Neoadjuvant chemotherapy in the treatment of muscle invasive bladder cancer with mixed histology

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Introduction: *We examined the effects of neoadjuvant chemotherapy (NC) in the treatment of muscle invasive urothelial carcinoma of the bladder in those with mixed histology (MH) versus those with pure urothelial carcinoma (UC).*

Materials and methods: *Between 2000-2012, 195 patients were identified with clinical stage T2-T4, N0-Nx, M0-Mx UCB who had either NC (+/- radical cystectomy) (n = 63) or radical cystectomy (RC) alone (n = 132). Tumors were classified as either pure UC or MH. Endpoints included downstaging to pT0 and overall survival. Multivariable Cox regression and the Kaplan-Meier method were used to estimate the effects of histological type and treatment given on overall mortality.*

Results: *The rate of downstaging to pT0 was higher in NC treated patients with both MH (p = 0.048) and pure UC (p < 0.0001), as compared to those in each group who did not receive NC. NC was not a significant predictor of overall survival for MH patients in a Cox multivariate model (p = 0.54). However, among all patients treated with NC, MH was found to be a predictor of poorer survival compared to UC (p = 0.02).*

Conclusions: *Prior evidence on the benefits of NC for patients with MH is mixed, but our data suggests that there is improvement in rate of pT0 on final pathology in those treated with NC, regardless of histology. Although patients with MH fare worse than those with pure UC in the setting of NC, given the significantly higher rate of pT0 at final pathology, strong consideration should be given to use of NC in the treatment of MH muscle invasive bladder cancer patients.*

Key Words: neoadjuvant chemotherapy, muscle invasive, mixed histology, bladder cancer

Introduction

There were approximately 73,510 new cases of urothelial carcinoma (UC) of the bladder in 2012.[1] While non-muscle invasive bladder cancer may be treated with transurethral resection (TURBT) and intravesical therapy, treatment for non-metastatic muscle invasive (cT2 or greater) disease is commonly radical cystectomy (RC) with bilateral pelvic lymphadenectomy. The survival benefit of neoadjuvant chemotherapy (NC) has been established, and is an emerging standard of care.[2,3]

While the majority of diagnosed patients have pure UC (95%), a small proportion of patients display concomitant non-urothelial histology, such as squamous cell (< 3%) and adenocarcinoma (< 2%).[4] The prevalence of mixed histological subtypes was recently demonstrated in a study of 448 TURBTs by Wasco et al,[5] which found that 25% of patients had divergent differentiation, of which all but one were invasive at presentation (40% squamous and 18% glandular). Evidence suggests that such histological subtypes have a worse prognosis than pure UC, although the currently accepted treatment for tumors of mixed histologic subtype is generally the same as for pure urothelial cell tumors.[6,7] Studies have demonstrated that patients with muscle invasive UC derive both a survival benefit and have an increased likelihood of eliminating residual cancer with neoadjuvant chemotherapy compared to those undergoing cystectomy alone.[2] The utility of neoadjuvant chemotherapy in treating mixed

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histology (MH) tumors is less established.[8] This study evaluates the role of NC on pathological downstaging and survival of patients with muscle invasive UCB in the context of tumor histology.

Materials and methods

A retrospective review of our institutional review board approved urologic oncology database was conducted to identify patients with clinical stage T2-T4, N0-Nx, M0-Mx UCB treated with either NC (with or without RC) or RC alone between 2000-2012. Clinical staging was defined according to the 6th edition of the Union Internationale Contre le Cancer (UICC) and the 2nd edition of the American Joint Committee on Cancer (AJCC) guidelines. A total of 195 patients fulfilled these eligibility criteria: 132 patients treated with RC alone and 63 patients treated with NC, with 26 of these who did not undergo subsequent radical cystectomy due to complete response. In those treated with NC, 29/63 (46%) received methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and 23/63 (37%) received gemcitabine/cisplatin (GC). The remaining patients were treated with various combinations of gemcitabine, carboplatin, methotrexate, and cisplatin.

Patients were separated into two groups, depending on whether their pathology demonstrated pure UC (n = 161) or MH (n = 34). MH included those who had UC with components of squamous (n = 29) or glandular (n = 5) differentiation based on cystectomy pathology, with biopsy histology used if complete response status was obtained or if cystectomy was not performed. Patients with other histological subtypes (small cell, micropapillary, signet ring cell, neuroendocrine, and clear cell) were excluded to maintain homogeneity of the MH group. Among those with MH treated with NC, 5/12 (42%) received MVAC, 3/12 (25%) received GC, and 4/12 (33%) received gemcitabine/carboplatin. Postoperative surveillance used a combination of CT scans q3-6 months, routine laboratory examination, physical exam, and urine cytology/pathological analysis at the discretion of their physician.

The primary endpoints of this study were overall survival and downstaging to pT0 at cystectomy. Some patients who received chemotherapy with neoadjuvant intent but became cT0 upon restaging by TURBT elected to not undergo radical cystectomy. All of these patients underwent re-TURBT with muscle in the specimen and further biopsy of any suspicious lesions/random bladder biopsies. Since these patients all had no evidence of extravesical disease on CT scan, we classified the absence of intravesical tumor on re-TUR in patients who failed to undergo cystectomy as evidence of disease downstaging to T0. Of the 26 patients who received NC only, 2 (8%) had MH and 16 (62%) were complete responders. Of the complete responders, 12 had random biopsies upon re-TUR, and 9 remained cT0 even upon additional cystectomy after re-TUR. Only 2 patients had documented recurrence of disease. The remaining non-responding patients refused cystectomy (n = 4), were found to have unresectable disease (n = 5), or were lost to follow up (n = 1). Twelve patients had no evidence of residual tumor upon pathological examination of cystectomy (pT0).

The proportions of patients with stage T0 at cystectomy or post-chemotherapy TURBT were compared between the two treatment arms while grouped by histological type using the Pearson chi-squared test. This same method was used to compare proportions of pT0 at cystectomy or post-chemotherapy TURBT between patients with pure UC versus MH grouped by treatment arm.

The effect of NC on all-cause mortality was assessed with the Kaplan-Meier method and the log-rank test. Multivariate Cox regression was also used to determine the effect of NC on overall survival in patients with MH. Survival time was measured from the date of RC (or date of first treatment with NC in those who never went on to receive RC) until the date of death. Primary covariates for the multivariate Cox model included treatment arm (NC +/- RC versus RC alone), age, sex, race, clinical stage, and surgical margin status. Treatment was also analyzed by histological type to determine if the effect of NC in patients with MH was any different in magnitude from the effect of treatment in patients with pure UC. All statistics were performed using Stata 11.0 software (Stata Corporation, College Station, TX, USA). Statistical significance is defined as $p \leq 0.05$, and all p values were two-sided.

Results

Patient characteristics according to their treatment and histological type are shown in Table 1. Among those receiving NC who went on to cystectomy at our institution (n = 37), the median time from first cycle until surgery was 140 days (mean, 190 days; range, 37-964 days). Median time after final cycle until surgery was 61 days (mean, 116 days; range 15-891 days). Median postoperative follow up was 18 months, with 94 total deaths (47%) during the study period. Table 2 shows the proportion of patients who had downstaging to pT0 on final pathology when comparing treatment arms within each histological type. Table 3 shows downstaging information when comparing histological types within each treatment

TABLE 1. **Baseline characteristics of the patients**

Characteristic	Mixed: NC	Mixed: RC alone	Pure UC: NC	Pure UC: RC alone	p value
N	12	22	51	110	
Mean age (yrs)	67	74	66	72	p = 0.0003
Clinical stage - no. (%)					p = 0.004
cT2	7 (58)	18 (82)	46 (90)	102 (93)	
cT3	3 (25)	4 (18)	2 (4)	4 (4)	
cT4	2 (17)	0 (0)	3 (6)	4 (4)	
Sex - no. (%)					p = 0.41
Male	7 (58)	13 (59)	34 (67)	81 (74)	
Female	5 (42)	9 (41)	17 (33)	29 (26)	
Race - no. (%)					p = 0.12
White	6 (50)	17 (77)	42 (82)	80 (73)	
Hispanic	2 (17)	1 (5)	0 (0)	5 (5)	
Black	0 (0)	2 (9)	1 (2)	8 (7)	
Other	4 (33)	2 (9)	8 (16)	17 (15)	

UC = urothelial carcinoma; NC = neoadjuvant chemotherapy; RC = radical cystectomy

TABLE 2. **Downstaging between treatment arms**

Histological type	Treatment arm	N	No. (%) with pT0	p value
Mixed	NC (+/- RC)	12	2 (16.7)	p = 0.048
	RC alone	22	0 (0)	
Pure UC				
	NC (+/-RC)	51	18 (35.3)	p < 0.0001
	RC alone	110	8 (7.3)	

UC = urothelial carcinoma; NC = neoadjuvant chemotherapy; RC = radical cystectomy

TABLE 3. **Downstaging between treatment arms**

Treatment arm	Histological type	N	No. (%) with pT0	p value
NC (+/- RC)	Mixed	12	2 (16.7)	p = 0.21
	Pure UC	51	20 (35.3)	
RC alone	Mixed	22	0 (0)	p = 0.19
	Pure UC	110	8 (7.3)	

UC = urothelial carcinoma; NC = neoadjuvant chemotherapy; RC = radical cystectomy

arm. Treatment with NC resulted in a higher rate of downstaging to pT0 compared to RC alone for both MH (p = 0.048) and UC (p < 0.0001) groups. Figure 1 shows that among patients treated with NC, those with downstaging experienced higher overall survival over time compared to those without downstaging (p = 0.0006) regardless of either UC or MH tumor type.

There was no significant difference in survival comparing patients who received NC versus those treated with RC alone, regardless of histology (p = 0.34), Figure 2. Among those with MH, NC did not confer a significant survival benefit by log-rank analysis (p = 0.41). When comparing overall survival based on histology, those with MH had significantly

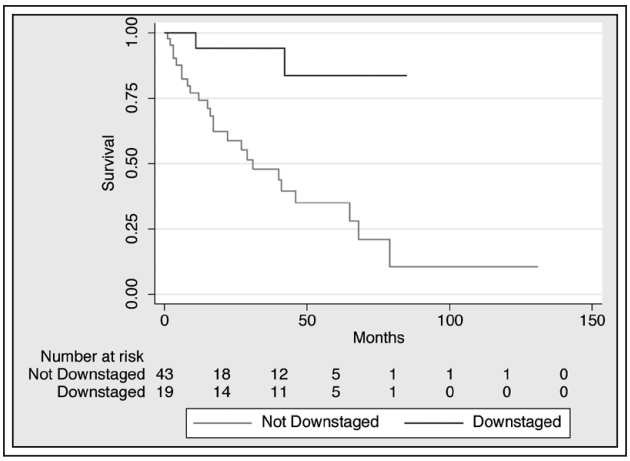

Figure 1. Kaplan-Meier analysis for overall survival in those treated with neoadjuvant chemotherapy stratified by downstaging to pT0.

shorter survival than those with UC (p = 0.04), Figure 3. This finding persisted for the patients who received neoadjuvant chemotherapy (p = 0.02), Figure 4, but was not observed for the patients who underwent immediate RC (p = 0.31), likely reflecting the poor survival for both tumor types, Figure not shown.

The multivariate Cox regression model in Table 4 demonstrates that among MH patients, giving NC did not impart a significant survival benefit (HR = 1.46; 95% CI 0.43-5.00; p = 0.54). Histology did not have any significant interaction with treatment arm (p = 0.40) or clinical stage (p = 0.90). Specifically age, race, sex, and clinical stage were not independently associated with overall survival.

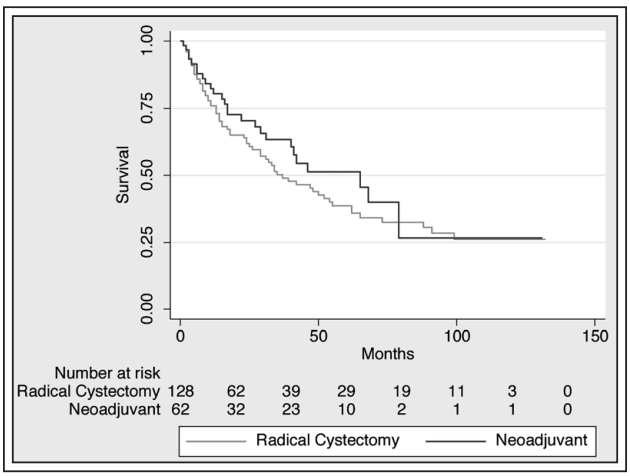

Figure 2. Kaplan-Meier analysis for overall survival stratified by treatment received.

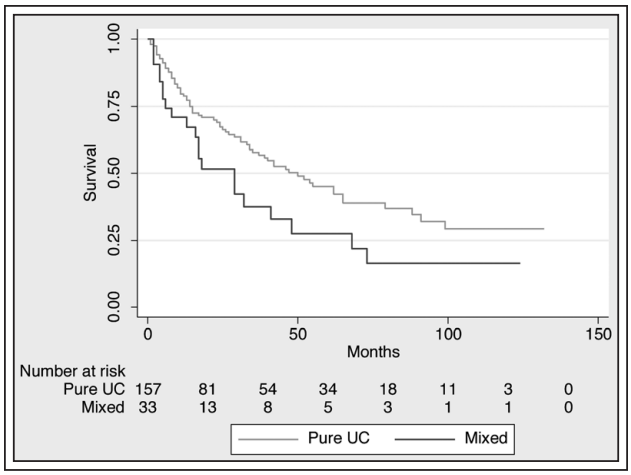

Figure 3. Kaplan-Meier analysis for overall survival stratified by histology.

Discussion

The survival benefit of NC in combination with RC is believed to be in part due to the treatment of micrometastases present at the time of cystectomy.[2,9] Previous trials have shown that cisplatinum based NC prior to cystectomy imparts a 20% reduction in the relative hazard of death among those with invasive urothelial bladder cancer,[10] with meta-analysis showing absolute survival benefit of 6.5%.[11] MH may be seen in up to 41% of cases of muscle invasive disease at final pathology, and it is therefore important to elucidate the impact on survival of neoadjuvant

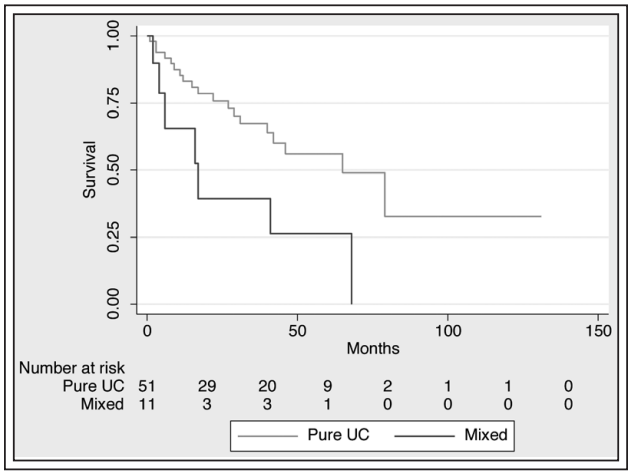

Figure 4. Kaplan-Meier analysis for overall survival among patients treated with neoadjuvant chemotherapy stratified by histology.

TABLE 4. **Overall survival in mixed histology patients**

Variable	HR	95% CI	p value
Age	1.01	0.97-1.06	0.60
Race	1.08	0.67-1.74	0.76
Sex	0.57	0.15-2.18	0.68
Clinical T stage	0.97	0.31-3.04	0.95
Positive surgical margin	4.99	1.42-17.54	0.01
Neoadjuvant chemotherapy	1.46	0.43-5.00	0.54

HR = hazard ratio; 95% CI = 95% confidence interval

chemotherapy in this common pathologic group.[5] MH has traditionally been associated with poorer outcome, with reports that mixed histology subtypes are relatively resistant to MVAC treatment.[12] However, a recent subanalysis of SWOG8710 data indicates that tumors with divergent differentiation treated with NC actually have increased survival compared to those given RC alone (HR 0.46), with significant pathologic downstaging of those with MH who were treated with NC.[8] However, we included all those treated with neoadjuvant chemotherapy with the intent of receiving cystectomy.

Our data demonstrates that while there is no significant survival benefit of administering NC, it did increase downstaging to pT0 regardless of histology: 16.7% in of those with MH ($p = 0.048$) and 35.3% percent of those with pure UC ($p < 0.0001$). Other reports have similarly shown that NC increases downstaging rates, leading to improved prognosis.[11,13] As the survival benefit of NC is considered to be strongly related to stage pT0 at the time of cystectomy, downstaging may be considered a surrogate marker for prognosis.[2,14] Indeed, this concept was confirmed when we compared the survival curves of those who were downstaged compared to those who were not, demonstrating a significantly increased survival in the former group, Figure 1.

While receiving NC is not a significant factor in affecting overall survival, having a mixed tumor is a prognostic indicator for a worse outcome in the setting of NC. Since patients in our study with MH had worse overall survival outcomes than those with pure UC, there is a need to develop treatments to increase the overall survival of this subgroup. Given that there were few patients who had mixed tumors and were treated with NC (n = 12) in our cohort, there is potential for Type II (false negative) error. Thus, if receiving NC offered a survival benefit for MH patients, it could have remained undetected.

A unique feature of our study is the inclusion of those who received chemotherapy with neoadjuvant intent, but never underwent cystectomy because of restaging as cT0 on repeat TURBT. Because of this difference in inclusion criteria, our results have implications to a different subset of patients with bladder cancer compared to prior studies demonstrating a survival benefit for those with muscle invasive bladder cancer given NC.[2,8] While cT0 on repeat biopsy may indicate no evidence of residual disease, a trial conducted by deVere White et al[15] showed that 60% of those determined to be cT0 on TURBT after chemotherapy still had pT2 disease at cystectomy. While our study was limited by not knowing the true pathologic stage at cystectomy of these cT0 patients, the high rate of random biopsies upon re-TUR and cT0 upon repeat cystoscopy after re-TUR in our cohort reinforce its use as a downstaging measure. Furthermore, it is unknown if mixed tumors with a post-chemotherapy cT0 status have increased survival from definitive local therapy or vigilant cystoscopic surveillance. Despite these limitations, our use of cT0 upon restaging TURBT as a measure for downstaging in NC treated patients still demonstrated increased survival in those who were downstaged.

Among those receiving NC, there was a prolonged median latency of 140 days (mean 190 days) between initiation of chemotherapy and cystectomy at our institution. The mean and median latency times were found to be similar to the SWOG8710 study (median 113 days, mean 115 days).[2] Chemotherapy was administered to all patients with neoadjuvant intent; no patient presented to our institution with chemotherapy given previously for another indication. While it is not clear if delaying definitive surgery by giving NC fails to prolong overall survival, studies have shown that among those not receiving NC, delaying cystectomy for more than 3 months from diagnosis of muscle invasion decreases overall survival.[16] This highlights the need to determine which patients are likely to benefit from

chemotherapy immediately after diagnosis.[14] Also, while overall survival among patients undergoing immediate surgery was found to be independent of histology (UC and MH had similar survival when undergoing immediate RC) we cannot deduce that this comparable survival is the result of a lack of delay in definitive treatment, as the retrospective nature of the study precludes determining why these patients underwent surgery without NC.

There are currently no standards to quantify the amount of variant histology present in a bladder tumor, so the heterogeneity in percentages of squamous and glandular differentiation compared to pure UC in our pathological samples is unaccounted for.[17] Prior studies have correlated > 80% urothelial component in MH with prolonged survival time.[12] One limitation of this study derives from the 10 year span over which pathology was analyzed and the lack of a centralized pathology re-review of specimens that predisposes to variation in the interpretation of MH.

The current EAU guidelines recommend that NC be given to patients with clinically operable, muscle invasive (N0 M0) urothelial carcinoma irrespective of further treatment.[3] However, NC should not be considered the primary therapy for these patients, and contraindications would include those with a performance status of ≥ 2 and/or impaired renal function. As patients with squamous or glandular components mixed with UC are treated as if they had pure UC, our results confirm that this represents an accurate algorithm for treatment.

Conclusion

In conclusion, our experience in administering NC in the setting of squamous and glandular differentiation does not indicate resistance to NC, but may in fact warrant its use. The increase in downstaging to pT0 of patients in both pure urothelial cell and MH groups who were treated with NC compared to those who proceeded to radical cystectomy alone highlights the beneficial effect of this treatment modality in preventing adverse pathological outcomes, which may be a surrogate for overall survival. Despite no significant direct survival benefit of NC for patients with mixed tumors, NC should be administered in the clinical setting to treat muscle invasive mixed bladder tumors, as it is not detrimental to overall prognosis and resulted in a significant pT0 rate of 16.7%. Having MH predisposes to a worse survival outcome, which emphasizes the need to delineate biomarkers to detect chemosensitive tumors in addition to developing effective therapies for treatment. □

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(1):10-29.
2. Grossman HB, Natale RB, Tangen CM et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003; 349(9):859-866.
3. Stenzl A, Cowan NC, De Santis M et al. Treatment of muscle-invasive and metastatic bladder cancer: update of the EAU guidelines. *Eur Urol* 2011;59(6):1009-1018.
4. Kantor AF, Hartge P, Hoover RN, Fraumeni JF Jr. Epidemiological characteristics of squamous cell carcinoma and adenocarcinoma of the bladder. *Cancer Res* 1988;48(13):3853-3855.
5. Wasco MJ, Daignault S, Zhang Y et al. Urothelial carcinoma with divergent histologic differentiation (mixed histologic features) predicts the presence of locally advanced bladder cancer when detected at transurethral resection. *Urology* 2007;70(1):69-74.
6. Black PC, Brown GA, Dinney CP. The impact of variant histology on the outcome of bladder cancer treated with curative intent. *Urol Oncol* 2009;27(1):3-7.
7. Rogers CG, Palapattu GS, Shariat SF et al. Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. *J Urol* 2006;175(6):2048-2053; discussion 2053.
8. Scosyrev E, Ely BW, Messing EM et al. Do mixed histological features affect survival benefit from neoadjuvant platiMHm-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis of Southwest Oncology Group-Directed Intergroup Study (S8710). *BJU Int* 2011; 108(5):693-699.
9. Bassi P, Ferrante GD, Piazza N et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 1999;161(5):1494-1497.
10. Sherif A, Holmberg L, Rintala E et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two Nordic studies. *Eur Urol* 2004;45(3):297-303.
11. Winquist E, Kirchner TS, Segal R, Chin J, Lukka H. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. *J Urol* 2004;171(2 Pt 1): 561-569.
12. Jozwicki W, Domaniewski J, Skok Z, Wolski Z, Domanowska E, Jozwicka G. Usefulness of histologic homogeneity estimation of muscle-invasive urinary bladder cancer in an individual prognosis: a mapping study. *Urology* 2005;66(5):1122-1126.
13. Sonpavde G, Goldman BH, Speights VO et al. Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. *Cancer* 2009;115(18):4104-4109.
14. Rosenblatt R, Sherif A, Rintala E et al. Pathologic downstaging is a surrogate marker for efficacy and increased survival following neoadjuvant chemotherapy and radical cystectomy for muscle-invasive urothelial bladder cancer. *Eur Urol* 2012;61(6):1229-1238.
15. deVere White RW, Lara PN Jr, Goldman B et al. A sequential treatment approach to myoinvasive urothelial cancer: a phase II Southwest Oncology Group trial (S0219). *J Urol* 2009;181(6):2476-2480; discussion 2480-2471.
16. Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. *Cancer* 2009;115(5):988-996.
17. Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. *Can Urol Assoc J* 2009;3(6 Suppl 4):S193-S198.