further research. The impact of SqD should be evaluated and possibly adjusted for in cohort studies or clinical trials evaluating the effectiveness of extended lymph node dissection for bladder cancer.

Identification of these adverse pathological features in tumor specimens may impact decisions regarding bladder sparing protocols or prostate sparing radical cystectomy.¹⁷ SCC is associated with resistance to chemotherapy and radiation.^{18,19} These patients may benefit from wide surgical resection and adequate lymphadenectomy to achieve local tumor control. Our finding that a positive soft tissue margin was associated with worse CSS and OS in patients with SCC suggests that pelvic recurrence is lethal. Conversely, patients with positive soft tissue margins and SqD may still benefit from platinum based chemotherapy, which has proven effective for urothelial carcinoma with mixed features, and suggests possible differences in molecular pathways for metastases in pure SCC.²⁰

Our findings must be interpreted in the context of the study design. This study is retrospective, and our results are limited by unmeasured factors affecting selection into treatment and confounding the associations between tumor characteristics and outcomes. Although we were able to control for numerous potential confounders, we were limited by the number of patients to include more predictors in our model. In addition, median followup length was a limitation of our study and potentially introduced bias for survivors in the SCC cohort with shorter median followup. Bladder cancer is a lethal malignancy and the median time to disease recurrence is 12 months.²¹ In addition, disease-free survival at 2 years correlates with long-term survival. Therefore, we do not expect our conclusions to change with longer followup.²² Finally, the proportion of SqD in the pathology specimen could not be obtained from the analysis, which limits the generalizability of the results.

We encourage prospective studies to evaluate the impact on patient outcomes of various treatments for the histological variants of urothelial carcinoma. Furthermore, a universally accepted definition of mixed histology should be developed and documentation should be standardized for future studies. Finally, methods should be developed to identify features of SqD in transurethraly resected tumors that can be applied in prospective studies to evaluate the impact of early detection on survival.

CONCLUSIONS

In this study we demonstrated no difference in CSS and OS between patients diagnosed with SqD and SCC who underwent radical cystectomy. However, compared to patients with

conventional urothelial carcinoma, CSS and OS were significantly worse for those with SCC and SqD. Patients with SqD and positive lymph nodes are at increased risk for mortality, and multimodal adjuvant therapy should be considered. Positive soft tissue margins after RCPLND are prognostic of worse survival in patients with SCC and, therefore, a wide surgical margin is critical to help achieve local tumor control and improve survival.

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Abbreviations and Acronyms

CSS	cancer specific survival
OS	overall survival
RCPLND	radical cystectomy and pelvic lymph node dissection
SCC	squamous cell carcinoma
SqD	squamous differentiation

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Overall survival (A) and cancer specific survival (B) curves for patients with SqD and SCC treated with RCPLND. TCC, transitional cell carcinoma.

Table 1

Summary of patient demographic and pathological characteristics

	SqD		SCC	p Value
Median pt age (IQR)	69 (58, 77)	71 (60, 77)		0.7
No. gender (%):				< 0.001
F	20 (30)	45 (58)		
M	47 (70)	33 (42)		
No. race (%):				0.5
Caucasian	60 (90)	70 (90)		
African-American	5 (7)	3 (4)		
Other	2 (3)	5 (6)		
No. pathological stage (%):				0.6
Localized (T2 or less)	19 (28)	18 (23)		
Extravesical (greater than T2)	48 (72)	60 (77)		
No. lymph node status (%):				0.16
Neg	49 (73)	65 (83)		
Pos	18 (27)	13 (17)		
No. soft tissue margin (%):				0.8
No	58 (87)	63 (81)		
Yes	9 (13)	12 (15)		
Missing	0 (0)	3 (4)		
No. neoadjuvant chemotherapy (%)	11 (16)	14 (18)		0.8

Table 2

Univariate Cox regression of patient and disease characteristics

	SqD			SCC		
	HR	95% CI	p Value	HR	95% CI	p Value
CSS:						
Age	0.99	0.96, 1.03	0.7	0.99	0.96, 1.02	0.6
Male	1.12	0.50, 2.51	0.8	0.71	0.33, 1.55	0.4
Extravesical disease (greater than T2)*	1.61	0.72, 3.60	0.2	1.71	0.65, 4.51	0.3
Pos lymph nodes	3.23	1.57, 6.67	0.002	1.42	0.60, 3.34	0.4
Pos soft tissue margin	1.22	0.47, 3.17	0.7	6.92	2.98, 16.10	<0.0005
OS:						
Age	1.00	0.97, 1.03	0.8	1.00	0.97, 1.02	0.8
Male	1.07	0.56, 2.07	0.8	0.87	0.51, 1.50	0.6
Extravesical disease (greater than T2)*	1.63	0.84, 3.15	0.14	1.59	0.80, 3.17	0.19
Pos lymph nodes	2.52	1.33, 4.77	0.004	1.01	0.51, 2.02	>0.9
Pos soft tissue margin	0.90	0.38, 2.14	0.8	3.68	1.84, 7.35	<0.0005

* Reference category is localized disease defined as T2 or less.