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Predictive factors for time to progression after hyperthermic mitomycin-C treatment for high risk non-muscle invasive urothelial carcinoma of the bladder: an observational cohort study of 97 patients

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Abstract

Background

Hyperthermic mitomycin-C (HM) is becoming established as a viable management alternative to radical cystectomy for patients with high risk non-muscle invasive bladder cancer (NMIBC).

Objective

To determine predictors of response to HM.

Design, Setting, and Participants

A longitudinal, cohort study of 97 patients with high risk NMIBC in a large, academic hospital in London.

Intervention

All cases received ≥4 HM instillations on a prophylactic schedule.

Outcome Measurements and Statistical Analysis

The primary outcome was time-to-progression (TTP) survival; secondary outcomes were overall survival (OS), cancer-specific survival (CSS), and adverse events. Descriptive statistics, Kaplan-Meier survival analyses, Cox proportional hazards modeling, and univariate and multivariable regression were performed.

Results and Limitations

Presence of complete initial response (no evidence of disease at first check video-cystoscopy and urine cytology) post-HM treatment was an independent predictor of good response to HM. Female patients and those without carcinoma in situ (CIS) also appeared to respond better to the intervention. The overall bladder preservation rate at a median of 27 months was 81.4%; 17/97 (17.5%) patients died over the course of the study. The study is limited by its follow up length and consequent number of events, and by missing information on important covariates like smoking history.

Conclusions

High risk NMIBC patients can be safely treated with HM and have good oncologic outcome. However, those without a complete initial response have a poor prognosis and should be counseled towards other treatment such as cystectomy. Female gender and lack of CIS may be good prognostic indicators for response to HM.

Patient Summary

HM is a safe alternative to bladder removal in many patients with high risk NMIBC. However, if there is any sign of disease at the first post-treatment check then the prognosis is poor and other treatments should be considered. Women and those without CIS might do better with HM.

Introduction

Urothelial carcinoma of the bladder is the second most common urologic malignancy in the United States with non-muscle invasive tumors accounting for 70-80% of cases. These tumors often recur and can progress to muscle invasion and metastatic disease, with high mortality rates. Hence, prevention of recurrence and progression is the mainstay of management; this requires frequent endoscopic surveillance and instillations, making non-muscle invasive bladder cancer (NMIBC) the single-most expensive cancer to treat[1, 2]. NMIBC can be characterized into risk categories using clinico-pathologic prognostic criteria; high risk patients have risks of recurrence and progression of 54-82% and 15-48% respectively[3]. While radical cystectomy prevents recurrence and progression in virtually all cases of high risk NMIBC it poses significant morbidity to the patient[4]. Hence, intravesical therapies such as bacillus Calmette-Guerin (BCG) are usually employed first-line. However, only 70% respond initially to this therapy and by 5 years more than half of cases have relapsed[5]; at that stage radical cystectomy remains the current gold standard. Newer therapies for high risk NMIBC especially in the BCG-failure setting are thus badly needed.

Intravesical chemotherapy alone, most commonly with mitomycin-C (MMC), has been shown to be inferior to BCG in treatment-naïve high risk NMIBC, and has not been found to be effective in BCG failures[6]. Sydenham in 1666 said, “Fever is a mighty engine which nature brings into the world for the conquest of her enemies”, and investigators have evaluated the role of combining thermal energy with chemotherapy in this disease, so-called hyperthermic mitomycin C (HM)[7]. An updated study of 83 patients with intermediate and high risk NMIBC randomized to HM *versus* MMC alone demonstrated 10-year disease-free survival rates of 53% and 15% respectively[8]. A systematic review of 22 studies suggested a

59% relative reduction in NMIBC recurrence when HM was compared to MMC alone, and a higher bladder preservation rate with HM[9]. Postulated mechanisms of action of HM are: transient and reversible damage to the bladder epithelium to increase the penetration of MMC into the bladder lining, increasing the permeability of MMC into tissue interstitium by increasing its diffusion coefficient, and directly improving the cytotoxic, anti-proliferative, and apoptotic effects of MMC[1, 10, 11]. Clinically, it is important that non-responders to HM are identified early such that subsequent cystectomy is not delayed and survival outcomes compromised; it has been shown that cystectomy performed within two years of initial BCG therapy improves outcomes[12]. However, none of the current literature has addressed this, and thus the purpose of the current study is to identify such predictive factors using a large observational cohort.

Methods

All 104 patients referred for treatment with HM at St.George's University Hospital, London, UK, from the start of the program in June 2006 until October 2013 were identified; the catchment area encompassed most of Southern England (*circa* 5 million people). All HM patients had high risk NMIBC as defined by 2014 EAU guidelines[13]. Patients were given an induction regimen with weekly treatments for 6-8 weeks with HM with Synergo system SB-TS 101 (temperature of 41-44C). Patients were assessed with 3-monthly cystoscopy and biopsy and urine cytology, plus annual CT/MRI. Those with complete or partial initial response continued on a 2-year maintenance regimen.

Cases were excluded from this study if given HM as part of an ablative strategy (n=3), if unable to tolerate side-effects and thus did not receive ≥4 instillations (n=3), and if they had

disease progression during the induction course which was therefore abandoned (n=1). No patients were excluded due to technical inability to perform the treatment; cases with prior pelvic radiation (n=9), cardiac pacemakers (n=6), on steroids (n=4), hip prosthesis (n=2), renal transplant (n=1), and neurogenic bladder (n=1) were all successfully treated. The final study cohort consisted of 97 patients.

Endpoints

The primary endpoint was time-to-progression (TTP), defined as the period of time between the date of start of HM treatment and the earliest date of detection of any of: institution of further treatment (BCG, cystectomy, radiotherapy, diverticulectomy), muscle invasion, extravesical disease, or distant metastases. For those patients who died without evidence of progression or who did not experience disease progression during the course of the study, survival times were censored at the last follow up alive and progression-free date, or date of death, as appropriate. Secondary endpoints were complete initial response (CIR), cancer-specific survival (CSS), overall survival (OS), and adverse events.

Statistical Methods Demographic and clinico-pathologic information for the study cohort was summarized using descriptive statistics. Presence or absence of carcinoma in situ (CIS) was indicated in both stage and grade classifications. Charlson comorbidity index (CCI) was recorded without age-adjustment [14] so that comorbidity and age could be included in the analysis as separate covariates. TTP survival was analyzed using Kaplan-Meier plots, log-rank tests and Cox proportional hazards modeling to adjust for prognostic factors. For exploration of multivariable models the number of covariates included did not exceed the

nearest integer of the ratio: number of events/20 [15].

Initial response was assessed at first check cystoscopy and urine cytology post-HM treatment. Stepwise regression, using Cox proportional hazards for TTP and logistic regression for initial response was undertaken where variables significant at 10% in the univariate model were included. The final multivariable model included those covariates which were significant at the 5% level. Overall and cancer-specific survivals were assessed only in terms of descriptive analysis with summary of follow-up time using the method of 'reverse Kaplan-Meier' [16]. Adverse events were recorded on a per patient basis for all study participants in a descriptive fashion.

Results

Table 1 reports the patient-tumor covariates of the study cohort. Most cases were male (81/97; 83.5%) and the median (IQR) age at the time of first instillation was 73 (66-79) years. 73/97 (75.2%) patients had the presence of CIS; one-half of patients (49/97; 50.5%) had high grade cancer as defined by the 1973 WHO grading system[17]. 80/97 cases (82.5%) had received BCG, one-sixth of whom (13/80; 16.3%) had also received other intravesical therapies. Most patients (55/97; 56.7%) had significant co-morbidity (≥ 1 on CCI). 70/97 subjects (72.2%) had a CIR, defined as no evidence of disease on first check video-cystoscopy and bladder biopsies as well as negative urine cytology, after HM induction course completed; others were pooled together into a no CIR category (27/97; 27.8%) for subsequent analysis.

Table 2 presents the joint frequency distribution of stage and grade in the study cohort. Since these variables may present collinearity when included in a multivariable analysis, a composite variable 'StageGrade' was generated by grouping all patients with any CIS together, and the non-CIS subjects separated by standard grade and stage categories (Table 3).

Primary Endpoint

60/97 (61.9%) patients did not progress over the study with a median (IQR) follow up of 27 (16-47) months; Figure 1A. In addition, there were 2 deaths that were presumed due to bladder cancer despite no evidence of disease progression before death, as no other cause of death could be ascertained. Of those that did progress, 18/35 (51.4 %) cases underwent radical cystectomy, with few subjects (3/35; 8.6%) being managed by other treatments (BCG, chemoradiation, and diverticulectomy). 14/35 (40%) patients progressed without further treatment being provided over the study period (Table 4). Of the subjects that underwent cystectomy, most had CIS alone on final histology (12/18; 66.7%), with 2/18 (11.1%) having no evidence of malignancy, and the remainder (4/18; 22.2%) having high grade bladder cancer varying from pTa to pT3 stage. None had nodal disease. 3/18 (16.7%) had CIS at the ureteral margin, and 15/18 (83.3%) had negative surgical margins. Figure 1B shows that TTP was significantly worse in males ($p=0.03$); also, the presence of any CIS was associated with a trend towards worse survival ($p=0.11$; Figure 1C). However, neither patient co-morbidities nor prior treatments affected TTP (data not shown). CIR though was very highly significantly associated with an improvement in TTP survival ($p<0.0001$; Figure 1D); median TTP for patients with no CIR was 1 year whereas more than half of CIR patients survived (after censoring) without progression for the duration of the study. For the Cox proportional

hazards, only grade and initial response were statistically significant at the 5% level; the test of assumption of proportional hazards and the plot for the final model showed that the assumption was valid (data not shown).

Secondary Endpoints

Initial response was assessed at a median (IQR) of 12 (10-15) weeks after the first HM treatment. One patient died between treatment completion and the first check cystoscopy, and was considered as no CIR for analysis purposes. Only gender was significant at the 10% level on univariate analysis and was the only factor therefore included in the multivariable model; however, it did not reach statistical significance (data not shown).

17/97 (17.5%) patients died over the course of the study; 7/17 (41.2%) died of bladder cancer and 10/17 (58.8%) of other causes; Kaplan-Meier plots are shown in Figures 2A & 2B for OS and CSS, respectively. The median follow up time was 31 months for OS and 29 months for CSS (data not shown). No deaths in the study cohort occurred in females and no deaths from bladder cancer occurred in patients that did not have CIS. Mortality was lower among those who achieved CIR (62/70; 88.6%) *versus* NCIR cases (18/27; 66.7%) surviving to the end of follow up.

In relation to adverse events from HM therapy that occurred at any time during the treatment period, 7/97 (7.2%) patients were hospitalized due to hematuria (n=3), urinary sepsis (n=3), and transient non-specific abdominal pain (n=1); all cases were managed conservatively and discharged home within 48 hours. 43/97 (44.3%) subjects suffered from moderate to severe cystitis-type symptoms including dysuria, nocturia, and bladder spasms, 24/97 (24.7%) patients had hematuria, and 14/97 (14.4%) got a urinary tract infection; all of these adverse events were self-limiting and none resulted in treatment abandonment.

Discussion

In this observational cohort of 97 patients referred from a catchment area of 5 million people in Southern England and treated with HM, most (61.9%) did not progress during the course of the study; the bladder preservation rate for the entire cohort was 81.4%. Significant predictors of progression were non-complete initial response, CIS, and male gender.

Hyperthermia causes inhibition of cellular respiration and synthesis of DNA, RNA, and proteins, blocking the cells in the S phase of the cell cycle; if cell repair mechanisms are not effective, this causes cell death[18]. Clinical trials in sarcoma, melanoma, tumors of the head and neck, lung, esophagus, breast, peritoneal organs, and genitourinary tract have all confirmed a synergistic effect of hyperthermia with chemotherapy[1]. Early studies in bladder cancer demonstrated that HM had an ablative effect on incompletely resected tumors[7, 19], and later studies confirmed its use in prophylaxis for high risk NMIBC, both pre- and post- BCG[6, 8, 18, 20-26]. Of 75 patients with primary or recurrent NMIBC that completed a randomized trial of MMC alone *versus* HM, 53% were tumor-free after 10 years and 86% had preserved their native bladders[8]. Another study of 24 patients with high-grade NMIBC received prophylactic HM and had a bladder preservation rate of 95.8% after a mean follow-up of 35.3 months[7]. While both these studies demonstrated higher bladder preservation rates than our study, this is likely due to the lower risk population they treated, including all risk categories of NMIBC in the first study and excluding CIS in the second study. Interestingly, in our study, CIS patients did significantly worse after HM, being more likely to be dead at final follow up (19.2%) than those with Ta (11.1%) or T1 (16.7%); no bladder cancer deaths occurred in non-CIS patients in our cohort. To our knowledge no other publication has examined the impact of CIS in the prognosis after HM. Another reason for

our comparatively low bladder preservation rate was that the vast majority (82.5%) of our cohort were BCG failures, 16.3% of whom had also failed other intravesical therapies. Nativ et al. treated 111 patients with recurrent papillary NMIBC (non-CIS and not limited to high risk cases) after prior BCG with HM and found a progression rate of only 3%[21], far lower than our rate of 38.1%; reasons for this are likely to be the adverse prognostic factor of CIS in our cohort, inclusion of non-high risk cases, and a shorter average follow up of just 16 months in their study. Due to this short follow up and consequent few outcome events, the study was unable to identify significant predictors of outcome after HM and found no difference in survival based on gender or grade, while in our study higher grade was associated with worse prognosis; further, no females died in our study bringing up the intriguing and novel hypothesis that women are more responsive to HM than men.

The most important predictor of progression in our study was no CIR, assessed at *circa* 3 months following the first instillation; CIR had an overwhelming decreased risk of progression with a hazard ratio of 0.144 on multivariable analysis, making this a potentially highly clinically useful method to determine which patients will respond well to HM.

The main rationale for HM prophylaxis is to avoid the morbidity and mortality of radical cystectomy which has been shown to be similar for NMIBC and muscle-invasive disease[27]; hence, it is imperative that HM is safe and tolerable. Prior studies have all confirmed this, with dropout rates due to adverse events being consistently below 10%[20-22]. In our study, 3/104 (2.9%) cases did not complete the induction course due to intolerable side effects and were not part of the final study cohort. The relatively tolerable side-effect profile of HM in our experience is consistent with other studies[7, 20, 21]; a systematic review of 22 studies found that adverse events after HM were not significantly higher than after MMC alone[9]. Further, in our study several patients with challenging medical conditions all successfully underwent HM.

Our study has some limitations; it is an observational cohort study with no control arm, and thus we cannot accurately make conclusions about the comparative effectiveness of HM *versus* other treatments. However, this has been investigated in other studies and is the subject of ongoing randomized trials comparing BCG to HM (clinicaltrials.gov; NCT00384891 & NCT01094964); our purpose herein was rather to examine predictors of response to therapy. Also, our study follow up was too short to determine predictors of survival; however, it is well established that progression rates in this population correlate well with mortality rates and are thus a good oncologic surrogate. Further, we lack data on important covariates that might have confounded our results, most notably smoking history, and this might at least partially explain why we found better outcomes in females.

The main finding of the current study is that any sign of disease on endoscopy or cytology at 3 months after HM is a strong indication to proceed to further therapy such as cystectomy; whether men and patients with CIS respond less well to HM is worthy of further investigation.

Conclusion

Hyperthermic mitomycin-C was safe, well tolerated, and efficacious in this observational Southern English cohort, confirming results of Continental European studies. Those with CIS and male gender appear to be poor responders to HM, though this requires further investigation. Importantly, histologic and cytologic confirmation of no evidence of disease on initial check at 3 months is highly predictive of a good response and rescinds the need for further other therapy.

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Legends

Figure 1. Kaplan-Meier time-to-progression analyses for: (a) the entire cohort (n=97); (b) male *versus* female patients; (c) cases with any carcinoma in situ *versus* no carcinoma in situ; (d) subjects with a complete initial response *versus* those without

Figure 2. Kaplan-Meier survival analyses for the whole cohort (n=97): (a) overall survival; (b) cancer-specific survival

Table 1. Baseline clinico-pathologic data for the whole cohort (n=97)

Table 2. Frequency distribution of stage and grade for the whole cohort (n=97)

Table 3. Combined variable for stage and grade as distributed in the study cohort

Table 4. Types and frequency of progression among the study cohort

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Figure 1

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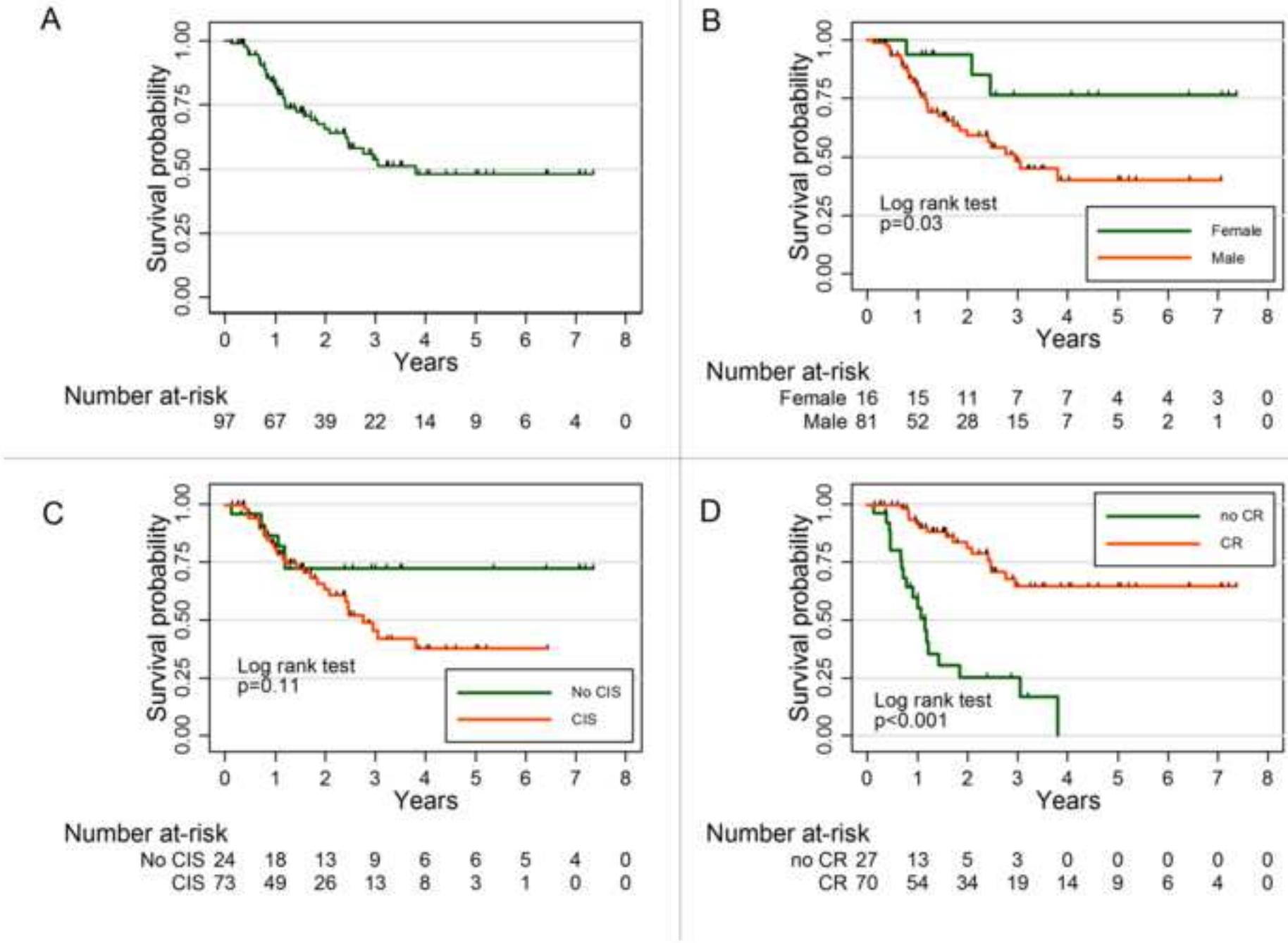

Figure 2

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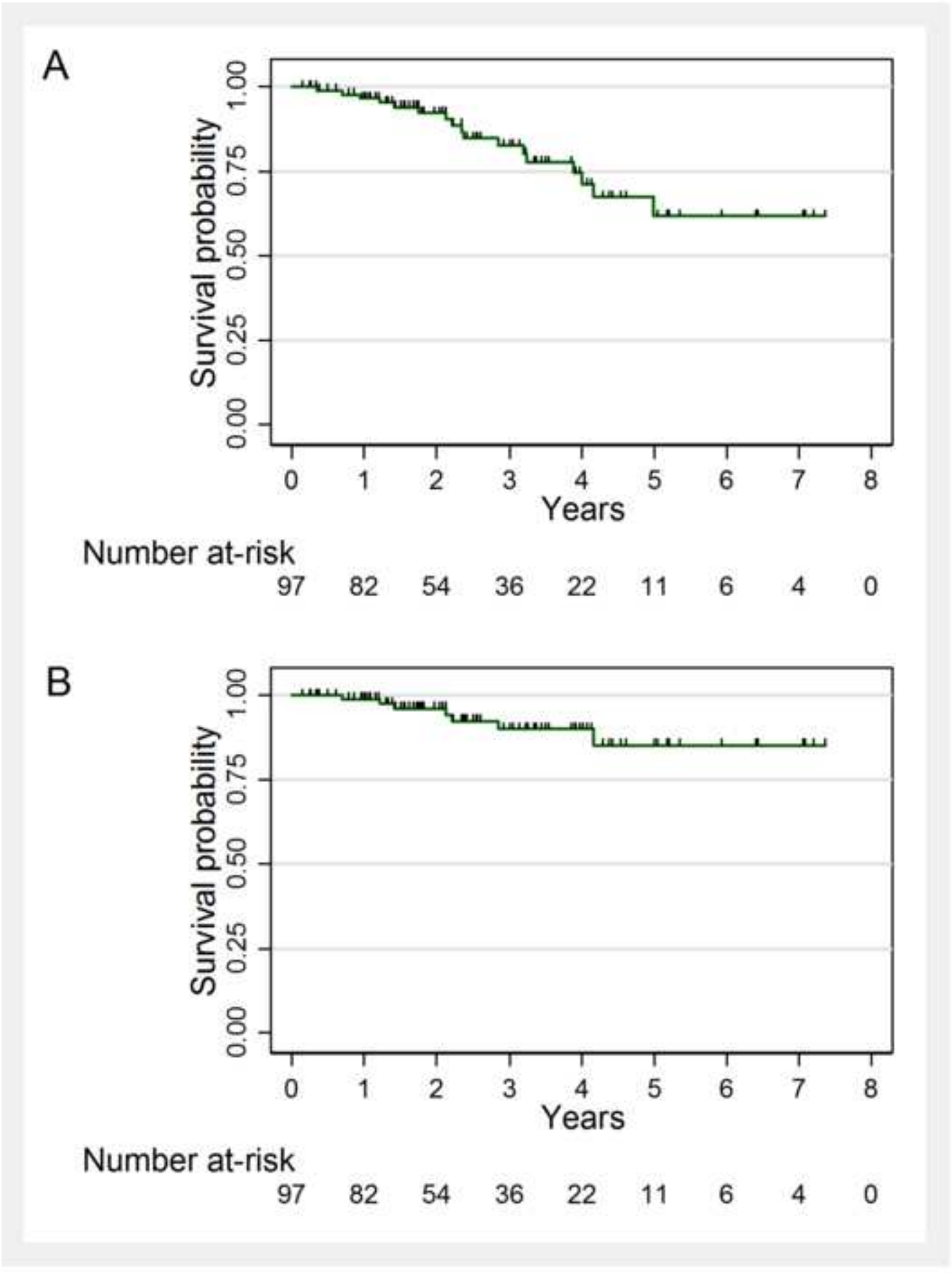

Table 1

Demographics and clinical characteristics	**Median**	**IQR**
Age	73	12
	n	**%**
Sex		
F	16	16.5
M	81	83.5
Stage		
Ta, no CIS	18	18.6
T1, no CIS	6	6.2
CIS only	31	32.0
Ta + CIS	21	21.6
T1 + CIS	21	21.6
Grade		
Moderate grade	17	17.5
High grade	49	50.5
N/A (CIS only)	31	32.0
Prior Treatments		
None	9	9.3
BCG only	67	69.1
BCG+other	13	13.4
Other	8	8.2
Charlson comorbidity Index		
0	42	43.3
1	35	36.1
2	15	15.5
3	5	5.1
Number of initial set of MMC-H treatments		
4	5	5.1
5	5	5.1
6	62	64.0
7	9	9.3
8	16	16.5
Initial response		
no CR	27	27.8
CR	70	72.2

IQR = interquartile range; CIS = Carcinoma in situ; BCG = Bacillus Calmette–Guérin vaccine; MMC-H = mitomycin hyperthermia; CR = complete response.

Table 2

Stage	Grade Moderate Grade	High Grade	N/A (CIS only)	Total
Ta, no CIS	10 55.6%	8 44.4%	0 0.0%	18 100.0%
T1, no CIS	0 0.0%	6 100.0%	0 0.0%	6 100.0%
CIS only	0 0.0%	0 0.0%	31 100.0%	31 100.0%
Ta + CIS	5 23.8%	16 76.2%	0 0.0%	21 100.0%
T1+ CIS	2 9.5%	19 90.5%	0 0.0%	21 100.0%
Total	17 17.5%	49 50.5%	31 32.0%	97 100.0%

n; %.
CIS = Carcinoma in situ.

Table 3

StageGrade	*n*	*%*
any CIS	73	75.3
Moderate Grade - Ta	10	10.3
High Grade - Ta	8	8.2
High Grade - T1	6	6.2

CIS = Carcinoma in situ.

Table 4

Progression	*n*	%
No progression	60	61.9
BCG	1	1.0
EV disease	9	9.3
Chemoradiation	1	1.0
Cystectomy	18	18.6
Death	2	2.1
Diverticulectomy	1	1.0
Mets	4	4.1
Muscle invasion	1	1.0

BCG = Bacillus Calmette–Guérin vaccine;
EV = extravesical

Take home message

No evidence of disease at the first post-therapy check cystoscopy and urine cytology is suggestive of a good response to treatment with hyperthermic mitomycin in high risk non-muscle invasive bladder cancer. Women and those without CIS may also fare better.