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The Natural History of Untreated Muscle Invasive Bladder Cancer

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ABSTRACT

Objective: To describe the natural history of untreated muscle invasive bladder cancer (MIBC) and compare the oncological outcomes of treated and untreated patients.

Methods: We utilized a database encompassing all patients with newly-diagnosed bladder cancer in Stockholm, Sweden between 1995-1996. The median follow-up for survivors was 14.4 yrs. Overall, 538 patients were diagnosed with BC of whom 126 patients had clinically localized MIBC. Patients were divided in two groups: those who received radical cystectomy or radiation therapy and those who did not receive any form treatment. Multivariable Cox or competing risks regressions were adopted to predict metastasis, overall survival (OS) and cancer specific mortality (CSM), when appropriate. Analyses were adjusted for age at diagnosis, sex, tumor stage, clinical N stage and treatment.

Results: 64 (51%) patients did not receive any definitive local treatment. In the untreated group, median (IQR) age at diagnosis was 79 (63-83) yrs versus 69 (63-74) in the treated group ($p<0.001$). Overall, 109 patients died during follow-up. At 6 mo after diagnosis, 38% of the untreated patients had developed metastatic disease and 41% experienced CSM. The 5-yr OS rate for untreated and treated patients was 5% (95%CI: 1,12%) versus 48% (95%CI: 36,60%), respectively. Patients not

receiving any treatment had a 5-yr cumulative incidence of CSM of 86% (95%CI: 75,94%) versus 48% (95%CI: 36,60%) for treated patients. Untreated patients had a higher risk of progression to metastatic disease (HR: 2.40; 95% CI: 1.28,4.51; p=0.006), death from any cause (HR:2.63; 95%CI: 1.65,4.19; p<0.001) and CSM (SHR:2.02; 95%CI: 1.24, 3.30; p=0.004).

Conclusions: Untreated patients with MIBC are at very high risk for near term cancer specific mortality. These findings may help balance the risks versus benefits of integrating curative intent therapy particularly in older patients with MIBC.

Keywords: Bladder Cancer; Natural history; Urothelial Cancer; Metastasis; Overall Survival.

1. Introduction

Bladder cancer (BCa) represents the 9th most commonly diagnosed cancer worldwide. In 2018, approximately 549,000 patients were diagnosed with BCa and roughly 200,000 succumbed to the disease. (1)

The prognosis and treatment modalities for BCa vary according to the stage at presentation. Non-muscle invasive BCa has a non-negligible risk of recurrence, but is associated with a relatively good prognosis in the context of standard treatment. Alternatively, despite curative intent treatment with radical cystectomy (RC) with pelvic lymph node dissection (PLND) and perioperative chemotherapy for the

treatment of muscle-invasive bladder cancer, a large subset of patients with MIBC still develop metastatic recurrence. (2-4)

Despite advances in diagnostic techniques and the availability of new biomarkers, (5, 6) approximately 25% of newly diagnosed patients will have muscle-invasive bladder cancer MIBC, and this value has remained overly stable with time. (7, 8)

The median age at diagnosis of BCa is slightly higher than 70 years.(9) Thus, medical comorbidities are not unlikely in this patient population and advanced age might pose the question whether treatment should be recommended or not. In fact, RC with PLND is associated with non-negligible rates of morbidity and mortality. (10-14)

To the best of our knowledge, the natural history, or anticipated survival without treatment, of MIBC has not yet been described. Addressing this point is not only relevant from a biologic perspective but it also represents a critical factor for patients and clinicians when weighing risks and benefits deriving from radical treatment.

In this study, we relied on a population-based dataset in an aim to describe the natural history of patients with MIBC who did not receive any additional treatment after transurethral resection of the bladder tumor (TURBT). The oncological outcomes in this group were compared to the ones of patients who received treatment with curative intent.

2. Materials and methods

2.1 Study population

All patients diagnosed with urothelial carcinoma of the urinary bladder, by means of TURBT, from January 1995 and December 1996 in the Stockholm (SE) county were prospectively collected in a population-based cohort consisting of 538 patients. (15) Histopathological results were reported according to the initial tumor, node, metastasis (TNM) classification from 1978. At the time of data collection, the Bergkvist classification had been used for tumor grading. (16) However, all the specimens were re-graded in 2001 by a single pathologist in accordance to the World Health Organization (WHO) 1999 malignancy grading system. (17) For the purpose of this study we analyzed 126 patients diagnosed with non-metastatic MIBC (cT2-4NanyM0). Treated patients receive definitive local treatment by means of radical cystectomy with extended pelvic lymph node dissection or radiation therapy.

2.2 Outcome, variables definition and follow-up

The primary endpoint of the present study, overall survival (OS), was defined as the occurrence of death from any cause. Cancer specific mortality (CSM) was defined as death secondary to BCa; all the other events were considered as other cause mortality (OCM). Time to the event was calculated from the time of TURBT.

The variables considered for the analysis included: age at diagnosis, sex, clinical stage, tumor grade, tumor size and treatment (yes versus no). Tumor size was estimated at the time of TURBT. For the treated patients, the treatment modality was also retrieved.

All patients were followed with cystoscopy and cytology every three to six months for two years and cystoscopy annually thereafter. Patients with high grade tumours were followed every three months continuously. Tumor recurrences were treated with TURBT. Vital statistics and cause of death were identified from death certificates. All patients were followed-up until death or to the most recent doctor's visit. The timing of imaging during follow-up was left at physician's discretion.

2.3 Statistical analysis

Descriptive statistics including frequencies and proportions were reported for categorical variables while medians and interquartile ranges (IQR) were reported for continuous variables. Differences between medians and frequencies were estimated with the Kruskal-Wallis test and the $\chi 2$ test, respectively.

The Kaplan-Meier method was employed to evaluate progression to distant metastasis and OS; whereas the cumulative incidence method was adopted to estimate CSM, after accounting for the competing event, *i.e.* OCM. The log-rank test was used to test the equality of the Kaplan-Meier survivor functions while the Pepe-Mori test was used to test the equality of the cumulative incidence functions.

A multivariable Cox model was generated to predict metastasis and OS, whereas a multivariable competing risks regression was used for the prediction of CSM, after accounting for OCM. All the analyses were adjusted for age at diagnosis, sex, clinical stage, tumor stage, and treatment administration.

Statistical analyses were performed using Stata 14 (StataCorp MP, College Station, TX, USA). All tests were 2-sided with a significance level set at $p<0.05$.

3. Results

3.1 Study population characteristics

Descriptive characteristics of the study population are reported in **Table 1**. Overall, 64 (51%) patients did not receive any definitive local treatment [39 (61%) men and 25 (39%) women]. Among these patients, 8 (8%) received palliative chemotherapy. A total of 62 (49%) patients received treatment with curative intent with radiation therapy [15 (24%)] or radical cystectomy [47 (76%)]. The median (IQR) age of the non-treated patients was 79 (73, 83) while the median (IQR) age in the treated group was 69 (63, 74), $p<0.001$.

Patients who did not receive treatment had higher tumor stage [T2: 36 (56%) and T3-4: 28 (44%)] versus those who received treatment [T2: 47 (76%) and T3-4: 15 (24%)], p=0.02. No differences were detected concerning sex, tumor grade, tumor size and clinical lymph node status.

3.2 Survival analysis

The median follow-up for survivors was 14.4 yrs; 109 patients died from any cause during follow-up, 63 and 46 in the untreated and treated groups, respectively. The median time to death from any cause was 9 versus 42 months in the untreated and treated group, respectively. Six, nine and 12 months after diagnosis, 41%, 50% and 58% of the patients in the untreated group had died. The 5-year OS rate for untreated patients was 5% (95% CI: 1, 12%) versus 48% (95% CI: 36, 60%) of the

patients who received treatment (p<0.001). The Kaplan-Meier survivor functions for the two groups are depicted in **Figure 1**.

In total, 59 patients progressed to distant metastasis, 30 in the untreated group and 29 in the treated group. The median time to metastasis was 14 months versus 180 months for the untreated and treated groups, respectively. Six, nine and 12 months after diagnosis, 23%, 30% and 35% of the patients in the untreated group had progressed to distant metastasis. The 5-year distant metastasis-free survival for untreated patients was 26% (95% CI 12%, 43%) versus 57% (95% CI 43%, 69%) for those patients who received treatment (p<0.001). The Kaplan-Meier functions for the development of distant metastasis are displayed in **Figure 2**.

Overall, 89 patients experienced CSM, 55 in the untreated group; and 34 in the treated group. There were 8 patients who died from other cause in the untreated group versus 12 among those who received treatment. The median time to CSM was 10 and 71 months in the untreated and treated group, respectively. At 6 months after diagnosis, 38% of the untreated patients had succumbed to BCa versus 6.5% in the untreated group.

Patients not receiving any treatment had a 5-year cumulative incidence of CSM of 86% (95% CI: 75, 94%) versus 48% (95% CI: 36, 60%) of the patients who received treatment (p<0.001); the 5-year OCM rate in the untreated cohort was 9% (95% CI: 4, 18%) versus 3% (95% CI: 1, 10%) in the treated cohort (p=0.6). **Figure 3** displays the cumulative incidence functions for patients who did not receive any form of treatment and for those who received treatment with curative intent.

On multivariable analyses, after adjusting for age at diagnosis, sex, clinical stage, tumor stage, and treatment, untreated patients had higher risk of death from any cause (HR: 2.63; 95% CI: 1.65,4.19; p<0.001), progression to distant metastasis (HR: 2.40; 95% CI: 1.28,4.51; p=0.006) and CSM (SHR: 2.05; 95% CI: 1.26, 3.34; p=0.004), **Table 2**.

Discussion

The natural history of superficial bladder cancer has been thoroughly described by Lee and Droller, (18) but there is still a fundamental lack of knowledge regarding patients with MIBC who do not receive definitive local therapy. The fundamental understanding regarding the natural progression of MIBC is especially important in balancing the risks of cancer-related morbidity and mortality versus treatment-related morbidity and mortality in older patients. Indeed, RC is associated with non-negligible morbidity as well as mortality (10-14) and radical treatment may affect patients' urinary, bowel, sexual function, self-image, and thus overall quality of life. (19) While the risks of definitive local therapy, such as radical cystectomy, have been described in detail and models have been developed to individual risk estimates and facilitate patient counseling, (10) the risks of leaving MIBC untreated have been markedly understudied. As a result, many treatment discussions, particularly in older patients, center on the potential complications associated with treatment in the context of the perceived competing risks of morbidity and mortality.

In an effort to dissect the natural history of untreated BCa we leveraged a population-based database, represented by the Swedish cohort. This cohort comprised all patients diagnosed with bladder cancer in 1995-1996. Among them,

126 patients were diagnosed with MIBC, 51% of the patients did not receive any form of treatment, whereas the remaining 49% received treatment with curative intent, by means of either surgery or radiation therapy. Only age and tumor stage were significantly different between the two groups. However, despite the advanced age at diagnosis, 86% of the non-treated patients experienced CSM within 5 years of TURBT with a median time to CSM of 10 months. Furthermore, the OCM rates for the treated and untreated cohorts were 3% and 9% respectively. Even with advanced age, patients diagnosed with MIBC were significantly more likely to die due to cancer than other causes.

Notably, almost half of the patients diagnosed with non-metastatic MIBC did not receive treatment with curative intent. This might be attributed to the advanced age at presentation but also to the potential comordibities of this subgroup of patients. Additionally, almost three decades ago, the imaging and treatment modalities so as the understanding of the disease were not the ones of present days. Taken together, these factors might have led physicians to discourage radical treatment.

Unfortunately, the lack of data regarding the presence or absence of comorbidities at diagnosis precludes us to account for this factor in our analyses. Probably, there has been an important selection bias towards treatment or not treatment at the time of diagnosis, considering the advanced age in the untreated group and a potentially non-negligible rate of comorbidities. However, the selection bias has likely not influenced our findings. In fact, CSM remained the leading cause of death in the untreated group despite the advanced age and the potential concomitant

comorbidities and no statistical significant difference was observed between the cumulative incidence of OCM between the treated and untreated group.

Regarding the treatment outcomes, the disease-free survival rate has been estimated to be about 50% in case of radical treatment. (2, 19) Relatively to this, non-definitive treatment, defined as repeated TURBT, palliative chemotherapy or radiation therapy, is associated with a 15 to 30 months shorter OS. (20) In our cohort, in case of absence of treatment we found that almost three patients out of four will eventually progress to distant metastatic disease with a median time to the diagnosis of distant metastasis of 14 months. We acknowledge that the follow-up modalities can influence our estimates so as the advances in imaging technologies over the past decades. The short median time to metastasis as well as the short median time to CSM might partly be attributed to misdiagnosis of metastatic disease when the diagnosis of MIBC was established. However, our results remain emblematic and they should be mentioned at the time of counseling.

In a systematic review, in case of radical treatment the 5-year CSM, and OS rates were found to be 66–80%, and 39–66% respectively. (21) In keeping with these results, in our patient population, the 5-year CSM rate in the group of patients who received treatment was 46%. Yet, these rates still remain unsatisfactory. It has been demonstrated that the administration of neoadjuvant chemotherapy (NAC) improves OS in patients with MIBC. (22-24) However, this treatment modality is associated with grade 3-4 toxicity in slightly more than 35% of the recipients (22) and some elderly patients may not be ideal candidates for NAC administration. Studies aimed at evaluating the role of novel potential treatments, including immunotherapy, both in

the neo- and adjuvant setting are ongoing, suggesting promising results with potentially better tolerability profile are ongoing,(25, 26) and these treatment modalities could potentially be more suitable in case of advanced age at presentation. One of the limitations of our study was the minimal use of chemotherapy given the time of diagnosis, 1995-96, which chemotherapy was not yet standard of care. This would hopefully only improve our treated patients outcomes.

The strength of our study lies in the nature of our data; this population-based dataset entails all the newly diagnosed BCa in the Stockholm county. All patients were diagnosed, treated and followed-up in the same facility. The length of the follow-up represents another remarkable aspect of the study cohort, rendering this database unique. However, limitations to the present study must be acknowledged. The small number of patients represents the main limitation to our study, yet it would be unethical to prospectively confirm our findings given the extremely poor outcomes that we have found. The absence of data concerning comorbidities represents another limitation as well as the lack of data on radiotherapy regimen. Finally, the follow-up protocol was left at physician's discretion and this might have influenced the time to the diagnosis of metastatic disease; similarly, changes in imaging modalities over the past three decades might partly alter findings in this regard.

5. Conclusions

Despite the old age and potential comorbidities of the untreated cohort, the rate of CSM remains high. More than 85% of the untreated MIBC patients succumbed to bladder cancer within five years of the diagnosis whereas less than 10% of the

patients died from other causes. The appropriateness of treatment should always be discussed, given the extremely poor prognosis if the disease is left untreated.

CONFLICTS OF INTEREST

None disclosed

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FIGURE LEGENDS

Figure 1. Kaplan-Meier curves illustrating overall survival for patients diagnosed with muscle invasive bladder cancer (MIBC) according to treatment administration. Log-rank test: $p<0.001$.

Figure 2. Kaplan-Meier curves depicting metastasis-free survival for patients diagnosed with muscle invasive bladder cancer (MIBC) according to treatment administration. Log-rank test: $p<0.001$.

Figure 3. Cumulative incidence function curves for patients diagnosed with muscle invasive bladder cancer (MIBC) demonstrating cancer specific mortality (CSM) and other cause mortality (OCM) according to treatment administration. Pepe-Mori test for CSM: $p<0.001$ and OCM: $p=0.6$.

Table 1. Descriptive characteristics of the patient population. Median (IQR) and frequencies (proportion) are reported for continuous and categorical variables, respectively.

Variable	Overall, *n*=126	No treatment, *n*=64 (51%)	RC or RT, *n*=62 (49%)	*p* value
Age at Dx, yr	74 (66, 80)	79 (73, 83)	69 (63, 74)	<0.001
Sex, n (%)				
Male	83 (66%)	39 (61%)	44 (71%)	0.2
Female	43 (34%)	25 (39%)	18 (29%)	
Tumor stage				
T2	83 (66%)	36 (56%)	47 (76%)	0.02
T3-4	43 (34%)	28 (44%)	15 (24%)	
Tumor grade*				
2	11 (9%)	3 (5%)	8 (13%)	0.1
3	115 (91%)	61 (95%)	54 (87%)	
Tumor size, cm	5 (3, 6)	5.0 (3.0, 6.0)	5.0 (3.0, 6.0)	0.8
Lymph Node Status				
N0/x	106 (84%)	50 (78%)	56 (90%)	0.06
N1	20 (16%)	14 (22%)	6 (10%)	

*According to WHO 1999

Dx: diagnosis; RC: radical cystectomy; RT: radiation therapy

Table 2. Cox proportional hazard model for predicting overall survival and distant metastasis and competing risks regression analysis for predicting cancer specific mortality, after accounting for other cause mortality.

Covariate	HR	95% CI	P value	HR	95% CI	P value	SHR	95% CI	P value
Age	1.03	1.01,1.05	0.01	1.00	0.97,1.03	0.9	1.03	1.00, 1.05	0.02
Sex									
Male	1			1			1		
Female	1.28	0.85,1.93	0.2	1.18	0.67,2.09	0.6	1.39	0.86, 2.24	0.2
Tumor stage									
T2	1			1			1		
T3-4	3.49	2.11,5.78	<0.001	1.86	0.89,3.87	0.1	4.31	2.67, 6.97	<0.01
Lymph Node Status									
N0/x	1			1			1		
N1	0.88	0.45,1.70	0.7	0.73	0.27,1.99	0.5	0.81	0.39, 1.68	0.6
Treatment									
RC or RT	1			1			1		
No treatment	2.63	1.65,4.19	<0.001	2.40	1.28,4.51	0.006	2.02	1.24, 3.30	0.005