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Comparison of Radical Cystectomy with Conservative Treatment in Geriatric (≥ 80) Patients with Muscle-Invasive Bladder Cancer

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ABSTRACT

Introduction: The aim of this study was to compare overall survival in elderly patients (≥ 80 years) with muscle-invasive bladder cancer (MIBC) undergoing either radical cystectomy (RC) or conservative treatment.
Material and Methods: We performed a retrospective, comparative analysis of overall- and cancer-specific survival in octagenarians with MIBC (≥ pT2) submitted to RC or conservative treatment. Uni- and multivariable Cox regression analysis were performed to assess predictors of overall survival. Cumulative hospital stay was also analyzed for all patients.
Results: The RC-group consisted of 33 patients with a mean age of 82.3 years (IQR 80.4-85.4 years) and the bladder preservation a cohort of 35 patients aged 83.8 years (IQR 81.8-88.2 years). No difference was detectable for overall survival (15.9 months versus 9.5 months; p = 0.18) and cancer-specific survival (23.5 months versus 19.5 months p = 0.71) or 90-day mortality (6.1% versus 14.3%; p = 0.43) between the two groups. Patients who received conservative treatment had a shorter cumulative length of hospital stay (p = 0.001). Age at the time of transurethral resection of the bladder (TUR-B) was an independent predictor of the overall survival (p = 0.004).
Conclusions: In this retrospective study, no clear survival benefit was observed for patients ≥ 80 years submitted either to radical cystectomy or conservative treatment. There was however a trend favoring radical cystectomy but this did not approach statistical significance. Octagenarians that underwent RC however spent more of their remaining lifetime in the hospital than those treated conservatively.

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INTRODUCTION

Bladder cancer is the 9th most common cancer diagnosed worldwide with more than 333,000 new cases and 130,000 deaths annually (1). As reported in a recent study of the Surveillance Epidemiology and End Result (SEER), the highest incidence of bladder cancer is observed at the age of 85 years (2). Treatment of bladder cancer is not without significant morbidity and mortality and the optimal management of bladder cancer in geriatric patients is not known. Demographic changes that predict increasing life expectancy will result in a rising number of geriatric bladder cancer patients.

Radical cystectomy (RC) remains the gold standard treatment for younger patients with muscle-invasive bladder cancer (MIBC) (3). In the elderly population, the oncologic superiority of RC to bladder preservation has not been demonstrated (4). In addition, RC demonstrates a 3-5-fold higher perioperative mortality in septuagenarians (5.4%) and octogenarians (9.2%) in comparison to patients ≤ 69 years (2%) (5). Some studies, however, have demonstrated that selected older patients have similar peri-operative outcomes as younger patients (6-8). Bladder sparing treatment in a selected group of octogenarians has also been successfully demonstrated by Wehrberger et al. (9).

To date, no prospective randomized trials are available comparing RC to conservative management in the geriatric population. In addition, very few retrospective, comparative studies have been performed. We therefore sought to evaluate the overall survival (OS) of patients 80 years old or older with MIBC who either underwent RC or a conservative bladder sparing treatment at two institutions.

MATERIALS AND METHODS

Study Population

In this retrospective study, patients aged 80 years or older with newly diagnosed MIBC (≥ pT2) were included from two institutions. The first group underwent RC and pelvic lymphadenectomy at the Department of Urology at the Central Hospital in Bolzano, Italy. None of the patients received neoadjuvant or adjuvant chemotherapy.

The second group received conservative treatment at the Donau Hospital Vienna, Austria. The bladder sparing protocol used at the Donau Hospital was for palliative and not curative intent. This does not meet the EAU guidelines for curative bladder sparing protocols. The cohort consisted of 35 consecutive patients (≥ 80 years), diagnosed with MIBC. All patients underwent a primary TUR-B, however adjuvant measures, such as repeated TUR-B (n = 17.49%) or external beam irradiation (n = 15.43%), were performed on an individualized basis. None of the patients received neoadjuvant or adjuvant chemotherapy or a salvage cystectomy.

Clinical end points of the study

Overall survival was defined as the period between the first TUR-B with MIBC (≥ pT2) in the specimen to the last follow-up or death. The second endpoint was the cumulative hospital stay. This included every day of hospitalization beginning and including the first TUR-B. To assess predictors of overall survival, Cox hazard ratios were calculated with univariate and multivariate analysis.

Clinical parameters

The following clinical parameters were evaluated in this retrospective study: age, body mass index (BMI), comorbidities and the American Society of Anesthesiologists score (ASA).

Oncological data

Tumor stage was classified according to the 2002 TNM classification approved by the Union International Contre le Cancer (10). All patients were diagnosed with a muscle invasive bladder cancer following TUR-B. Tumor staging was completed with computer tomography and/or magnetic resonance imaging and bone scan scintigraphy to exclude distant metastases.

Survival time was defined as time between diagnosing MIBC by TUR-B until death or date of last follow-up in both groups. Patients were followed at their respective institutions.

Statistical analysis

For the statistical analysis, the Statistical Package for Social Sciences, version 19 (SPSS Inc, Chicago, IL) was used. Continuous and non-normally distributed variables were presented as medians with interquartile ranges (IQRs). Differences between the institutions were calculated with the Mann-Whitney U and chi-square tests. All calculations with a level of significance were defined as $p < 0.05$. Kaplan-Meier plots were applied for estimating the overall mortality and cancer-specific mortality. Statistical significances were analyzed with the log-rank test. Univariate and multivariate Cox regression analyses were performed to assess predictors of overall survival.

RESULTS

Patient characteristics

A total of 68 patients were included in this retrospective, comparative study. The characteristics of the study population are listed in Table-1. Thirty--three patients received RC and 35 received conservative therapy as defined by TUR-B and/or radiation therapy. Median follow-up for the entire cohort was 12.4 months. Comorbidities and ASA-score were comparable between the two cohorts, yet patients managed with bladder preservation were slightly older (p = 0.046). The RC cohort consisted of 11 female and 22 male patients with a mean age of 82.3 years. Patients who received a bladder sparing approach consisted of 15 females and 20 males with a mean age of 83.8 years.

Therapeutic interventions and perioperative mortality

Radical Cystectomy

All patients who underwent RC (n = 33) received an incontinent urinary diversion as follows: colon conduit (n = 14), ileal conduit (n = 3), uretero--ureterocutaneostomy wrapped with omentum (n = 16). None of the patients received neoadjuvant radiotherapy and/or chemotherapy. The 30- and 90-day mortality for the RC group was 0% and 6% (2 patients), respectively. One patient died in consequence of a respiratory insufficiency after pneumonia. Another patient died due to cardiac insufficiency.

Conservative treatment

In the conservative group (n = 35), all patients underwent TUR-B. Fifteen patients (43%) underwent radiation therapy (65 Gy) on an individualized basis. A total of 17 patients (49%) received a second TUR-B. Two patients (6%) underwent a third TUR-B. The 30- and 90-day mortality in this cohort was 0% and 14.3% (5 patients), respectively.

Regarding the five patients who died within 90 days, two died due to urosepsis, the cause of death of other three was unknown, but they were 99, 90 and 82 years old.

A total of 25 patients (71.4 %) were able to void spontaneously, five (14.3%) maintained an indwelling catheter and five patients (14.3%) had no detailed voiding data.

Endoscopic or surgical re-interventions requiring anesthesia after radical cystectomy or primary TUR-B

In the group of patients with conservative treatment, 19 secondary TUR-B have been performed due to recurrent, conservatively uncontrollable macrohematuria or as an elective intervention in case of confirmed tumor/recurrence/progression (see in detail: therapeutic interventions and perioperative mortality). Another patient received a palliative uretero-ureterocutaneostomy without cystectomy.

The group of patients after RC underwent secondary intervention in 12 % (n = 4): One patient underwent a revision for ureteral neoimplantation after a stenosis of the ureterointestinal anastomosis. One patient had to undergo a re-laparotomy after developing an abdominal fascial dehiscence, another patient after presenting with sepsis and acute abdomen of unclear etiology. Another patient underwent re-laparotomy at five months postoperatively due to the development of ileus.

Outcomes

Hospitalization was significantly shorter with conservative treatment

The median time of hospitalization (including first TUR-B, cystectomy to last follow-up/death) for the RC cohort was 50 days (IQR 31.5-77.5), whereas the median time of hospitalization in the conservatively treated group was 24 days (IQR 14-46.5). The cumulative hospital stay was significantly different between the two cohorts (p = 0.001). The conservative group spent 8.7% (IQR 3.6-23.3%), whereas the RC group 12.9% (IQR 3.6-23.3%) of their remaining life-time in the hospital.

No difference in overall survival between RC and conservative treatment

The median OS for the cohort treated with RC was 15.9 months (95%CI 6.9-24.9) compared to 9.5 months (95%CI 4.5-14.4) for the patients who underwent conservative treatment. Although there exists a trend towards improved survival in the RC group, this was not statistically significant (p = 0.175) (Figure-1a). For cancer-specific survival, no statistical significant difference was found (p = 0.710) (Figure-1b). At the end of data collection,

Table 1 - Clinical and pathologic characteristics of 68 patients with muscle invasive urothelial carcinoma of the bladder treated with radical cystectomy at the Hospital of Bolzano or conservative treatment at the Donau Hospital of Vienna.

Institution/Procedure	Entire Cohort (n = 68)	Bolzano Radical Cystectomy (n = 33)	Donau Hospital Vienna Conservative Treatment (n=35)	P-value
Age before TUR-B, median (IQR)	83.4 (81.0-86.3)	82.3 (80.4-85.4)	83.8 (81.8-88.2)	0.046
Gender male n (%)	42 (61.8%)	22 (66.7%)	20 (57.1%)	0.374
BMI median (IQR)	24.22 (21.98-26.37)	24.44 (22.50-27.21)	24.01 (21.08-26.08)	0.148
ASA (%)				
1	2(2.9%)	0(0%)	2 (6.7%)	0.286
2	22(32.4%)	11(33.3%)	11 (36.7%)	
3	39(57.4%)	22(66.7%)	17 (56.7%)	
pT (TUR)				
pT2	63 (94%)	30 (93.8%)	33 (94.3%)	0.996
pT3	2 (3%)	1 (3.1%)	1 (2.9%)	
pT4	3 (3%)	1 (3.1%)	1 (2.9%)	
CIS present	11 (16.2%)	6 (18.2%)	5 (14.3%)	0.749
Grading				
G2	2 (2.9%)	2 (6.1%)	0 (0%)	0.224
G3	66 (97.1%)	31 (93.9%)	35 (100%)	
Tumor diameter/size				
< 3cm	15 (22.1%)	7 (21.2%)	8 (22.9%)	0.870
> 3cm	53 (77.9%)	26 (78.8%)	27 (77.1%)	
Tumor focality				
Monofocal	22 (32.4%)	14 (42.4%)	8 (22.9%)	0.120
Multifocal	46 (67.6%)	19 (57.6%)	27 (77.1%)	
90d Mortality	7 (10.3%)	2 (6.1%)	5 (14.3%)	0.429
Cumulative Hospital stay median (IQR)	35 (22-68)	50 (31.5-81.0)	24 (13.75-46.25)	0.001

BMI = Body mass index; **ASA =** American Society of Anesthesiologists Score; **CIS =** Carcinoma in situ; **IQR =** Interquartile range; **TUR-B =** Transurethral resection of the bladder

Figure 1 a - Kaplan Meier plots assessing overall survival in patients with muscle invasive urothelial carcinoma of the bladder treated with radical cystectomy (RC) or with bladder preserving therapy.

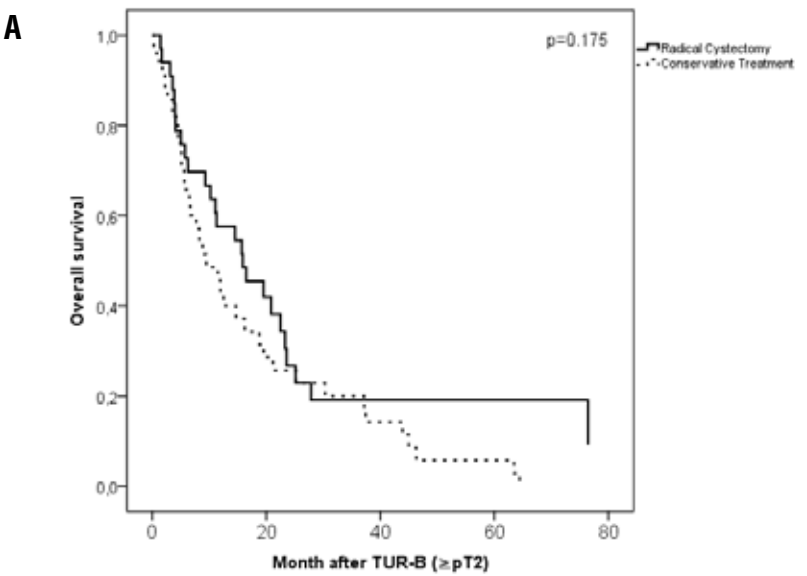
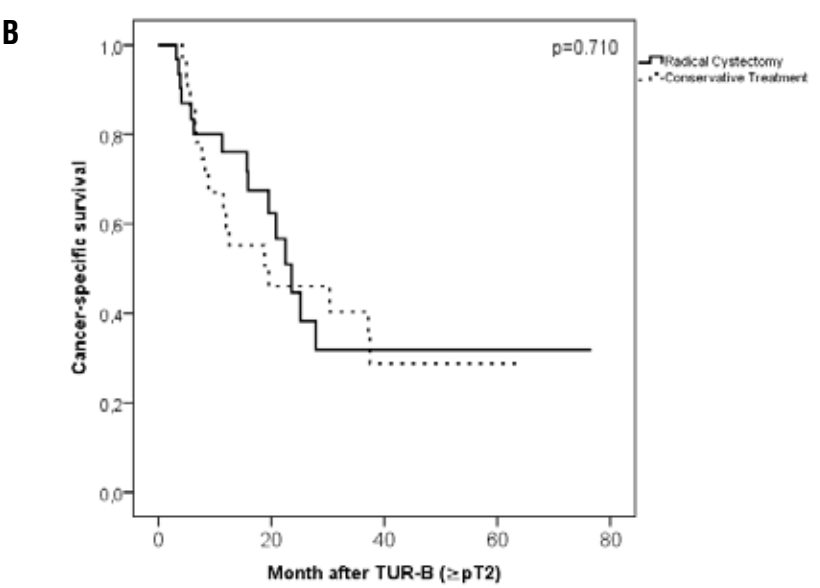


Figure 1 b - Kaplan Meier plots assessing cancer-specific survival in patients with muscle invasive urothelial carcinoma of the bladder (MIBC) treated with radical cystectomy (RC) or with conservative treatment (TRU-B+/-radiation therapy).



eight patients (24%) in the RC group were alive and none in the conservatively treated group.

Univariate and multivariate Cox regression analysis assessing overall survival

Table-2 depicts uni- and multivariable Cox regression analyses of OS for the entire cohort. Only age at the time of TUR-B was an independent predictor of OS (HR 1.1, 95%CI 1.04-1.22, p = 0.004). All other variable such as: BMI, gender, ASA, diameter and focality of UC did not reach statistical significance. The treatment option (RC vs. conservative treatment) was not a significant predictor of OS (HR 1.427, 95% CI 0.852-2.391, p = 0.177).

DISCUSSION

Bladder cancer incidence peaks at the age of 85 years (2) and the number of elderly patients with bladder cancer is expected to triple secondary to the demographic changes predicted for our aging population (11). The optimal management of geriatric patients with invasive bladder cancer will increasingly become an important issue. In younger patients with MIBC, RC remains the gold standard of therapy (3,12). However, geriatric patients have a higher number of relevant comorbidities resulting in an enhanced surgical risk. Prout et al. (13) reported that patients > 74 years old with MIBC have a higher incidence of cardiac disease, chronic anemia and therefore higher ASA--scores than younger patients. Liberman et al. (5) noticed a 3-fold and 5-fold rise of perioperative mortality of RC in septuagenarians (5.4%) and octogenarians (9.2%) respectively, when compared to patients younger than 69 years (2%).

The aim of our study was to compare RC and conservative treatment for MIBC in patients 80 years old and older. The principal findings of this retrospective comparative study were (i) there was no significant difference in overall, cancer specific survival and 90-day mortality between both groups (albeit a trend favoring RC); (ii) patients who received conservative therapy had a

Table 2 - Uni- and multivariable Cox regression analysis for overall survival.

	Univariable Analysis		Multivariable Analysis	
Variables	Hazard Ratio (95%CI)	P-Value	Hazard Ratio (95%CI)	P-Value
Treatment (RC = Reference)	1.427 (0.852-2.391)	0.177	1.242 (0.652-2.367)	0.177
Gender (male = Reference)	1.012 (0.599-1.712)	0.964	0.706 (0.375-1.329)	0.281
BMI (continuous)	0.982 (0.953-1.012)	0.232	0.987 (0.959-1.015)	0.347
ASA Score (continuous)	0.864 (0.524-1.423)	0.565	0.946 (0.551-1.626)	0.841
Age at TUR-Bladder (≥ pT2)	1.140 (1.065-1.220)	<0.001	1.124 (1.038-1.217)	0.004
Diameter of Urothelial Carcinoma (< 3cm = Reference)	1.238 (0.678-2.260)	0.488	1.787 (0.868-3.667)	0.115
Focality (Monofocal=Reference)	0.951 (0.549-1.646)	0.857	1.101 (0.602-2.011)	0.756

BMI = Body mass index; **ASA =** American Society of Anesthesiologists Score; **RC =** Radical cystectomy

shorter cumulative length of hospital stay than patients who underwent RC and (iii) age at the time of TUR-B was an independent predictor of the OS.

The lack of survival advantage of RC in geriatric patients confirms previous studies. Using the SEER data base, Chamie et al. (4) compared the OS of octogenarians, who either underwent conservative therapy or who received RC. The median OS was 18 months for patients who underwent RC (n = 904) and 15 months in those (n = 1.227) who received conservative therapy. In a recent study, Yoo et al. compared 27 octogenarians with MIBC who underwent either RC (41%) or non-RC-treatment (59%). In this series, RC did not improve OS compared to other treatment modalities (14). In our cohort, the median OS for the patients treated with RC was 15.9 months compared to 9.5 months for the patients who underwent conservative treatment. Although this difference did not reach statistical significance, a trend towards improved survival with RC was observed. Achieving statistical significance may have been hindered by our small sample size, however this study is in agreement with the aforementioned studies that have not demonstrated an oncological superiority of RC over conservative treatment in patients ≥ 80 years.

In the absence of convincing oncological evidence to support either therapeutic option, Morgan et al. (15) attempted to provide an alternative approach for elderly patients with MIBC. In a cohort of 220 patients older than 75 years who underwent RC, the authors aimed to identify parameters that impact post-operative mortality. A nomogram for predicting 90-day mortality was established. The 90-day mortality of the entire study cohort was 12.7 % (n = 28). Advanced age (HR 2.30, 95%CI 1.22-4.32) and lower preoperative albumin (HR 2.50, 95%CI 1.40-4.45) were significant predictors of 90-day mortality. Due to the increased mortality and complication rate in this population, Wehrberger et al. (9) proposed a risk-adapted approach for geriatric patients with MIBC based on tumor stage, co-morbidities and chronologic age secondary to the high morbidity and mortality. In the absence of randomized studies, further work will need to be performed looking at predictors for optimal treatment in elderly patients.

The main advantage of RC is the prevention of local symptoms such as recurrent hematuria, clot retention, upper urinary tract dilatation with renal impairment, and voiding symptoms such as urgency and urge incontinence. Lodde et al. (16) evaluated this particular quality of life aspect in 24 primary MIBC patients who received bladder preservation therapy. The mean age of these patients was 81 years (range 68-92) with a mean follow-up of 680 days. Mean hospital stay was 109 days (range, 13-253 days) equivalent to 16% of the remaining survival time. Because of local complications, seven patients (29%) ultimately underwent salvage cystectomy. The authors therefore questioned the role of conservative management of patients with primary MIBC (16). These discouraging data are in contrast to the present series where no patient required salvage cystectomy and the majority was able to void spontaneously. Although the mean age in Lodde's series was 81 years, some younger patients were included who were more likely to have undergone salvage cystectomy (16).

We recognize the limitations of our study including its retrospective nature, data from two separate hospitals and its sample size. However, a prospective randomized study for MIBC in elderly patients is very unlikely to be performed. Our comparative analysis from one center that did not perform radical cystectomy in patients ≥ 80 years versus another one that offered this approach might provide some useful information. During the study period (1997-2010) all patients (≥ 80 years) at the Donau Hospital underwent conservative treatment. All patients received at least one TUR-B and 43% received adjuvant radiotherapy. No patient at the Donau Hospital during this time period underwent a RC. In contrast, at the Central Hospital of Bolzano, RC was offered to all patients.

We also recognize that the conservative treatment at the Donau Hospital was not uniform. Only 15 patients (43%) received external beam irradiation (65Gy) for palliative reasons. In this advanced age group with multiple co-morbidities, the bladder sparing protocols were highly individualized and at the discretion of the treating urologists. However, none of the patients received chemotherapy or subsequent RC and were only

treated with TUR-B and radiation. Finally, we cannot make valid statements for quality of life issues. Issues involving hematuria, voiding dysfunction and incontinence play a valuable role in the decision making process and must be considered.

Despite these methodological limitations, this is the first attempt to compare two approaches in the management of geriatric patients with MIBC. This is a clinical scenario that the urologist will face with increasing frequency as the population ages. In the absence of prospective, randomized multicenter trials, including quality of life evaluations, the decisions to treat or not to treat will be difficult. The importance of the oncological outcome in patients ≥ 80 years, that due to their high age and comorbidities have a reduced life expectancy, has to be questioned. With similar life expectancy in both study groups, the palliation of disease-related complications and symptoms seems to be important for the improvement of the quality of life within the remaining life time. Further studies such as these, as well as studies stratifying risks and co-morbidities are necessary in order to help make appropriate treatment decisions in this group of patients.

CONCLUSIONS

In this retrospective study, no clear survival benefit was observed for patients ≥ 80 years receiving either radical cystectomy or conservative treatment. There was however a trend favoring radical cystectomy but it did not approach statistical significance. Octogenarians that underwent RC spent more of their remaining lifetime in the hospital than those receiving conservative treatment. Aspects such as quality of life, control of local symptoms and time spent hospitalized remain important aspects in determining care in these elderly patients.

ABBREVIATIONS

MIBC = Muscle invasive bladder cancer
RC = Radical cystectomy
OS = Overall survival
BMI = Bbody mass index
ASA = American Society of Anesthesiologists
TUR-B = Transurethral resection of the bladder
IQR = Interquartile range

CONFLICT OF INTEREST

None declared.

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