ORIGINAL RESEARCH

Increased One-Year Mortality Among Elderly Patients After Radical Cystectomy for Muscle-Invasive Bladder Cancer: A Retrospective, Observational Comparative Study

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Introduction: Muscle invasive bladder cancer (MIBC) is a common malignancy amongst elderly. Increasing life expectancy, prevalence of smoking, lifelong exposure to environmental pollutants and immunosenescence contribute to growing number of cases. Traditionally, radical cystectomy (RC) with pelvic lymph node dissection (PLND) constituted the mainstay of treatment for MIBC, but despite proven feasibility in elderly population, it has been associated with significant burden of morbidity, mortality, and complications.

Study Objective: We aimed to re-evaluate the safety and efficacy of RC amongst the elderly patients with MIBC.

Material and Methods: This single-center, retrospective, observational comparative study was conducted among 568 patients who underwent RC due to MIBC between 2003 and 2021. We evaluated the influence of chronological age (<70 vs ≥70 years) on clinical, demographic, and pathological variables related to MIBC and RC.

Results: Elderly patients had similar clinical and pathological features of disease compared to their younger counterparts; nonetheless, they more often received simplified urinary diversion, ie ureterostomy (60.25% vs 39.33%, p<0.001) and had no PLND (15.76% vs 8.5%, p=0.01) during RC. Furthermore, more elderly patients were treated for secondary MIBCs and fewer had history of smoking. Severe complication and 90-day mortality rates were comparable between groups; however, the elderly had significantly higher all-cause mortality at one year post RC (46.67% vs 33.25%, p=0.003). On multivariate analysis, one-year mortality risk was independently associated with elderly age (HR=2.119, 95% CI: 1.227–3.660, p=0.007), rural residency (HR=1.760, 95% CI: 1.043–2.968, p=0.034), extravesical extension of tumor (HR=2.109, 95% CI: 1.155–3.850, p=0.015), lymph node metastasis (HR=2.268, 95% CI: 1.290–3.987, p=0.004) and omission of PLND (HR=6.064, 95% CI: 2.926–12.568, p<0.001).

Conclusion: Radical cystectomy in elderly patients is associated with significant one-year mortality. Our study emphasizes the unmet need for considerate planning of treatment for MIBC in potentially vulnerable groups of elderly patients. Efforts are needed to reliably identify those unlikely to benefit from surgery and facilitate patient-centered choice of alternative therapies.

Keywords: urinary bladder neoplasms, cystectomy, elderly, outcomes, urinary diversion, patient-centered care

Introduction

Urothelial bladder cancer (UBC) is a prevalent malignancy in elderly population. Apart from well-established environmental risk factors like tobacco smoking and occupational exposure to carcinogens, aging of the population significantly contributes to increasing incidence of UBC.[1] Incidence rates from the Surveillance, Epidemiology and End Results

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(SEER) database range from 70 per 100,000 for 65–69 years old, to 174 per 100,000 for octogenarians.[2] Age dependence of UBC, along with latency between carcinogen exposure and development of cancer are likely driven by interactions of exposure intensity and duration, genetic susceptibility and increasingly studied phenomenon of immunosenescence.[3] Majority of patients are being diagnosed in their sixth or seventh decade of life, with approximately 25% of new cases presenting with muscle-invasive bladder cancer (MIBC). Moreover, a substantial proportion of high-risk and very high-risk non-muscle invasive UBCs will eventually progress to MIBC despite conservative management.[4] Correspondingly, there is an increasing population of elderly patients with MIBC that creates new challenges for personalized, multi-disciplinary approach to therapy. Radical cystectomy (RC) with pelvic lymph-node dissection (PLND), preceded by neoadjuvant chemotherapy (NAC) is considered standard of surgical approach to treatment for MIBC, but despite proven feasibility in geriatric population, it remains a morbid operation, carrying significant risk of complications and early mortality.[5–7] More recently, a bladder sparing combined modality treatment (CMT) has been advocated as a less invasive option for geriatric patients with MIBC however, despite similar long-term outcomes to RC, the procedure remains underutilized, and elderly patients offered substandard forms of treatment.[8–10]

We therefore aimed to re-evaluate the safety and efficacy of RC amongst our patients with MIBC with specific attention paid to the elderly part of the cohort. We hypothesized that the adverse events of RC will occur more frequently in older patients compared to younger ones whilst treatment efficacy would decrease with age.

Materials and Methods

Ethical Approval

This single-center, retrospective, observational comparative study was exempt from further review by the Institutional Review Board (Bioethical Committee) of the Pomeranian Medical University, Szczecin, Poland (protocol number KB-0012/136/11/2021/Z) and was conducted with respect to regulations set forth by the Declaration of Helsinki. Involved patients were routinely consented for participation in research, specifically for use of their anonymized treatment data for scientific purposes.

Study Population

We included 568 patients who underwent RC due to pathologically confirmed MIBC at the Department of Urology and Urological Oncology of the Pomeranian Medical University, Szczecin, Poland between 2003 and 2021. We evaluated the influence of patients chronological age (<70 years vs ≥70 years) on variables related to their treatment for MIBC. Clinical data included gender, urban vs rural residence, smoking status/history, RC delay, exposure to NAC. Surgical variables comprised type of surgical approach: laparoscopic vs open, number of removed lymph nodes, types of urinary diversion, incidence of severe complications and proportion of palliative cystectomies. Pathologic features of disease included local stage distribution, lymph node and surgical margin status, and were complemented with short term (90-day and 1-year) overall mortality rates. We performed two separate evaluations of early mortality: one encompassing the entire study cohort, and additional with censoring of palliative procedures. Cystectomies were considered palliative in cases of cT4b and/or M1 MIBCs. Complications were graded with Clavien-Dindo system, with grades 3 to 5 considered severe. We excluded patients who underwent partial bladder resections and those with previous pelvic radiotherapy. Due to retrospective nature of the study some of data was not available for the entire study cohort, hence some of the analyses were performed on smaller samples.

Statistical Analysis

Data was checked for internal consistency by 2 independent reviewers. Descriptive statistics included mean and standard deviation (SD) for normally distributed data. Normality of distribution and homogeneity of variance were evaluated with Shapiro–Wilk test and Levene test, respectively. Qualitative data was presented as numbers and expressed in percentages. Data was presented in two age categories ie, <70 and ≥70 years old. Single variables were compared using an independent *t*-test for parametric variables, and a Chi-square test for non-parametric variables. Univariate and multi-variate stepwise approach Cox Proportional Hazard models were performed to assess risk factors of one-year overall

mortality. Covariates in multivariate model included: age, residence status, smoking status, primary vs progressing MIBC, pathologic T-stage and pathologic N-stage. We considered the p value <0.05 statistically significant and all p values were two-sided. All tests were performed with Statistica software, version 13.5 (StatSoft, Inc., Tulsa, OK, USA).

Results

The study cohort comprised 76.24% of men and gender proportions were consistent within analyzed age subgroups. Median age within the elderly cohort was 74 years (IQR 71.5–77 years), as compared to 62 years (IQR 57–66 years) for the remaining study population, p<0.001. The majority of patients included in our study underwent an upfront RC with eventual adjuvant treatment depending on final pathologic stage (n=464). The multidisciplinary, NAC-based approach has been routinely offered to patients eligible for cisplatin since 2017 and NAC was administered before RC to 104 patients until the mid-2021. The overall uptake of NAC over the period analyzed in present study averaged 18.3% and there was no significant difference in exposure to NAC between the elderly patients and remaining study population.

Regarding risk factors of UBC, the majority of patients in our study cohort (88.52%) reported history of smoking. Within analyzed subgroups: only 5.33% of elderly patients were actively smoking at the time of treatment, 78.67% were former smokers, whereas 16% never smoked. These proportions were significantly different in a subgroup of younger patients with 30.77% of active smokers, 59.76% of former smokers and 9.47% of nonsmokers, respectively, p<0.001 (Table 1). Moreover, there was significantly higher proportion of secondary MIBCs: 40.24%, resulting from progression of non-muscle invasive UBC amongst the elderly, compared to the remaining study population: 22.95%, p=0.004. Slightly lower proportion of seniors reported rural residence: 20% vs 29.03%, p=0.027. Of note, there was no significant difference in delay of surgical treatment between both study groups (Table 1).

Considering surgical technique of RC, there were similar proportions of palliative cystectomies in both study groups with: 6.7% and 6.06% for younger and older patients respectively, p=0.779. However, older patients were more likely to receive simplified urinary diversion with higher proportion of ureterostomies than remaining study population: 60.25% vs

Table 1 Baseline Patients' Characteristics

Variable	Age (Years)		p
	<70	**≥70**	
Totals, n (%); (n = 568)	403 (70.95)	165 (29.05)	
Age – median (IQR)	62 (57–66)	74 (71.5–77)	<0.001
Sex, n (%); (n = 568)			0.963
Male	307 (76.18)	126 (76.36)	
Female	96 (23.82)	39 (23.64)	
Residency status			0.027
Urban	286 (70.97)	132 (80.00)	
Rural	117 (29.03)	33 (20.00)	
Smoking status (n = 244)			<0.001
Nonsmoker	16 (9.47)	12 (16.00)	
Previous smoker	101 (59.76)	59 (78.67)	
Current smoker	52 (30.77)	4 (5.33)	
Time to cystectomy (n = 503)			0.418
≤90 days	218 (61.58)	86 (57.72)	
>90 days	136 (38.42)	63 (42.28)	
NAC, n (%); (n = 568)			0.772
No	328 (81.39)	136 (82.42)	
Yes	75 (18.61)	29 (17.58)	

Abbreviation: NAC, neoadjuvant chemotherapy.

39.33%. Consistently, there were significant differences in proportions of patients with ileal conduits and orthotopic neobladders: 38.51% and 1.24% versus 53.21% and 7.46% for the elderly and younger patients respectively, p<0.001 (Table 2). No PLND was performed during RC in 15.76% of the elderly patients (pNx), as opposed to 8.5% of younger patients, p=0.01, despite comparable local stage distribution, and proportion of node-negative disease in both subgroups (Table 3). The 90-day all-cause mortality rates were comparable in both groups, however there was significantly higher one-year all-cause mortality among elderly patients: 46.67% as compared to 33.25% in their younger counterparts, p=0.003 (Table 4), with corresponding HR=2.119 95% CI (1.227–3.660), p=0.007. After censoring of palliative cystectomies (10 and 27 patients from the elderly and younger groups respectively), the one-year overall mortality remained significantly higher in elderly: 43.8%, as compared to 30.85% in younger subgroup, p=0.004 (Table 5). Moreover, in multivariate analysis, older age remained an independent risk factor for increased one-year all-cause mortality, along with rural residency, higher pathologic stage, positive and unknown lymph node status (Table 6).

Discussion

Our study has shown that older age is an independent risk factor for increased one-year all-cause mortality among patients with muscle-invasive bladder cancer undergoing radical cystectomy, along with rural residency, higher pathologic stage, positive and unknown lymph node status. The early mortality rates, evaluated at 90-days, were comparable between the two subgroups. Our results emphasize the unmet need for considerate planning of treatment for MIBC in potentially vulnerable groups of elderly patients. Efforts are needed to reliably identify those unlikely to benefit from surgery and facilitate patient-centered choice of alternative therapies.

Planning treatment of MIBC in the elderly patient population has never been more complex. First of all, debate is ongoing on the very definition of an old age.[11] With increasing life expectancy in developed countries and corresponding tendency for healthier lifestyle, a historical threshold of an old age established at 65 years, is becoming increasingly inadequate in prediction of patient's physiological performance.[12] At the same time, population of patients with bladder

Table 2 Variables Related to Radical Cystectomy

Variable	Age (Years)		p
	<70	**≥70**	
Surgical approach, n (%); (n = 568)			0.120
Open	313 (77.67)	118 (71.52)	
Laparoscopic	90 (22.33)	47 (28.48)	
Urinary diversion n (%); (n = 550)			<0.001
Ureterostomy	153 (39.33)	97 (60.25)	
Ileal conduit	207 (53.21)	62 (38.51)	
Neobladder	29 (7.46)	2 (1.24)	
PLND yield, n (%); (n = 491)			0.052
≤10	102 (28.49)	50 (37.59)	
>10	256 (71.51)	83 (62.41)	
Surgical margin, n (%); (n = 561)			0.114
Negative	333 (83.46)	126 (77.78)	
Positive	66 (16.54)	36 (22.22)	
Palliative cystectomy; (n = 568)			0.779
No	376 (93.3)	155 (93.94)	
Yes	27 (6.7)	10 (6.06)	
Complications, Clavien-Dindo grade			0.353
No complications + minor (grade 1–2)	301 (74.69)	117 (70.91)	
Severe complications (grade 3–5)	102 (25.31)	48 (29.09)	

Abbreviation: PLND, pelvic lymph node dissection.

Table 3 Pathologic Features of Bladder Cancer

Variable	Age (Years)		*p*
	<70	**≥70**	
History of MIBC (n = 265)			0.004
Primary	141 (77.05)	49 (59.76)	
Secondary	42 (22.95)	33 (40.24)	
Pathological T stage (n = 563)			0.341
pT0	40 (10.50)	20 (12.12)	
pTis/Ta/T1	49 (12.25)	12 (7.27)	
pT2	71 (17.75)	24 (14.55)	
pT3	129 (32.25)	60 (36.36)	
pT4	109 (27.25)	49 (29.70)	
Pathological N stage, n (%) (n = 565)			0.010
pN0	232 (58.00)	99 (60.00)	
pN+	134 (33.50)	40 (24.24)	
pNx	34 (8.50)	26 (15.76)	

Abbreviation: MIBC, muscle-invasive bladder cancer.

Table 4 Short-Term Mortality Data of Entire Cohort

Variable (n=563)	Age (Years)		*p*
	<70	**≥70**	
Early all-cause mortality (≤90 days)	18 (4.47)	12 (7.27)	0.175
One-year all-cause mortality	134 (33.25)	77 (46.67)	0.003

Table 5 Short-Term Mortality Data with Censoring of Palliative Cases

Variable (n = 531)	Age (years)		*p*
	<70	**≥70**	
Early all-cause mortality (≤90 days)	14 (3.72)	11 (7.10)	0.095
One-year all-cause mortality	116 (30.85)	68 (43.87)	0.004

Table 6 Multivariate Stepwise Cox Regression Analysis of Individual Risk Factors Predicting One-Year All-Cause Mortality After Radical Cystectomy

	Estimate	**SD**	**Chi-Square**	**HR**	**Lower 95% CI**	**Upper 95% CI**	***p* value**
Age (Ref. <70)	0.751	0.279	7.260	2.119	1.227	3.660	0.007
Residency status (Ref. Urban)	0.565	0.267	4.487	1.760	1.043	2.968	0.034
Smoking status (Ref. nonsmoker)							
Previous smoker	0.203	0.389	0.272	1.225	0.572	2.625	0.602
Current smoker	0.807	0.447	3.256	2.240	0.933	5.381	0.071
History of MIBC (Ref. primary)	−0.702	0.315	4.953	0.496	0.267	0.920	0.026
Surgical approach (Ref. open)	−0.476	0.241	3.881	0.622	0.387	0.998	0.049
Pathological T stage (Ref. ≤pT2)	0.746	0.307	5.902	2.109	1.155	3.850	0.015
Pathological N stage (Ref. pN0)							
pN+	0.819	0.288	8.087	2.268	1.290	3.987	0.004
pNx	1.802	0.372	23.494	6.064	2.926	12.568	<0.001

Abbreviations: CI, confidence intervals; HR, hazard ratio; SD, standard error.

cancer includes a significant proportion of those "biologically older", suffering from multiple comorbid conditions which stem from long-term exposure to smoking.[13,14] Several authors demonstrated clinical utility of RC even in octogenarians,[14–16] nevertheless we chose the age threshold of 70 years, which more adequately identifies "true elderly" patients within Polish population, still characterized by lower life expectancy compared to Western countries.[17,18] Similar age threshold was adopted in a study of Görgel et al which evaluated the outcomes of RC among elderly patients in Turkey.[19]

Patients from the elderly group were nearly twice more often treated for secondary MIBC, resulting from progression of a non-muscle invasive disease on conservative management, than their younger counterparts. Since the majority of UBCs present as non-muscle invasive disease, patients who progress on endoscopic and intravesical treatment are likely to be older. In a systematic review and meta-analysis of Pones et al patients with secondary MIBCs were on average 13 months older than those with primary MIBCs, but had no significant difference in long-term overall survival.[20] This is in contrast to several previous studies, reporting unfavorable long-term outcomes of RC in patients with secondary MIBCs, including inferior response to neoadjuvant chemotherapy.[21–23]

Our study found a very high proportion of patients with history of smoking, yet older patients were significantly less likely to actively smoke at the time of treatment. Given that significant part of our elderly population had secondary MIBCs, this may represent the influence of longer duration of urological care with education on harms of smoking. The diagnosis of UBC and the upcoming/ongoing treatment for cancer provide a suitable opportunity to address lifestyle modifications, as patients are more likely to get motivated and quit smoking.[24] Unfortunately, as Bjurlin et al revealed in their study among over 600 American urologists, only one in five regularly discussed smoking cessation with patients with UBC, whereas 55.6% never did so.[25] Therefore, urologists shall recognize their role in patient education, and specifically in patients with bladder cancer, they should guide the change towards healthier lifestyle.[26] Of note, we found that 16% of elderly patients had no history of tobacco exposure, compared to 9.5% of their younger counterparts. Overall, there was 11.5% of never-smoking patients in our population, which is in keeping with data from questionnaire study from Westhoff et al, who found no tobacco exposure in 12% of their cohort of 1793 patients.[27] The proportion of UBC cases attributable to occupational exposure is declining, with a review paper of Burger et al assuming 20% of UBCs being related to occupational carcinogens, whereas epidemiological studies from Westhoff et al and Rushton et al reported on much lower proportions of 5 and 7.1%, respectively.[27–29] Bearing above in mind, it remains plausible that higher proportion of tobacco unrelated UBCs amongst senior patients may represent a longer latency carcinogenesis related to low intensity occupational and environmental exposure to carcinogens facilitated by immunosenescence.[3] The phenomenon of immunological aging is being widely studied in many fields of medicine, including geriatric oncology in the context of disease pathogenesis and response to treatment, particularly in the era of immunotherapy with checkpoint inhibitors.[30,31]

Our study showed that despite comparable pathologic stage distributions of disease, elderly patients more frequently underwent simplified surgery compared to those from younger subgroup. This included omission of PLND in nearly 16% of RCs (pNx) and simplified urinary diversion in a form of ureterostomy in 60% of patients. Importantly, patients in whom PLND was not performed (pNx) had six-fold higher risk of one-year all-cause mortality than had node-negative patients, indicating that the reason for omission of PLND was unresectable nodal disease, rather than intention for reducing morbidity of RC in a potentially vulnerable subgroup of elderly patients. These findings are consistent with the study from Abdollah et al, who recognized a detrimental effect of PLND omission during RC on survival across a broad range of local stages. The authors analyzed data from SEER database, and found that omitting PLND took place in one-quarter of RCs leading to significantly increased cancer-specific mortality in organ-confined and overall mortality in locally advanced (pT3-4) UBC respectively.[32] Results from our study corroborate the widely recognized tendency for elderly patients with MIBC to receive substandard forms of therapy – a tendency often associated with inferior treatment outcomes.[33,34] In a national patient cohort analysis John et al evaluated treatment choices for nonmetastatic MIBC in England and found that 47% of 2519 patients diagnosed in 2016 received nonradical therapy. Radical radiation therapy and RC were offered to 29% and 24% of patients respectively. Notably, the median age of patients in this cohort reached 76 years, emphasizing the need to appropriately address the issue of curative treatment for MIBC in progressively aging population.[10] Whenever RC is considered, the role of thorough patient preparation should not be underestimated. This

may include preoperative pathways like "Cystocare", which comprises medical optimization of comorbidities, gradual increase in exercise, nutritional education and psychological support within support group meetings.[35] In a postoperative setting, the enhanced multidisciplinary care pathways like ERAS (Enhanced Recovery After Surgery) and NEEW (Nutrition, Exercise, Education and Wellness) were also reported to improve early outcomes.[36,37] In line with previous reports, our study found that RC in the elderly population is feasible and may be accomplished without incurring an excessive risk of severe complications, compared to younger patients.[19] Moreover, 90-day mortality rates observed in our study (4.47% and 7.27% for younger and older patients respectively) remain consistent with data from the literature. The study from Porter et al evaluated data from the State of Washington, and reported 90-day unadjusted mortality rates after RC of 5.4%, 6.9% and 8.4% for high, medium and low volume hospitals respectively, whereas Nielsen et al found an overall 90-day mortality rate of 7.2% in their National Cancer Database analysis.[7,38]

Notwithstanding, nearly half of operated seniors from our cohort died within one year from surgery. This high mortality rate signifies the unmet need for appropriate patient selection and multidisciplinary treatment planning amongst the elderly and frail patients. The planning process shall integrate evidence-based standards of care, at the same time considering individual aspects related to aging, comorbidities, reduced physiologic reserve, cognitive and self-care capabilities along with availability of support in place of residence.[33,39] We found risk of one-year mortality significantly higher in patients living in rural areas, which signifies the detrimental effects of limited access to specialist medical care, nursing support and greater distance to treating hospital. These findings are in keeping with study by Deuker et al, who reported on higher overall and cancer specific mortality among rural residents with bladder cancer, compared to patients living in urban areas.[40] Furthermore, rural residency was associated with increased mortality among cancer patients for most of evaluated cancer types and locations.[41]

Our study has several limitations which need to be acknowledged. We retrospectively analyzed data from a single academic tertiary department gathered over 17 years and looked at the correlations between chronological age and several clinical, demographic, and pathological variables, to provide some real-world evidence on how elderly patients handle the surgical treatment of MIBC. Given the 12-year difference between median ages in our study subgroups, we have not performed a typical long-term overall survival analysis, as this comparison could have been biased due to differences in life expectancy and competing mortality between these two subgroups. Instead, we decided to limit survival assessment to 90-day and one-year mortality rates, to better assess the clinical utility of bladder extirpation among the elderly. Moreover, we had no pre- and post-surgery quality-of-life data available for analysis, hence were unable to evaluate if RC meets eventual palliative objectives in this vulnerable cohort of patients. Additionally, we were lacking robust data on comorbidities or performance scores for significant part of the cohort, and we were unable to incorporate biological age into our multivariate model. For the same reason, we had to constrain some of our analyses to smaller samples thus reducing power (ie smoking status, primary versus secondary MIBC). We had limited data on smoking with either "active", "past" or "non-smoking" status reported, without information on duration and intensity of exposure. Despite these shortcomings, we trust our study provides significant insights on value of RC among elderly patients. With advances in surgical techniques and perioperative care more of these vulnerable and frail patients would survive radical cystectomy, but as our study demonstrated, this will not translate into survival advantage in substantial proportion of them. Those unlikely to benefit from surgery shall be identified early and offered curative alternatives, likely with broader utilization of CMT.[42]

Conclusion

Radical cystectomy in elderly is associated with substantial burden of one-year mortality, emphasizing the need for considerate planning of treatment for muscle-invasive bladder cancer in this vulnerable group of patients. A thorough geriatric, oncological, and anesthetic evaluation of elderly patients is mandatory, and decision on radical cystectomy shall be taken within multidisciplinary team only after careful consideration of available alternatives.

Abbreviations

CMT, combined modality treatment; HR, hazard ratio; IQR, interquartile range; MIBC, muscle invasive bladder cancer; NAC, neoadjuvant chemotherapy; PLND, pelvic lymph nodes dissection; RC, radical cystectomy; SD, standard deviation; UBC, urothelial bladder cancer.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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