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Authors

Yap, Stanley A
Pugashetti, Neil
Chandrasekar, Thenappan
et al.

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The Promise and Disappointment of Neoadjuvant Chemotherapy and Transurethral Resection for Muscle Invasive Bladder Cancer: Updated Results and Long-Term Followup

Stanley A. Yap,* Neil Pugashetti, Thenappan Chandrasekar, Marc A. Dall'Era, Christopher P. Evans, Primo N. Lara, Jr. and Ralph W. deVere White

From the Department of Urology (SAY, NP, TC, MAD, CPE, PNL, RWdeVW) and Division of Hematology/Oncology, Department of Internal Medicine (PNL), University of California, Davis, University of California Davis Comprehensive Cancer Center (SAY, MAD, CPE, PNL, RWdeVW) and Division of Urology, Department of Surgery, VA Northern California Health Care System (SAY), Sacramento, California

Abstract

Introduction: Radical cystectomy with neoadjuvant chemotherapy is the standard of care for patients with localized muscle invasive urothelial carcinoma of the bladder. One of the strongest predictors of survival in these patients is pathological response to initial treatment. Our objective was to determine whether we could stratify the need for radical cystectomy based on pathological response to neoadjuvant chemotherapy.

Methods: We present a cohort of patients with muscle invasive urothelial carcinoma of the bladder to whom surveillance and bladder preservation were offered if complete response was achieved following neoadjuvant chemotherapy. Descriptive statistics and survival analysis were performed to assess overall, cancer specific and metastasis-free survival. Patients were stratified based on pathological response to neoadjuvant chemotherapy.

Results: A total of 60 patients were included in the cohort, of whom 32 (55%) had absence of residual disease on post-neoadjuvant chemotherapy transurethral resection and 27 (45%) had persistent disease. Of patients undergoing surveillance 52% maintained the bladder without evidence of recurrence. By comparison, of those with recurrence only 20% preserved the bladder and were without evidence of disease.

Conclusions: Long-term followup shows a subset of patients achieving good outcomes while preserving the bladder. However, we also observed an inability to reliably identify this subset of

Abbreviations and Acronyms

CSS = cancer specific survival

MFS = metastasis-free survival

MIBC = muscle invasive urothelial carcinoma of the bladder

NAC = neoadjuvant chemotherapy

OS = overall survival

RC = radical cystectomy

TURBT = transurethral resection of bladder tumor

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* Correspondence: Department of Urology, 4860 Y St., Suite 3500, Sacramento, California 95817 (telephone: 916-724-2823; FAX: 916-734-8094; *e-mail address:* syap@ucdavis.edu).

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patients given current clinical and pathological markers. Until we are able to achieve that goal, the safest oncologic approach remains neoadjuvant chemotherapy followed by radical cystectomy.

Key Words: urinary bladder neoplasms, neoadjuvant therapy, drug therapy, survival

Radical cystectomy with neoadjuvant chemotherapy is the standard of care for patients with localized muscle invasive urothelial carcinoma of the bladder. One of the strongest predictors of survival in these patients is pathological response to initial treatment. Patients demonstrating pT0 disease on radical cystectomy specimen following neoadjuvant chemotherapy benefit from 5-year survival of 85%, compared to 57% among the entire cohort receiving combination therapy (neoadjuvant chemotherapy and radical cystectomy).[1] This finding provided the foundation for using biological response as a marker to guide therapy.

Although less understood and with limited data, the rationale is present for the role of sequential therapy in which patients who are without evidence of disease on post-NAC TURBT undergo surveillance rather than immediate RC. A sequential approach to this disease in patients with pathological response to NAC has been reported with some success in prior institutional series, including work previously published by our own group.[2–4] In the current study we present a cohort in which a sequential strategy of management was used and for which we now have extended followup. These patients offer unique insight into the nature of this disease and how best to treat these individuals given the current understanding and therapeutic methods. Important lessons have been learned from this group, and more importantly, they offer guidance into the future management of this disease.

Methods

Patients

We retrospectively studied patients with nonmetastatic MIBC treated at our institution between 1997 and 2007. Patients with clinical concern for nodal disease were not included, and thus this cohort represents a well selected cN0 population. Patients with primarily urothelial pathology were included, with all other histological variants excluded. All consecutive patients treated by a single surgeon were included in this cohort and subsequent analysis. No specific tumor size limitations were implemented, and inclusion criteria allowed for patients presenting with hydronephrosis, multifocality or carcinoma in situ in biopsy specimens.

All patients underwent at least 1 TURBT elsewhere with attempt at complete resection, although specific margin status was not assessed. All pathology was reviewed at University of California, Davis by a dedicated uropathologist before proceeding with any treatment course. All patients underwent either 3 or 4 cycles of platinum based NAC. The standard platinum based chemotherapy was cisplatin, which most of the patients received. Those who were not eligible for cisplatin received second-line therapy with carboplatin.

On conclusion of NAC patients underwent restaging TURBT and were stratified based on pathology into those with (greater than T0) and without (T0) persistent disease. Patients underwent restaging with chest and abdominal imaging and had to exhibit no radiological evidence of disease (either local or distant) to be classified as T0. Patients with persistent disease underwent immediate RC, whereas patients with T0 status were given the option of initial surveillance. Surveillance included cystoscopy at 3-month intervals, and chest and axial abdominal imaging at 6-month intervals for the first 2 years.

Following a balanced discussion all 32 patients with complete clinical response opted for surveillance. The cohort represented a population of patients treated by a single urological oncologist. The proposed sequential approach was discussed with all patients at the initial consultation, at which point all patients agreed to the approach, which was dependent on pathological response following NAC. Referral patterns and patient interest in this specific physician were largely related to a dedicated interest in the use of NAC as well as exploring options in bladder preservation. The current cohort thus represented a self-selected patient population without specific bias or selection related to disease characteristics.

Statistics

Descriptive analysis was performed for the entire cohort. Primary outcomes identified and reported included radical cystectomy rate and survival (overall, cancer specific and metastasis-free). Patients were stratified based on their pathological response to NAC and assessed within the subgroups of higher than stage cT0 disease following NAC, cT0 following NAC without recurrence and cT0 following NAC with recurrence.

Kaplan-Meier analysis was used to assess overall, cancer specific and metastasis-free survival, and patients were

stratified by disease status following NAC. Cox proportional hazards models were used to assess the association between disease status following NAC and overall, cancer specific and metastasis-free survival.

Results

A total of 60 patients were included in the final cohort, of which 32 (55%) were cT0 on post-NAC TURBT and 27 (45%) had persistent disease. Mean followup for the entire cohort was 60 months. The majority of patients were male (82%), and mean and median ages at diagnosis were 71 years. Following a balanced discussion all 32 patients with complete clinical response opted for surveillance.

Five-year OS, CSS and MFS rates for the cohort were 65%, 73% and 66%, respectively. Five-year survival was divergent among various patient subgroups and was significantly driven by disease status and recurrence pattern. Patients with the worst survival were those with higher than stage cT0 disease on post-NAC TURBT. OS, CSS and MFS rates at 5 years for this group were 51%, 53% and 34%, respectively.

Patients without persistent disease (cT0) following NAC had better survival despite undergoing surveillance rather than immediate RC, with cancer specific and metastasis-free survival rates of 85%. However, outcomes for subsets within this group varied significantly depending on recurrence status (table 1). Among patients initially achieving T0 status following NAC the mean and median times to recurrence were 37 and 23 months, respectively.

Of patients opting for surveillance 17 (52%) maintained the bladder without evidence of recurrence and 15 (48%) had recurrence. Of those with recurrence 7 are disease-free at a mean followup of 133 months, although only 3 have the bladder intact. A total of 7 patients either died of urothelial carcinoma or are alive with metastatic disease, of whom 3 presented with metastatic disease and 4 presented with local recurrence before metastasis (fig. 1). The 4 patients who died of urothelial carcinoma did so at a mean of

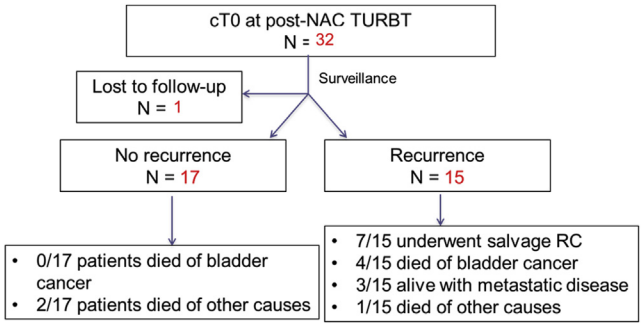

Figure 1. Outcomes in 32 patients opting for surveillance. *N*, number.

26 months (table 2). Of patients who had recurrence with metastatic disease median survival from time of recurrence was 4.5 months.

Kaplan-Meier analysis revealed significant differences in CSS and MFS between subgroups with higher than stage cT0 disease following NAC, cT0 following NAC without recurrence and cT0 following NAC with recurrence ($p < 0.05$, fig. 2). Cox proportional hazards analysis identified significant associations between absence of disease following NAC (cT0) and improved overall (HR 0.36, 95% CI 0.14 to 0.94), cancer specific (HR 0.23, 95% CI 0.07 to 0.75) and metastasis-free survival (HR 0.22, 95% CI 0.09 to 0.55).

Discussion

This unique cohort offers insight into the outcomes of sequential management of this disease. The essential knowledge gained lies in the group of patients with no evidence of bladder tumor on repeat resection and who initially underwent surveillance. These patients fare better than their counterparts with persistent disease despite initially undergoing surveillance and with more than half of the patients having an intact bladder. pT0 status on repeat TURBT was the single strongest predictor of improved survival and continues to be a key marker of treatment response. The initial predictive ability of post-NAC pathological response served as a biological marker that offered promise in its

Table 1.
Five-year survival

	No. Pts	% Overall Survival	% Ca Specific Survival	% Metastasis-Free Survival
All pts*	60	65	73	64
Higher than stage cT0 disease after NAC	27	51	53	34
cT0 after NAC without recurrence	17	83	100	100
cT0 after NAC with recurrence	15	66	73	73

*One patient was lost to followup.

Table 2.
Outcomes and followup of patients with initial cT0 disease on post-NAC TURBT with subsequent recurrence

	No. Pts	Mean Mos Followup (range)	No. Cystectomies (No. pT0N0 disease)
No further evidence of Ca	7	133 (43–203)	4 (2)
Alive with metastatic disease	3	127 (105–158)	2 (2)
Died of urothelial Ca	4	25.5 (13–29)	1 (1)

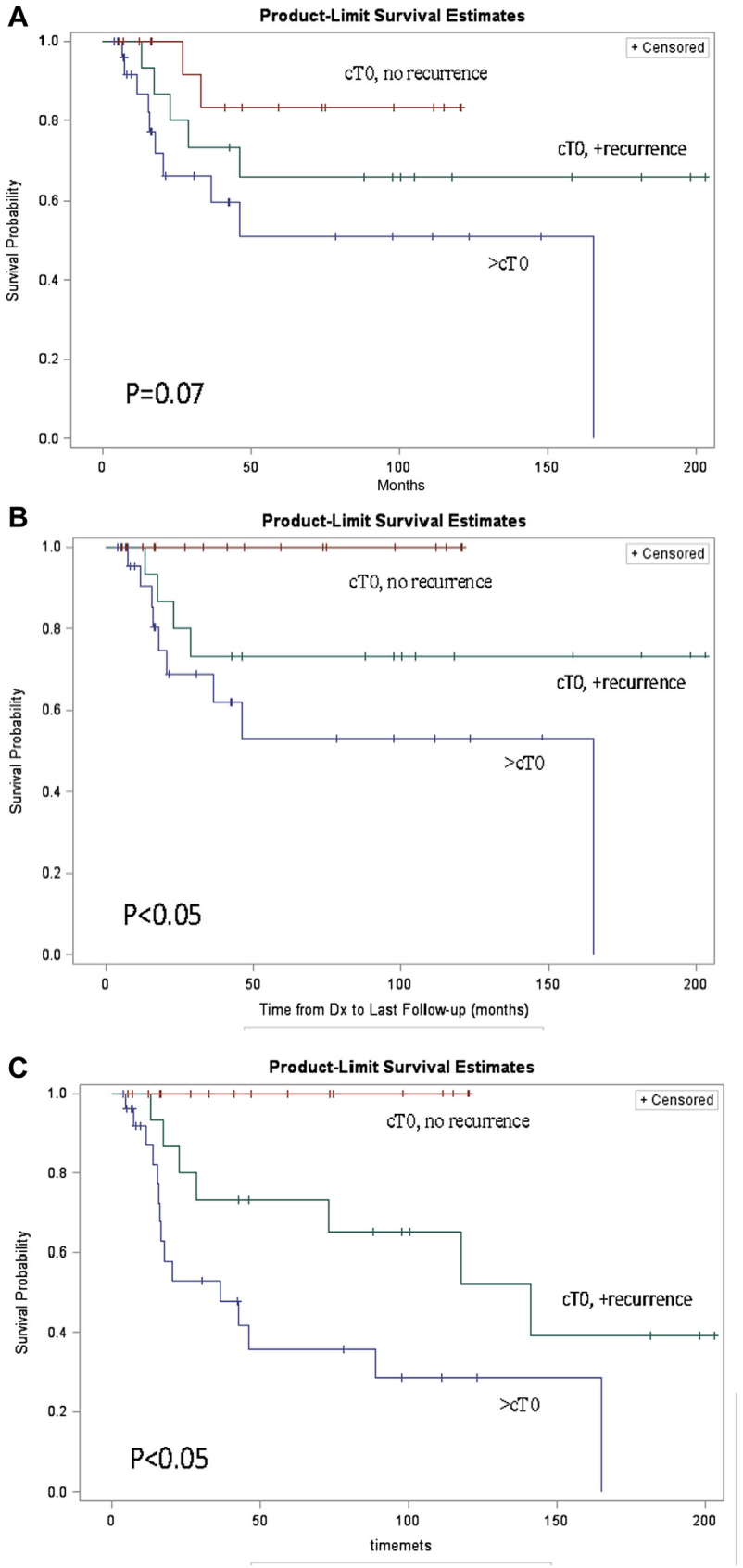

Figure 2. Kaplan-Meier curves for overall (*A*), cancer specific (*B*) and metastasis-free survival (*C*) stratified by disease and recurrence status following NAC for MIBC. Cases were categorized as higher than stage cT0 disease following NAC, cT0 following NAC without recurrence and cT0 following NAC with recurrence. *timemets*, time to metastasis (months).

ability to guide subsequent therapy. Such patients were carefully identified from the entire population with localized MIBC undergoing NAC and radical cystectomy.

Management of MIBC with bladder preservation rather than RC is not entirely novel, with other series describing similar survival ranging from 58% to 76%.[3–7] Treatment protocols and selection criteria vary, although as a whole this strategy appears to provide reasonable outcomes in carefully selected, low risk patients. Initial series assessed the role of radical TURBT as monotherapy in patients with muscle invasive disease, showing reasonable rates of cancer specific and progression-free survival with careful patient selection.[8] Other series have explored protocols similar to the current study using TURBT along with chemotherapy as a bladder preserving approach for muscle invasive disease.[9] Finally, extensive and more contemporary literature exists demonstrating the feasibility of bladder preserving trimodal therapy. Patients undergo TURBT followed by concurrent radiation and chemotherapy. Large series have revealed high rates of complete response and bladder preservation while achieving survival rates similar to cystectomy series, again in patients who have been carefully selected.[10–12] Also among these reports were previously published data from our own institution, where we argue the feasibility of such an approach.[4]

Patients in the current cohort electing to undergo surveillance did not do poorly, with CSS and MFS of 85%. However, with longer followup data it becomes apparent that disease trajectories fall into 1 of 2 distinct categories with divergent outcomes, ie those with recurrence and those without recurrence. With mean followup of 60 months half of the patients maintained the bladder without evidence of recurrence. These individuals would arguably have been overtreated with RC. The other half of patients subsequently had recurrence and had worse survival outcomes. Only 3 of 15 patients remain without evidence of disease with the bladder intact, and 7 of the 15 have undergone salvage cystectomy. Some of these patients may have missed a window of treatment with immediate RC as several presented with metastatic disease or had progression despite salvage RC. Markedly worse outcomes in this subset of patients must be appreciated, as there remains room for improvement.

The current data offer room for interpretation regarding thresholds for supporting such a bladder preserving approach and determining landmarks for survival at which point such a therapy could be considered feasible. Finding the balance of reducing morbidity without compromising recurrence and survival is difficult. Although the current series shows reasonable outcomes with careful selection, the longer followup indicates rates of failure that are unacceptable, especially given that many of these failures may have been preventable with immediate radical cystectomy. The burden of morbidity associated with radical cystectomy is significant but potentially preventable disease progression and cancer specific mortality shifts that balance back toward the standard of care of NAC and radical cystectomy.

Understanding the limitations of this retrospective, single institution analysis the long-term followup of this cohort reveals that a subset of patients are able to achieve good outcomes with preservation of the bladder. However, we also demonstrate the inability to reliably identify these patients given clinical features and pathological response to NAC. Absence of persistent disease (cT0) following NAC, although initially hypothesized to be an adequate marker, is insufficient to identify patients not requiring immediate RC. We present a therapeutic approach with less than ideal outcomes but as inspiration to continue work to better understand how to stratify patients and reliably assess treatment response in this disease. Until we are able to achieve that goal, the safest oncologic approach remains NAC followed by RC.

Conclusions

We present long-term followup of a cohort of patients with MIBC who achieved complete response following NAC and were treated with surveillance and bladder preservation. We observed a subset of patients achieving good long-term outcomes while preserving the bladder. However, we also show the inability to reliably identify this subset of patients given current clinical and pathological markers. Until we are able to achieve that goal, the safest oncologic approach remains NAC followed by RC.

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Editorial Commentary

The authors present a series of patients who had a complete clinical response (cT0) to neoadjuvant chemotherapy given for cT2N0 or greater urothelial cell carcinoma. Those with a complete response were offered observation. In this small, retrospective, nonrandomized series 52% of patients who achieved a complete response remain cancer-free.

The study has some significant shortcomings, which the authors acknowledge, including lack of data on initial clinical stage, completeness of initial resection and type or number of cycles of chemotherapy. The importance of this information cannot be overstated. A completely resected small cT2 tumor is likely quite different from a large cT3 tumor with multifocal carcinoma in situ, where complete resection is unlikely. Indeed, patients with a pathological complete response (ypT0) at cystectomy who had cT4 disease before chemotherapy have been shown to have significantly inferior survival compared to those with lower stages.[1]

Also, of the 48% of patients who did not remain cancer-free half died (or will die) regardless of whether they underwent cystectomy. Although it is encouraging that many patients with a complete response to neoadjuvant chemotherapy will remain disease-free, it is also disheartening to know that a proportion of patients who have the best clinical response to chemotherapy, and who are likely to be cured by consolidation cystectomy, die of their disease. Therefore, I agree with the authors that until we can accurately predict which patients are likely to remain disease-free without cystectomy, we must continue to advocate for cystectomy following neoadjuvant chemotherapy.

Jeffrey M. Holzbeierlein
Department of Urology
University of Kansas Health System
Kansas City, Missouri

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