

## Comparison of the Clinical and Pathologic Staging in Patients Undergoing Radical Cystectomy for Bladder Cancer

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### ABSTRACT

*Purpose:* Radical cystectomy (RCx) is perhaps the most effective therapeutic approach for patients with muscle-invasive bladder cancer. Unfortunately, clinical staging is imprecise and the degree of understaging remains high. This study retrospectively evaluated patients undergoing RCx with regard to pathologic outcomes and degree of upstaging to better identify features that may lessen clinical understaging.

*Materials and Methods:* 141 consecutive patients with urothelial bladder carcinoma who were candidates for RCx with curative intent were retrospectively evaluated. Preoperative clinical and pathological (i.e. TURBT) features were compared to pathological outcomes in the cystectomy specimen. Patients were also evaluated as to whether cystectomy was performed as their primary (n = 91) versus secondary (n = 50) treatment for recurrent/progressive disease. Date of cystectomy ( $\leq 5$  years vs.  $> 5$  years prior to study) was also analyzed.

*Results:* Of the 141 patients, 54% were upstaged on operative pathology. The greatest degree of upstaging occurred in those with invasive disease preoperatively (cT2-T3). Twenty-six percent of all patients had node-positive disease, and 75% of cT3 patients were node-positive. Seven of 101 (7%) patients with clinical T2 disease were unresectable at the time of surgery. In the primary (vs. secondary) RCx group, more patients were upstaged (63% vs. 40%), non-organ confined (62% vs. 38%), and LN positive (31% vs. 20%). In the more modern cohort, the degree of upstaging was not improved.

*Conclusions:* Pathologic findings after RCx often do not correlate with preoperative staging. Over half of patients undergoing cystectomy are upstaged on their operative pathology. An improved understanding of the relative frequency of upstaging in cystectomy patients may have important implications in the decision-making and selection for neoadjuvant and adjuvant therapies for these high-risk populations.

*Key words:* bladder cancer; neoplasm staging; cystectomy; pathology

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### INTRODUCTION

After prostate cancer, bladder cancer is the most common urologic and the fifth most common overall malignancy.

In 2005, there were approximately 63,000 new cases of bladder cancer diagnosed and over

13,000 disease-related deaths in the United States (1). The majority of new bladder tumors are superficial (60 - 75%) and of those, up to 20% can be expected to progress to muscle invasive disease (2). Nevertheless, a significant number of muscle-invasive tumors are diagnosed at initial presentation in patients with no prior history of TCCa.

The most common therapeutic approach for invasive bladder cancer is radical cystectomy. Recent improvements in surgical technique and perioperative management have reduced complication rates and operative mortality for this procedure (3,4). Despite the improvements in surgical morbidity, up to 50% of patients undergoing cystectomy will experience local or distant recurrence. Unfortunately, most of these patients who are destined to recur are not easily distinguished upon pre-operative evaluation. Such findings highlight the significant clinical understaging that occurs in bladder cancer patients undergoing cystectomy. Our inability to prospectively identify non-organ-confined disease or systemic micrometastases remains a shortcoming of current preoperative evaluation. Consequently, many patients are upstaged at the time of surgical exploration and extirpation.

This retrospective review sought to characterize patients who are upstaged at the time of cystectomy in order to better identify pre-operative factors, which may contribute to more aggressive/advanced disease. Factors including cross-sectional imaging (and improvements that may have occurred in recent years), impact of bladder-sparing therapies (i.e. those undergoing a primary versus secondary cystectomy), as well as other clinical and demographic factors were also evaluated.

## MATERIALS AND METHODS

We retrospectively examined the medical records of 141 consecutive patients with urothelial cancer of the bladder that underwent radical cystectomy (RCx) for clinically-localized disease and with curative intent from 1990 to 2002. Age, race, gender, tumor grade, clinical stage, pathological stage information for each patient were extracted.

Patients were also analyzed as to whether RCx was performed as primary therapy after their initial diagnosis (primary cystectomy or PRCx) (n = 91), or whether RCx was performed for recurrent or progressive disease after bladder-sparing treatments were first utilized (secondary cystectomy or SRCx)

(n = 50). Of note, PRCx patients had no prior history of intravesical therapies and received no neoadjuvant treatment modalities (e.g. chemotherapy or radiation therapy). In the SRCx group, all patients had received bladder-sparing regimens after their initial diagnosis including intravesical BCG immunotherapy (n = 41), intravesical chemotherapy (n = 8), partial cystectomy (n = 3), radiation therapy (n = 2), or a combination of these modalities.

In addition, comparisons were made with regard to date of cystectomy (before 1997, n = 54 vs. 1997-2002, n = 87) in order to evaluate for possible improvements in clinical staging that may have occurred in the most recent 5 years (e.g. improvements in resolution of cross-sectional imaging).

All cystectomy specimens were received fresh in pathology, opened anteriorly, pinned open and fixed overnight in 10% buffered formalin. The next day, the external aspect of the bladder was inked, and margin sections were taken of the ureters and urethral margins. Standard bladder sections were taken to include 3-4 samples of any grossly visible tumor to include the areas of deepest gross invasion, sections of any mucosal abnormality, and random sections of the dome, anterior, posterior, right lateral and left lateral wall, and trigone. Sections of any attached organs were taken if present. In male patients, two sections of each lobe of the prostate and one section from right and left seminal vesicles were taken as initial sampling, with additional sections submitted if significant findings were present on these initial sections. One section of each submitted lymph node was taken. All sections were routinely processed, paraffin embedded, and stained with hematoxylin and eosin.

The nonparametric Jonkheere-Terpstra method was used to test for ordered differences among categories. With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories. The nonparametric Wilcoxon signed-rank test was used on calculated pair difference values. All p values were adjusted using the Bonferroni method to account for multiple testing or comparisons. Statistical analyses were performed with SAS statistical software, Version 8.2, SAS Institute Inc., Cary, NC.

## RESULTS

The clinical characteristics of the patient cohort are shown in Table-1. Of note, there were no differences in age, gender composition, or racial composition between those upstaged versus those who were not. It should be noted that only 4 patients (2.8%) were classified as low grade or grade-1: all others were classified as high grade or grade-2 or 3. Since the vast majority were classified as moderate or high grade, grade was not therefore not a useful distinguishing or predictive characteristic with regarding to upstaging of disease.

Of 141 patients, 54% were upstaged at pathologic staging. The degree of upstaging stratified by clinical stage is shown in Table-2. The greatest degree of upstaging occurred in those with invasive disease pre-operatively (cT2-T3). Of note, 26% of all patients were ultimately proven to have node-positive disease, and 75% of those with clinical T3

disease were node-positive. In addition, 7 of the 101 (7%) patients with clinical T2 disease were found to be unresectable at the time of surgery (bulky adenopathy, significant local extension/fixation). Those undergoing PRCx were upstaged to a greater degree (63% vs. 40%) for the entire cohort and at each level of clinical stage.

Table-3 shows the clinical stage, and Table-4 demonstrates the pathological staging of the entire cohort. Tables-3 and 4 also stratifies these results based on patients undergoing PRCx vs. SRCx. The median time between diagnosis and cystectomy was significantly different between the PRCx group (2 months; 0-6 months) vs. the SRCx group (22 months; 5 - 149 months). Whereas most patients in the PRCx group were clinical T2 or higher (87%), those patients undergoing SRCx were less often clinical T2 or greater (58%). This difference also was observed upon comparisons of pathological staging as well. More patients were upstaged (63% vs. 40%), non-organ confined (62% vs. 38%), and lymph node positive (31% vs. 20%) in the PRCx versus SRCx group.

The vast majority of all patients underwent CT imaging (11%) with the remainder of patients undergoing MRI (89%). When patients were stratified into those staged  $\leq 5$  years versus  $> 5$  years, a greater percentage of patients underwent CT imaging before 1997 (93%) than in the most recent time period (87%). When patients were stratified into those staged  $\leq 5$  years versus  $> 5$  years there were no significant differences between these time periods with regard to upstaging. (Table-2 and Figure-1).

**Table 1 – Patient characteristics.**

Patient Cohort	N = 141
Mean Age (range)	66 years (32-86 years)
Gender	
Male	100 (71%)
Female	41 (29%)
Race	
Caucasian	122 (87%)
African American	16 (11%)
Other	3 (2%)

**Table 2 – Clinical stage and degree of upstaging.**

Clinical Stage	% Upstaged: All patients	% Upstaged PRCx	% Upstaged SRCx	% Upstaged > 5 years	% Upstaged $\leq 5$ years	% Nodal Disease
Ta,Tis,T1 (n = 33)	30	42*	24	28	33	0
T2 (n = 101)	62	68*	52	54	60	40
T3 (n = 4)	100	100	100	100	100	75
T4 (n = 3)	0	0	0	0	0	33

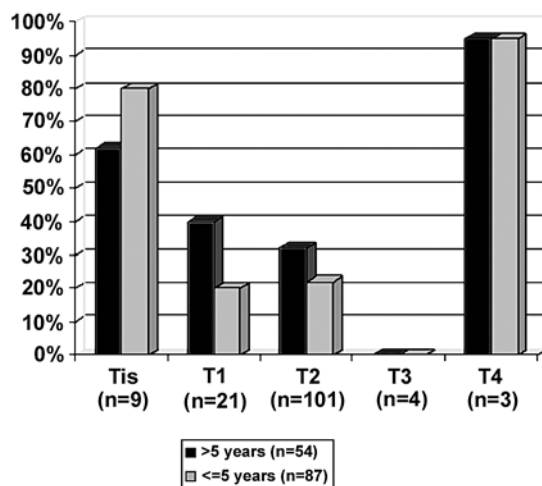
\* $p < 0.05$  vs. SRCx

**Table 3** – Clinical stage of patients undergoing cystectomy.

Clinical Stage	All	Primary RCx	Secondary RCx
≤ T1 (n = 33)	23%	13%*	42%
T2 (n = 101)	72%	81%*	54%
T3 (n = 7)	5%	6%	4%

\**p* < 0.05 vs. SRCx**Table 4** – Pathologic stage of patients undergoing cystectomy.

Clinical Stage	All	Primary RCx	Secondary RCx
≤ T1 (n = 38)	27%	19%*	42%
T2 (n = 29)	21%	20%*	20%
T3/4 (n = 37)	26%	25%	18%
N+ (n = 36)	26%	31%	20%

\**p* < 0.05 vs. SRCx**Figure 1** – Percentage of patients upstaged stratified by clinical stage and date performed.

## COMMENTS

It is clear that patients with clinically-localized disease are not necessarily a uniform population with varying outcomes with regard to operative pathology and, accordingly, disease-free survival (DFS). For example, of patients with clinically-localized disease, those with organ-confined disease (pT0-pT2, N0) on surgical pathology have 5-year DFS rates exceeding 70%, while those who are found to have non-organ-confined disease (pT3-4, N+) have rates of less than 30%. Our inability to prospectively identify non-organ-confined disease remains a shortcoming of current pre-operative evaluation. Consequently, many patients (over half in the present series) are upstaged at the time of surgical exploration and extirpation. To this end, several investigators have sought to identify strategies to better identify and stage such patients pre- and intra-operatively including the use of molecular and immunohistochemical markers (e.g. p53), novel imaging techniques (e.g. photon emission computed tomography/CT (SPECT/CT) and ferumoxtran-10-enhanced MR imaging), and directed (e.g. sentinel node detection) or extended lymph node dissection (5-9).

Nevertheless, several reasons may account for this large degree of surgical upstaging, including delay between diagnosis (i.e. TURBT) and cystectomy. Recent studies have suggested that such a delay is associated with worse pathological findings at the time of cystectomy. Chang et al. have shown that delaying definitive surgery more than 90 days confers a worse pathologic stage with significantly more non-organ-confined disease (2). Similarly, Sanchez-Ortiz et al. have also demonstrated that when cystectomy is delayed greater than 12 weeks, patients had higher pathological stage and overall decreased survival (3). This time period varies from patient to patient as some seek additional opinions, pursue neoadjuvant therapies, or are completing a metastatic evaluation and clinical staging. Nevertheless, such delays may worsen pathological and survival outcomes, and attempts should be made to avoid such a delay.

This study sought to identify whether patients who were delayed from undergoing their radical

cystectomy due to prior bladder-sparing therapies (SRCx) had a higher risk of understaging than those who underwent radical cystectomy as their initial mode of treatment (PRCx). In other words, do initial bladder sparing interventions (e.g. intravesical therapies) contribute to increased surgical upstaging and worse pathological outcomes as compared those who undergo immediate cystectomy? Interestingly, this was not the case. In fact, those undergoing PRCx actually fared worse in the both clinical and pathologic findings and were understaged to a lesser degree, especially in clinical stage T2 and T3 disease. However, the belief that SRCx patients fare better than PRCx patients is almost certainly attributable to a selection bias. Patients in the SRCx group were likely more favorable candidates from the outset: the decision to utilize bladder-sparing therapies are likely due to, in part, more favorable clinical and pathological features. Indeed, this group had a higher percentage of T1 (and CIS) tumors at the initial staging.

Thus, one should not extrapolate that patients will fare better if there is a delay in definitive therapy with regard to radical cystectomy, particularly with invasive disease. It merely suggests that selected patients may be appropriate candidates for bladder-sparing modalities and should not necessarily expect a worse pathologic staging if conservative measures fail and they progress to cystectomy. Still, despite the more favorable outcomes with regard to pathological staging seen in the SRCx group, 40% of these patients were ultimately understaged and 38% had pT3/T4 or node-positive disease at the time of cystectomy. That is, those who receive delay in treatment may still be subject to relatively high incidence of upstaging and extravesical disease on operative pathology. Such findings suggest that some patients in this group would fare better with earlier cystectomy.

In addition to the potential role of delay in upstaging of patients undergoing cystectomy, limitations in the clinical staging of invasive bladder cancer may also lead to surgical upstaging by failing to recognize non-organ confined disease at the time of diagnosis. The lack of an appropriate and reliable serum, urine, or other molecular marker for bladder

cancer forces reliance on standard methodology for clinical staging. Thorough endoscopic resection of all visible tumors (with an appropriate sampling of muscle), bimanual exam, and cross-sectional imaging provide clues in determining the clinical course of bladder cancer. For large volume disease, current CT and MRI can be reliable in determination of clinical stage. Subtle invasive disease or tumors with low volume or small nodes are less accurately staged with these imaging modalities, however. Accordingly, multiple studies have shown disappointing correlation between clinical and pathologic stages using existing axial imaging. Specifically, computed tomography (CT) has been shown to have limited accuracy in correlating clinical to pathologic stages. Paik demonstrated CT accuracy to be around 55% with understaging at 39% (10). Barentsz et al. reported CT accuracy ranged from 40 to 92% but MRI had up to a 30% accuracy improvement over CT (11). Low volume lymph node disease is found in a third of invasive disease, and is difficult to discern on CT or MRI. Herr reported two-thirds of patients in a series with node positive disease were understaged (12). Indeed, our data demonstrates that over half of patients are upstaged on operative pathology, and 7% of clinical T2 patients are found to be unresectable at the time of surgery. Ultimately, CT lacks the ability to reliably detect small volume extravesical disease or demonstrate lymph node metastases. Some have speculated that positron emission tomography (PET) may be useful in prospectively distinguishing localized tumors from regional or distant disease, but recent studies have demonstrated that current PET imaging is at best two-thirds reliable in staging node-positive bladder cancer disease and is still an expensive modality not found at many tertiary centers (13-15).

Even with improved resolution of more recent CT or MRI scanners, better outcomes with regard to clinical staging does not seem to follow. This was evident across the time span of our retrospective review. Despite marked advances in our radiographic modalities, which are integral to clinical staging, we saw no difference in the stage discrepancy in patients who were staged more than 5 years ago compared to those within the past 5 years (Figure-1).

An important limitation of our study is the retrospective nature of this analysis. Such an analysis does not allow for quantification of the degree of upstaging based upon suboptimal transurethral resection or nor does it stratify patients who underwent multiple TUR procedures. Bayrakatar and colleagues published a series that demonstrated substantial overstaging in TUR, which led to premature radical surgery (16). However, Dalbagni et al. showed understaging at the time of cystectomy was negligible in T1 disease after performing a restaging TUR procedures (17). Still, the many differing TUR techniques employed by the referring urologists in this study contribute to added variability of clinical staging.

In addition, a retrospective analysis does not account for the impact of selection bias on those undergoing PRCx versus SRCx, and makes interpretation of those results inherently imperfect (see discussion above). Nevertheless, this report reflects the patient population observed at a tertiary care facility at which the referral population is often varied especially with regard to decision-making for and selection of prior therapies.

Lastly, a large part of this analysis was based clinical and pathologic staging without regard to tumor grade. However, only 4 patients (< 3%) were low grade or grade-1 in this series. In other words, the cystectomy population was almost uniformly high grade, which thereby makes the predictive ability of tumor grade, with regard to upstaging, unattainable.

## CONCLUSION

Pathologic findings after definitive radical cystectomy for urothelial carcinoma of the bladder does not often correlate with preoperative staging. Consequently, more than half of patients undergoing cystectomy will be upstaged on their operative pathology. Patients who undergo secondary RCx (for recurrent/progressive disease after initial bladder-sparing modalities) have more favorable pathology at the time of cystectomy and are understaged to a lesser degree than patients who receive a primary radical cystectomy. However, these findings may be

tempered by a selection bias that is likely found in this subgroup. Still, a significant number of these patients undergoing SRCx will be understaged and found to have extravesical disease at the time of cystectomy. An improved understanding of the relative frequency of upstaging in cystectomy patients may have important implications on the decision and selection for neoadjuvant and adjuvant therapies for these high-risk populations.

## CONFLICT OF INTEREST

None declared.

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## **EDITORIAL COMMENT**

In this retrospective study, authors demonstrate the difficulties in accurate preoperative clinical staging in patients undergoing radical cystectomy (RC). This study highlights several important issues. Firstly, there are no reliable diagnostic tools available to accurately stage bladder cancer (BC). There is an urgent need to develop accurate imaging studies and markers to stage the disease accurately and predict the prognosis. Secondly, this study demonstrates that more than 50% of patients undergoing RC are under staged and

perhaps unfairly denied neoadjuvant chemotherapy. This may support the argument that all patients with  $\geq$  T2 bladder cancer may benefit from neoadjuvant chemotherapy (1).

Timing of RC in patients with CIS and T1 high grade bladder cancer is controversial (2). Accurate staging of patients undergoing intravesical BCG therapy and in those who failed BCG therapy is important as studies have demonstrated disease progression to higher stage ( $>$  T2) in patients undergoing RC (3,4).

Until accurate imaging studies and markers are available, thorough bimanual examination during transurethral resection remains an important staging tool. As authors suggested patients should be formally counseled regarding potential under staging preoperatively.

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