Incidence, Clinicopathological Risk Factors, Management and Outcomes of Nonmuscle Invasive Recurrence after Complete Response to Trimodality Therapy for Muscle Invasive Bladder Cancer

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Purpose: We describe the incidence, clinicopathological risk factors, management and outcomes of recurrent nonmuscle invasive bladder cancer after a complete response to trimodality therapy of muscle invasive bladder cancer.

Materials and Methods: We retrospectively reviewed the records of 342 patients with cT2-4aN0M0 muscle invasive bladder cancer and a complete response after trimodality therapy from 1986 to 2013. Using competing risks analyses we examined the association between baseline clinicopathological variables and nonmuscle invasive bladder cancer outcomes. Kaplan-Meier and the generalized Fleming-Harrington test were used to compare disease specific and overall survival.

Results: At a median followup of 9 years nonmuscle invasive bladder cancer recurred in 85 patients (25%) who had had a complete response. On Kaplan-Meier analysis baseline carcinoma in situ was associated with recurrent nonmuscle invasive bladder cancer ($p = 0.02$). However, on multivariate analysis carcinoma in situ and other baseline clinicopathological characteristics did not predict such recurrence. Patients with recurrent nonmuscle invasive bladder cancer had worse 10-year disease specific survival than those without recurrence (72.1% vs 78.4%, $p = 0.002$), although overall survival was similar ($p = 0.66$). Of the 39 patients (46%) who received adjuvant intravesical bacillus Calmette-Guérin 29 (74%) completed induction therapy and 19 (49%) reported bacillus Calmette-Guérin toxicity. Three-year recurrence-free and progression-free survival after induction bacillus Calmette-Guérin was 59% and 63%, respectively.

Conclusions: After a complete response to trimodality therapy nonmuscle invasive bladder cancer recurred in 25% of patients, developing in some of them more than a decade after trimodality therapy. No baseline clinicopathological characteristics were associated with such recurrence after a complete response. Patients with nonmuscle invasive bladder cancer recurrence had worse disease specific survival than those without such recurrence but similar overall survival. Adjuvant intravesical bacillus Calmette-Guérin had a reasonable toxicity profile and efficacy in this population. Properly selected patients with recurrent nonmuscle invasive bladder cancer after a complete response may avoid immediate salvage cystectomy.

Key Words: urinary bladder neoplasms; neoplasm invasiveness; neoplasm recurrence, local; BCG vaccine; mortality

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
CR = complete response
DSS = disease specific survival
MIBC = muscle invasive bladder cancer
NMIBC = nonMIBC
OS = overall survival
PFS = progression-free survival
RC = radical cystectomy
RFS = recurrence-free survival
SRC = salvage RC
TMT = trimodality therapy
TURBT = transurethral bladder tumor resection

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TRIMODALITY therapy with maximal TURBT followed by concurrent chemoradiation is a viable alternative to RC in select patients with MIBC.[1,2] A recent NCDB (National Cancer Database) review estimated that 7.6% of patients with MIBC in the United States from 2004 to 2008 received TMT or radiation therapy alone.[3] In select patients TMT can provide an equivalent chance for long-term survival and allow patients to maintain the native bladder. CR rates of 70% to 80% have been reported with 5-year DSS rates of 60% to 70%.[2,4]

In patients who receive TMT there is a 13% to 40% risk of intravesical recurrence of NMIBC or MIBC after a CR.[5] SRC is indicated in patients without a CR to TMT and in those with recurrent MIBC after an initial CR.[6] However, clinicopathological risk factors and optimal treatment strategies in patients with NMIBC recurrences after an initial CR are less clear.[7,8] Furthermore, data are lacking on response rates and the tolerability of intravesical BCG for NMIBC recurrences in this population.

In this study we examined the incidence and clinicopathological risk factors associated with NMIBC recurrences after a CR to TMT. In addition, we describe the management and oncologic outcomes associated with recurrent NMIBC with a focus on the tolerability, toxicity and efficacy of adjuvant intravesical BCG.

MATERIAL AND METHODS

Patient Cohort

We performed an institutional review board approved retrospective review of the records of 342 patients with a CR to TMT for MIBC, including 85 in whom NMIBC subsequently developed, from September 1986 to April 2013 at our institution. The 133 incomplete responders to TMT were excluded from study (fig. 1).

Trimodality Therapy Protocol Design and Treatment

The protocol included patients with cT2-T4aN0M0 MIBC and an adequately functioning bladder. Institutional protocols changed during the study period and were described previously.[2,4,9] Briefly, after maximally safe TURBT[10] the patients were treated with induction radiation sensitizing chemotherapy and 40 Gy external beam radiation therapy. CR was assessed after induction chemoradiation and defined as a normal examination with the patient under anesthesia with negative urine cytology and cystoscopic biopsy at the original tumor site and any suspicious areas. Those with a CR then received consolidation therapy consisting of an additional 24 to 25 Gy external beam radiation therapy. Adjuvant cisplatin based chemotherapy was administered in some patients contingent on comorbidities and treatment protocol.

Followup

Patients underwent examination under anesthesia, cystoscopy with biopsy of the initial tumor site and visibly concerning lesions, and urine cytology after induction and consolidation chemoradiation. Thereafter office cystoscopic surveillance and urine cytology were performed every 3 months for the first 2 years, every 6 months for years 3 to 5 and yearly for life thereafter. Surveillance also included axial imaging of the chest, abdomen and pelvis.

Incomplete responders after induction or consolidation chemoradiation were advised to undergo immediate SRC, which was also performed if recurrent MIBC was identified during surveillance. At the discretion of the treating urologists NMIBC recurrences were considered for TURBT with or without intravesical therapy, or SRC based on recurrence pathology, patient performance status, bladder function and comorbidities. Recurrence followup depended on pathological stage and chosen treatment.

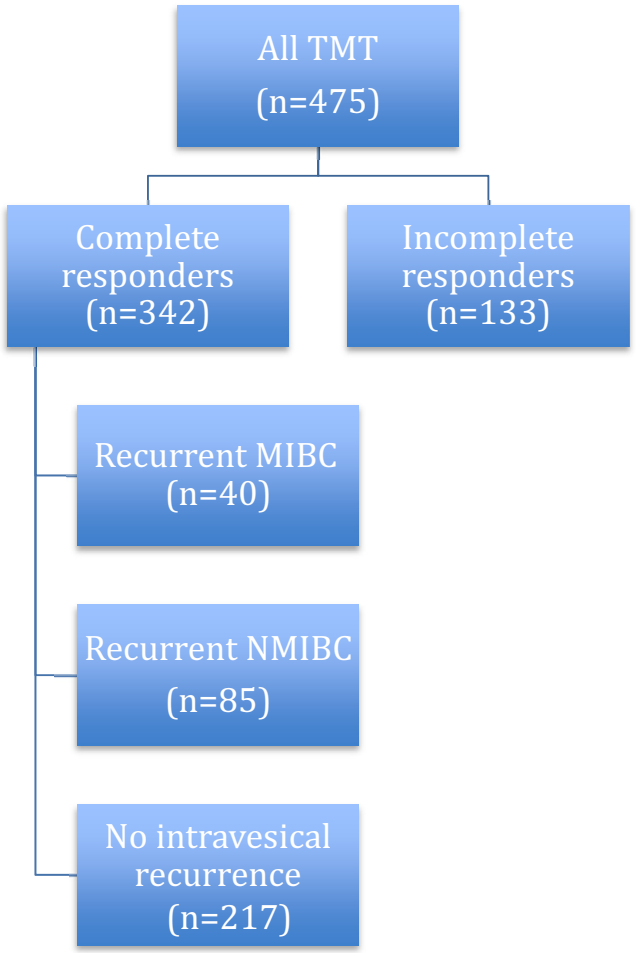

Figure 1. Initial response and intravesical recurrences in all patients treated with TMT.

Outcomes and Survival End Points

Time to NMIBC recurrence was defined as the years from the start of TMT to recurrence. The site of recurrent NMIBC (at or not at the site of the original MIBC) was not