Impact of Maximal Transurethral Resection on Pathological Outcomes at Cystectomy in a Large, Multi-institutional Cohort

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ABSTRACT

Introduction

While the presence of residual disease at the time of radical cystectomy (RC) for bladder cancer is an established prognostic indicator, controversy remains regarding the importance of maximal transurethral resection (TUR) prior to neoadjuvant chemotherapy (NAC). We sought to characterize the influence of maximal TUR on subsequent pathologic and survival outcomes using a large, multi-institutional cohort.

Methods

We identified 785 patients from a multi-institutional cohort undergoing RC for muscle invasive bladder cancer (MIBC) after NAC with data on extent of TUR. We employed bivariate comparisons and stratified multivariable models to quantify the effect of maximal TUR on pathologic findings at cystectomy and survival.

Results

Of 785 patients, 579 (74%) underwent maximal TUR. Incomplete TUR was more frequent in patients with more advanced clinical tumor (cT) and nodal (cN) stage ($p<0.001$ and $p<0.01$, respectively), with more advanced ypT stage at cystectomy and higher rates of positive surgical margins ($p<0.01$ and $p<0.05$, respectively). In multivariable models stratified by cT stage, maximal TUR was associated with complete response (ypT0N0) in patients with more advanced (cT3/4) disease (adjusted odds ratio (aOR) 2.70, 95% confidence interval (CI) 1.09-6.69), as well as with pathologic downstaging (aOR 2.14, 95% CI 1.01-4.52). In Cox proportional hazards analysis maximal TUR was not associated with overall survival (adjusted hazard ratio 0.8, 95% CI 0.6-1.1).

Conclusions

In patients undergoing TUR for MIBC prior to neoadjuvant chemotherapy, maximal resection may improve pathologic response at cystectomy specifically in patients with more advanced cT stage. However, the ultimate effects on long term survival and oncologic outcomes warrant further investigation.

Introduction

Among patients who undergo radical cystectomy (RC) for bladder cancer, approximately half will die of their disease within ten years.[1] Current management paradigms for muscle-invasive bladder cancer (MIBC) include platinum-based neoadjuvant chemotherapy (NAC) in eligible patients prior to RC with an overall survival benefit demonstrated across multiple cohorts compared to surgery alone.[2–4] Patients with the most favorable prognosis following NAC are those who are found to be free of residual tumor at the time of cystectomy (ypT0N0).[5–10]

Less clear, though, is the importance of maximal transurethral resection (TUR) of bladder tumor for both rates of pathological response at RC and long term oncological outcomes. On one hand, complete TUR is able to render some patients pT0 at cystectomy regardless of NAC, which may in turn confer similar survival benefits in node negative patients.[11] For these reasons, maximal TUR is an important component of multimodal bladder preserving therapy in patients who do not undergo cystectomy.[12,13] However, while maximal TUR may debulk the primary tumor within the bladder, unlike systemic therapy it is not able to address occult micrometastasis and so its impact on survival may be more limited. Furthermore, there may be additional perioperative risks such as bladder perforation and bleeding associated with more extensive TUR.

Existing data on the implications of maximal TUR for pathological response and long term outcomes is equivocal and mostly based on single-institution experiences. Some authors have reported improved pT0 rates following maximal TUR, as well as reduced

recurrence and improved survival.[14–17] Conversely, other studies have found limited to no impact of maximal TUR on these same outcomes.[18,19] Specifically, the additional value of maximal TUR prior to NAC followed by cystectomy is unclear. We sought to characterize the effect of maximal TUR prior to NAC on pathologic outcomes at cystectomy and subsequent survival in a large, multi-institutional cohort.

Methods

Study Population

We used data from a large, multi-institutional bladder cancer database of 1,865 patients previously described.[20] Patients were eligible for inclusion if they had muscle-invasive disease at TUR (≥cT2) and histology of primary urothelial carcinoma (UC). Squamous and glandular differentiations of urothelial carcinoma were included. We excluded patients who were missing information on the completeness of TUR (n=938), had baseline metastatic disease (n=17), variant histology other than squamous or glandular differentiation (n=247), and female sex with cT4 disease (n=49). This yielded a final cohort of 785 patients.

Covariates and Outcomes

We included baseline demographic variables (age, sex, smoking status, race, body mass index (BMI)) as well as clinical characteristics from the time of initial TUR (clinical tumor (cT) and nodal (cN) stage, histology, and presence of lymphovascular invasion (LVI)). Maximal TUR was defined as visually complete based on the clinical judgement of the treating urologist. We assessed the chemotherapy agents and the number of

cycles administered. We also obtained tumor and nodal stage as well as the presence of positive surgical margins from the cystectomy specimen.

Primary outcomes were complete pathological response at cystectomy and pathological downstaging. For the purposes of comparison, we created two definitions of complete response: ypT0N0 and ypT0/TisN0. Downstaging was defined as ypT≤1N0.

Statistical Analysis

We used descriptive statistics to characterize our cohort based on extent of TUR. Comparisons were performed with Chi-squared and Fisher's exact tests for categorical data and Student's t-test or Wilcoxon rank sum test where appropriate for continuous data. We then constructed multiple logistic regression models to examine the role of maximal TUR in predicting pathologic response. Covariates were selected in an *a priori* fashion and included age, race (white/nonwhite), sex, presence of lymphovascular invasion at TUR, clinical site of care, and extent of neoadjuvant chemotherapy received (whether the individual received at least 3 cycles of treatment with a regimen including cisplatin). In order to limit the influence of pre-cystectomy tumor stage, we performed stratified modeling by creating separate models for patients with cT2 and cT3/4 disease. Survival analysis was conducted using Cox proportional hazards modeling with the same covariates as our logistic regression models. All analysis was completed in Stata (StataCorp LLC, College Station, TX). Institutional review board approval was obtained from each participating institution.

Results

Baseline characteristics of the 785 patients included are displayed in Table 1, of whom 579 (74%) underwent maximal TUR. Those who received maximal TUR were more likely to be white males with lower cT stage. Table 2 displays the clinical characteristics of both groups. There were some differences in the chemotherapeutic regimens utilized, however no significant differences in the number of chemotherapy cycles administered. In these unadjusted comparisons, patients who underwent maximal TUR were more likely to have a lower pathological stage at cystectomy ($p<0.01$) and less likely to have positive surgical margins ($p=0.02$).

Unadjusted comparisons of outcomes by TUR completeness are displayed in Table 3. A significantly higher rate of downstaging was observed in the maximal TUR group ($p<0.001$), as well as a significantly higher rate of complete response when defined as ypT0/TisN0 ($p<0.01$). When complete response was defined as ypT0N0 at cystectomy there were no significant differences in the unadjusted comparison. In multivariable logistic regression models controlling for baseline characteristics and cT stage at TUR similar results were observed and are displayed in Table 4.

To better understand the effect of maximal TUR independent of cT stage, multiple logistic regression models stratified by cT stage are also displayed in Table 4. Maximal TUR was not a significant predictor of any of the outcomes modeled in cT2 patients, however it was significantly predictive of both definitions of complete response as well as of downstaging in cT3/4 patients. Median overall survival (OS) in this cohort was 4.9

years. Maximal TUR was not significantly associated with OS in unadjusted comparison (hazard ratio 0.8, 95%CI 0.6-1.1).These results were similar after adjustment for patient and clinical covariates (Figure 1).

Discussion

Maximal TUR was associated with pathologic response at cystectomy in this large, multi-institutional cohort of patients with MIBC. This effect was only present in patients with higher cT stage at the time of TUR and was robust across multiple definitions of complete response. However, this did not impact subsequent overall survival. Taken together, these results suggest that while there may be benefit to maximal TUR when safely feasible, at least for the short term prognostic indicator of pathologic response, it remains unclear whether there are associated long term benefits to survival.

These findings help to clarify existing beliefs regarding the importance of maximal TUR prior to cystectomy. Several prior reports have questioned the association between maximal TUR and subsequent outcomes. Zamboni et al. retrospectively examined 727 patients undergoing RC and found that while incomplete TUR was strongly associated with more advanced stage disease at cystectomy, there was no association between TUR completeness and subsequent survival outcomes.[18] Importantly in contrast to our study, their cohort did not receive NAC and the observed rates of T0/Ta/Tis at RC were significantly lower regardless of TUR status when compared to our cohort (2-3% vs. 38%). It is difficult to compare these results directly given the widely disparate rates of complete response, which is a more critical outcome regardless of NAC or TUR extent.[3]

Ghandour et al. reported on 100 patients who received NAC followed by RC, and did not observe any differences in pathological outcomes or subsequent survival outcomes based on TUR completeness.[19] The rates of pathologic response observed in their cohort were similar to our study. Even among patients rendered cT0 by TUR and NAC, Kukreja et al. reported only 36% were ypT0 at cystectomy and did not identify any preoperative factors predictive of pathologic response in multivariable analysis.[21] Conversely, James et al. described an association of maximal TUR with pathologic response at cystectomy, however this relationship only achieved significance in patients who had received NAC.[14] Graffeille et al. found in a cohort of 486 patients, 18% of whom received NAC, that complete TUR was the strongest predictor in multivariable models both for pathologic outcomes (complete response or downstaging) as well as recurrence-free and cancer-specific survival.[17] Columbia University also recently published their institutional results and found that complete TUR was associated with superior survival outcomes as well as pathologic response at cystectomy among patients with clinically localized bladder cancer who received NAC.[16]

In combination with this existing literature, our findings suggest that there may be a benefit to maximal TUR prior to NAC and RC in patients with MIBC. This is consistent with prior work showing that some patients are downstaged by TUR alone, and that these patients have better long term outcomes following cystectomy.[1,11,15,22] Interestingly, in our stratified models we observed that this effect was isolated to those patients with higher stage disease (cT3/4). One possible explanation for this is that the predominant effect of TUR lies in debulking the primary tumor, which is more

pronounced in more aggressive disease, although depth of invasion is not always correlated with overall tumor size. The concept of maximally safe TUR is an important element of trimodal bladder-preserving therapy for these reasons, and incomplete TUR prior to chemoradiation protocols has been associated with subsequent failure and need for salvage cystectomy.[23] These findings argue against the approach of merely using TUR to obtain adequate tissue for diagnosis and then proceeding to NAC and RC. However, these benefits did not translate into a survival analysis in our study. While the hazard ratio for maximal TUR was favorable, it may be that the effect of maximal TUR prior to NAC is outweighed by other factors such as staging of the primary tumor. Interestingly, these implications will likely become more complex as the availability of adjuvant therapies such as nivolumab become more available.[24] The effect of potentially downstaging based on maximal TUR could lead to ineligibility for adjuvant therapy with unclear impacts on overall survival after surgery. The balances of additional costs and morbidity will also need to be carefully weighed.

These results must be interpreted in the context of several limitations. First, this is a retrospective analysis and so subject to some degree of inherent residual bias. Additionally, it is likely that the subjective interpretation of maximal TUR may vary between surgeons. However our analysis controls for clinical treatment site in our multivariable approach, and a strength of this cohort is its large, multi-institutional nature.

Conclusion

We found in a large, multi-institutional cohort of patients undergoing NAC and RC for MIBC that maximal TUR was associated with pathologic response at cystectomy. This effect was isolated to patients with more advanced clinical T stage. We did not observe differences in subsequent overall survival based on TUR completeness. Further research should help clarify longer term outcomes in these patients, and the degree to which maximal TUR may represent a clinical target prior to subsequent treatment.

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Table 1. Baseline demographic and clinical factors.

	Maximal TUR N=579	Incomplete TUR N=206	P value
Age, years (median, IQR)	64 (57-71)	66 (58-73)	0.27
Sex (% male)	84	71	<0.001
Smoking status (% never smoker)	28	25	0.45
Race			<0.01
White	468 (81)	140 (68)	
Black	23 (4)	10 (5)	
Asian	6 (1)	1 (1)	
Other/Unknown	9 (2)	5 (2)	
Missing	73 (12)	50 (24)	
BMI, kg/m^2 (median, IQR)	28 (25-32)	27 (25-31)	0.34
Clinical T Stage			<0.001
cT2	397 (69)	99 (48)	
cT3	135 (23)	93 (45)	
cT4	43 (7)	14 (7)	
Clinical N stage			<0.01
cN0	511 (88)	165 (80)	
cN+	58 (10)	39 (19)	

Table 2. Clinical factors at TUR and cystectomy.

	Maximal TUR N=579	Incomplete TUR N=206	P value
TUR Histology			0.09
UCC	486 (84)	187 (91)	
UCC with squamous differentiation	72 (12)	16 (8)	
UCC with glandular differentiation	17 (3)	3 (1)	
Lymphovascular Invasion at TUR			<0.001
Yes	105 (18)	38 (18)	
No	195 (34)	141 (68)	
Missing	279 (48)	27 (13)	
Chemotherapeutic regimen			<0.001
MVAC*	123 (21)	63 (31)	
GC	348 (60)	119 (58)	
Other	108 (19)	24 (11)	
Chemotherapy cycles			0.07
<3	62 (11)	23 (11)	
3	220 (38)	86 (42)	
4	222 (38)	78 (38)	
>4	33 (6)	15 (7)	
Pathological T stage			<0.01
ypT0	140 (24)	40 (19)	
ypTis/Ta/T1	143 (25)	32 (16)	
ypT2	84 (15)	37 (18)	
ypT3/4	200 (35)	97 (47)	
Pathological N stage			<0.01
ypN0	442 (76)	134 (65)	
ypN+	113 (20)	62 (30)	
Positive surgical margins	51 (8.8)	28 (14)	0.02

*Includes both MVAC and dose dense MVAC

Table 3. Unadjusted pathologic cystectomy outcomes by TUR completeness.

	Maximal TUR	Incomplete TUR	P value
Complete response (ypT0N0)	132 (23)	37 (18)	0.15
Complete response (ypT0/TisN0)	200 (35)	49 (24)	<0.01
Downstaging (ypT≤1N0)	253 (44)	59 (29)	<0.001

Table 4. Unstratified and stratified multiple logistic regression models, reported as adjusted odds ratio (aOR) (95% confidence interval).

Unstratified models*	Maximal TUR aOR
Complete response (ypT0N0)	1.43 (0.89-2.31)
Complete response (ypT0/TisN0)	1.67 (1.08-2.59)
Downstaging (ypT≤1N0)	1.64 (1.08-2.50)
Stratified models**	
Complete response (ypT0N0)	
cT2	1.15 (0.65-2.02)
cT3/4	2.70 (1.09-6.69)
Complete response (ypT0/TisN0)	
cT2	1.37 (0.80-2.33)
cT3/4	3.55 (1.57-8.06)
Downstaging (ypT≤1N0)	
cT2	1.56 (0.92-2.63)
cT3/4	2.14 (1.01-4.52)

* Models include age, sex, race, LVI at TUR, receipt of at least 3 cycles of cisplatin based chemotherapy, clinical site of care, and cT stage.

** Models include the same variables as unstratified models with the exception of cT stage, which was collapsed to cT2 versus cT3/4 and used as the stratification variable.

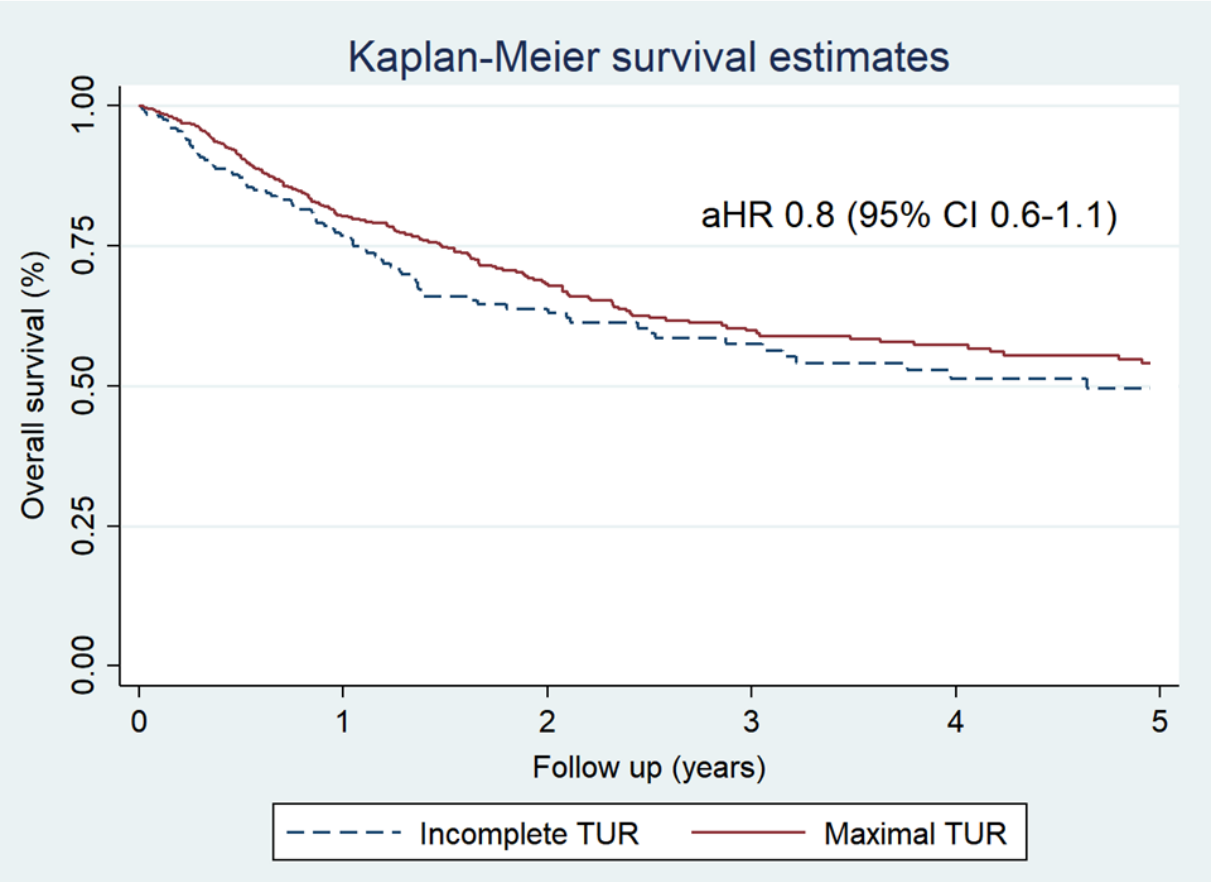

Figure 1. Kaplan-Meier survival estimates of 5 year overall survival stratified by TUR completeness. After adjustment, maximal TUR was not associated with overall survival.