The feasibility of radical cystectomy in elderly patients

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ABSTRACT

Objective: In this study, we aimed to investigate the relationship between age and tumor characteristics and to evaluate oncologic results after radical cystectomy in bladder cancer with respect to age.

Material and methods: We reviewed 460 patients retrospectively who underwent radical cystectomy. Patients were divided into two groups according to age: ≥ 70 (Group 1), and < 70 (Group 2). We compared tumor pathological characteristics and the results of long-term follow-up in both groups. The first group included 76 (16.7%), and the second group 379 (83.3%) patients. The mean age of the patients was 73.3 ± 3.01 years (70–85) in Group 1 and 58.3 ± 7.47 years (34–69) in Group 2. The American Society of Anesthesiologists (ASA) score was less than three in all of the patients, and there was no risk for major surgery.

Results: No statistically significant difference was found between groups with respect to pathological T stage ($p=0.567$), lymph node involvement ($p=0.179$), or histological grade ($p=0.567$). Perioperative mortality rates were 3.9, and 3.4% in groups 1 and 2, respectively ($p=0.218$). Perioperative complication rates were 14.7, and 17.5% for groups 1, and 2 respectively ($p=0.578$). Five-year disease-specific survival (DSS) rates were 57.0, and 51.6% Groups 1, and 2, respectively. The mean DSS periods were 82.05 ± 4.88 and 71.68 ± 8.53 months for Groups 1, and 2, respectively. Five-year overall survival rates were 43.9% for Group 1 and 45.9% for Group 2. The mean overall survival times were 54.02 ± 8.47 , and 69.25 ± 4.97 months for Groups 1, and 2, respectively. In Cox regression analysis, tumor stage ($p=0.012$) and lymph node involvement ($p<0.001$) were significant factors that affected the survival in both groups. None of the patients received neoadjuvant radiotherapy or chemotherapy.

Conclusion: We found that oncological outcomes of radical cystectomy performed with the indication of bladder tumor were comparable between young and elderly. We believe that age *per se* should not constitute a contraindication for radical cystectomy operations.

Key words: Bladder cancer; elderly patients; radical cystectomy.

Introduction

Nowadays, life expectancy increases in parallel with developments in technological, and medical opportunities. In the United States of America (USA) for every newborn, average life expectancy is almost 80 years. Currently, in developed Western countries, the proportion of the population aged more than 65 years to population in general is around 15 percent, and in the year 2020 it is expected to exceed 20 percent.^[1] Therefore, some authors have advocated that lower limit of old age should be set at advanced ages above 65 years.^[2] It has been reported that in the USA, in the year 2030, one of every five individuals will be 65 years of age or above, and in that case older individuals will need more sophisticated medical care.^[3] In the year 2006, nearly 104.400 newly diagnosed bladder cancer cases, and 36.500

bladder cancer-related deaths were reported.^[4] The term elder population has been generally defined as the people aged 75 and over, and the bladder cancer is the fifth most frequently seen cancer, still 40% of the patients are newly diagnosed cases.^[5] The incidence of bladder cancer increases prominently with age, and it most often occurs after the age of 70.^[6] Radical cystectomy is the standard treatment in localized muscle-invasive bladder cancer.^[7] Some studies have shown that in the selected elder patient population group, improved outcomes of radical cystectomy, and urinary diversion operation are comparable to those obtained in the young population.^[8] It has been indicated that in selected elder patients with invasive bladder tumours, radical cystectomy can be safely performed with improved tolerability.^[9] Our aim in this study is to investigate the correlation between age of the patients, and

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tumoral characteristics of bladder cancer whose incidence increases with advanced age, and evaluate its impact on oncological outcomes after radical cystectomy.

Material and methods

In this study, data of 460 patients who had undergone cystectomy in our clinic between the years 1991-2010 with the indication of bladder cancer were retrospectively analyzed. All patients were preoperatively consulted with the departments of cardiology, and chest diseases, and those with cardiac, and pulmonary diseases were directed to non-surgical therapy. Intestinal cleansing was performed immediately before the operation. The patients were divided into two groups as those who had undergone radical cystectomy before (Group 1), and after the age 70 (Group 2). Both groups were compared as for pathologic characteristics of the tumour, long-term follow-up results, perioperative mortality, and complications. Both groups were analyzed with respect to diversion types, pathological stage, grade, lymphatic involvement, and histological subtype. All patients had American Society of Anesthesiologists (ASA) score of <3, and cases did not carry risks for major surgery. From all patients consent forms were obtained preoperatively.

Ethics committee approval was received for this study from the ethics committee of Izmir Ataturk Training and Research Hospital.

Statistical analysis

For all statistical evaluations Windows for Statistical Package for Social Sciences (SPSS) version 16.0 was used. As descrip-

tive statistics, frequencies, percentages, means, and standard deviation values were calculated. For comparisons of qualitative variables, chi-square, and of quantitative variables *t*-test, and one way analysis of variance were used. $P < 0.05$ was considered as the level of statistical significance.

Results

A total number of 460 patients (420 men, and 40 women) were included in the study, and allocated into 2 groups (Group 1, total $n=79$; 16.1%, 69 men, and 10 women; and Group 2, $n=381$; 823.9%; 351 men, and 30 women). Mean ages in Groups 1, and 2 were 73.3 ± 3.01 years, (range, 70-85 yrs) and 58.3 ± 7.47 years, (range, 34-69 yrs), respectively. Perioperative mortality rates were 3.9, and 3.4 1% in Groups 1, and 2, respectively ($p=0.218$). Perioperative complication rates were 14.7, and 17.5% in Groups 1, and 2 respectively ($p=0.578$).

Five-year disease-specific survival rates were 57.0, and 51.6% in Groups 1, and 2, respectively. Disease-specific mean survival times were $71.68 (\pm 8.53)$, and $82.05 (\pm 4.88)$ months in Groups 1, and 2, respectively ($p=0.774$). Five-year overall survival (OS) rates were found to be 43.9, and 45.9%, in Groups 1, and 2, respectively. Mean OS times were 54.02 ± 8.47 , and 69.25 ± 4.97 months in Groups 1, and 2, respectively ($p=0.254$) (Figure 1).

In Groups 1, and 2, the patients underwent Bricker type urinary diversion (53.1 vs. 48.1%), neobladder (50.8 vs. 28.2%), and ureterocutaneostomy (13.9% vs. 11.8). Other types of diversion are shown in Table 1.

Figure 1. Disease-specific survival (a) , and overall survival of all patients (b) Kaplan-Meier curve

Table 1. Types of diversions in groups

Type of diversion	Group 1 (n)	(%)	Group 2 (n)	(%)
Ureterocutaneostomy	11	13.9	45	11.8
Bricker	42	53.1	183	48.1
Neobladder	25	30.8	108	28.2
MAINZ 2 pouch	1	1.2	33	8.6
Hemicoch pouch	-	-	12	3.1
Total	79	100	381	100

Table 2. Distribution of the pathologic stages of the cases among groups

Pathologic grade	Group 1 (n)	(%)	Group 2 (n)	(%)	p
T0	0	0	2	0.7	0.631
T1	16	20.2	61	15.5	
T2a	7	8.8	46	12.07	
T2b	22	27.8	85	22.3	
T3a	11	13.9	47	12.3	
T3b	15	18.9	81	21.2	
T4	8	10.1	59	15.4	
Total	79	100	381	100	

In histopathological evaluation of the cases, mostly stage pT2b (27.8%), and then pT1 (20.2%) were observed. In Group 2, most frequently pT2b (22.3%), then pT3b (21.2%) were seen. Pathological grades of all cases in both groups are shown in Table 2.

Majority of the cases (97.5%) in Group 1 had Grade 2, and 3 tumours, while in only 2.5% of the cases had Grade 1 tumours. In Group 2, most of the cases (93.1%) had Grade 2, and 3 tumours, and in only 6.9% of the cases, Grade 1 tumours were detected (Table 3).

As a result of bilateral pelvic node dissections, in only 22.8% of the cases in Group 1, lymph node involvement was observed. However in only 28.08% of the cases in Group 2, lymph node involvement was detected (Table 4).

Transitional cell carcinoma (TCC) was detected in 82.2% of the cases in Group 1, while in the remaining 17.8% of the cases non-transitional cell carcinoma (non-TCC) were found. In Group 2, transitional, and non-transitional carcinomas were detected in 78.2, and 21.8% of the cases, respectively. To investigate the impact of age on survival *per se*, other factors influential on survival were taken into consideration, and Cox regression analysis was performed. As a conclusion, we didn't observe any impact of age on survival, on

Table 3. Distribution of the grades of the cases among groups

Grade	Group 1 (n)	(%)	Group 2 (n)	(%)	p
1	2	2.5	24	6.9	0.567
2	24	30.3	87	21.9	
3	53	67.2	271	71.2	
Total	79	100	381	100	

Table 4. Lymph node status of the groups

Lymph node involvement	Group 1 (n)	(%)	Group 2 (n)	(%)	p
Present	18	22.8	107	28.08	0.179
Absent	61	77.2	272	71.32	
Total	79	100	381	100	

the contrary, tumour histology ($p=0.012$), and lymph node involvement were found to be influential parameters on survival ($p<0.001$). None of the patients received neoadjuvant radio-and/or chemotherapy.

Discussion

Bladder cancers are heterogenous tumours with a variable clinical natural course. At one end of the spectrum low-grade tumours with low progression rates, and on the other end high-grade tumours with higher progression rates, and malignity potential are found. At initial diagnosis, 70% of the bladder cancers are superficial tumours. The detected superficial tumours consist of Ta (70%), T1 (20%) tumours, and carcinoma in situ (10%).^[10] Though, various types of cancers can be seen in the urinary system, most frequently those originating from the transitional epithelium were encountered.^[11] Less than 5% of the bladder cancers are squamous cell carcinomas, and adenocarcinomas are seen less frequently.^[12] Squamous cell carcinomas are more frequently seen in regions where schistosomiasis are endemic.^[13]

Among men in the Western world, bladder cancer ranks fourth after prostate, lung, and colon cancers. It is the eight most frequently seen cancer type among women.^[14] A 5-10% of the cancers seen among men in Europe, and USA constitute bladder cancers. In men younger than 75 years of age the risk of development of bladder cancer is 2-4%, and only 0.5-1% of the women contract bladder cancer.^[15]

Elder population has been categorized in three subgroups as young-old (aged 65-74 yrs), old (aged 75-84 yrs), and very old (aged >85 yrs).^[16] With aging, physiologic reserve decreases, and functions of many vital organs, and systems are restricted significantly. In the presence of any comorbidity, their condi-

tion aggravates further, restricts their capability to overcome the problems incurred by major surgical procedures. Advanced age is a challenging issue for the urologists who plan to perform cystectomy. In most of these patients, one or more than one comorbidities as nutritional deficiencies, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, and diabetes mellitus can be found.^[17] In the literature Various perioperative mortality, and complication rates have been cited in the literature for older patients who had undergone radical cystectomy operations. Perioperative mortality rates have been defined for the first 30th or 90th postoperative days.^[7,18-21] In our study, perioperative mortality has been evaluated for the first 30th postoperative days. In our patient group, perioperative mortality, and complication rates were observed in 3.9, and 14.7% of the cases, respectively.

Postoperative complications observed after urinary diversion operations are considered in two categories as follows:^[22]

1. Complications not specific to urinary diversions
2. Complications specific to urinary diversions
 - a) Complications related to the intestinal segment used
 - b) Complications related to ureterointestinal anastomosis
 - c) Complications specific to conduits

The experience of the medical center concerning radical cystectomy was also emphasized in the perioperative evaluation of mortality. In centers defined as 'high-volume hospitals', more than 10 cystectomy operations were performed annually, and significantly lower rates of perioperative mortality were observed.^[23] In our clinic, every year approximately more than 20 radical cystectomy operations are performed.

In the literature, 5-year survival rates in older patients who had undergone radical cystectomies change between 5, and 54 percent. In our study group average 5-year survival rate was 43.9 percent. Our 5-year survival rate is in accordance with the literature data, and it is higher when compared with many other studies. Our higher survival rates can be explained by better performance status of our patients, and our overwhelming experience with radical cystectomy operations.^[19,21,23,24]

American Society of Anesthesiologists (ASA) described a scoring system to categorize the preoperative physical health state of the patients.^[25] Accordingly:

- ASA 1. Otherwise normal healthy patient.
 ASA 2. Patient with a mild systemic disease.
 ASA 3. Patient with a severe systemic disease.
 ASA 4. Patient under a life-long risk of life-threatening systemic disease.

ASA 5. Deadly ill patient without any chance of living if not operated.

ASA 6. Patient with reported brain death waiting for an organ transplantation.

Some studies have demonstrated significant increases in perioperative mortality in patients aged >70 years.^[13,26] A statistically significant difference was not found between both of our study groups. This finding might be attributed to lack of any cardiac, and pulmonary comorbidities in our patient group. Some studies have underlined the importance of ASA scores in predicting the onset of postoperative complications.^[22,27] In our study, ASA scores of all cases were lower than 3 points. It has been reported that in patients in whom radical cystectomy was performed with the indication of muscle- invasive or recurrent bladder cancer, age does not constitute a contraindication by itself.^[28]

Rosario et al.^[29] published comparative radical cystectomy results in various age groups. Preoperative comorbidity, and surgical morbidity were more frequently seen in the elderly group, however postoperative mortality rates were reported as 3% in the young, and 0% in the elder population. Leibovitch et al.^[30] performed radical cystectomies on a total of 174 consecutive patients with invasive bladder cancer aged <70 (n=132/69), and ≥70 (n=42/63), years, and applied alternative treatments (transurethral resection+intravesical/systemic chemotherapy, external radiotherapy, partial cystectomy or supportive therapy) to 21 cases with similar disease stage, and health state. One-year mortality rates were similar both in the young, and old patient populations in the cystectomy group (9, and 14%, respectively), however it was reported as 86% in the elderly patient group who had undergone alternative therapies. Based on these results, the authors argued against relinquishing from performing cystectomy in elderly patient population only for their advanced ages. The issue of cystectomy in older patients has been comprehensively analyzed, and published by Figueroa et al.^[31] from University of Southern California. The investigators compared the outcomes of 404 older (aged ≥70 yrs) or 762 younger (<70 yrs) cases who had undergone cystectomies for invasive bladder cancer. The authors found similar surgical morbidity, hospital stay, early, and late-term mortality, and cancer recurrence rates in both groups. Overall mortality rates were relatively lower in this large scale patient population (in the elder population, 2.8%, and in the younger population, 2.2%) Interestingly, perioperative mortality was not reported in 52 patients aged ≥80 years. We have to emphasized that the investigators generally selected healthy patients with adequate cardiac, and pulmonary functions for cystectomy. In the past, treatment of invasive bladder cancer in older patients had been mostly realized with alternative methods other than cystectomy. Even though it is hard to arrive at definitive conclusions because of complexities in the

patient selection, and lack of prospective data, most of the published outcomes are not unfortunately encouraging. Holmang et al.^[32] reported average survival rate after radical radiotherapy as 16 months, and local recurrence rate with or without distant metastases as 53 percent.

Holmang et al.^[33] reported that 5 years after transurethral resection (TUR), only 14 of the patients survived, and most of the patients were lost secondary to progression of the cancer. In recent years, transurethral resection + chemo-radiation combination, and bladder preservation protocols have been tried. Shipley et al.^[34] reported that in 65% of the patients bladder preservation was possible with a 5-year survival rates of 54 percent. Investigators noted that in none of the patients any adverse effect was not encountered which required cystectomy. These outcomes are promising, however they should be supported by other studies.

For the muscle-invasive (T2-4aN0(Nx)M0) bladder cancer patients radical cystectomy is accepted as standard treatment method which can yield 5-, and 10-year survival rates of nearly 50-65%, and 40-45%, respectively.^[35] The most important independent prognostic factors which are known to effect these outcomes included pathologic stage of the tumour, and lymph node involvement.^[36] In patients with muscle-invasive bladder cancer, transurethral resection, radiotherapy, and chemotherapy have not been evaluated individually as curative methods, and they are not recommended as monotherapy in treatment guidelines.^[7] As a bladder preservative approach, many studies have reported 60-80% complete response rates, and long-term survival rates (5-year survival rates, 50-60%) comparable to radical surgery in selected patient series who had undergone multimodal treatment consisting transurethral resection, and subsequent application of chemo-radiotherapy. With the application of this approach 40-45% of the patients can maintain their lives at the end of 5 years with their intact bladders.^[37] Absence of any histopathological evidence of tumour (pT0) in specimens of re-TUR applied following primary TUR-MT is an important independent positive prognostic factor. The most important disadvantage of bladder preserving approach is application of cystectomy as a “delayed” intervention in case of treatment failure with decreased success rates. Requirement of life-long closer follow-up, and increased patient compliance, and its applicability only in specialized multidisciplinary centers are main factors restricting use of this therapeutic approach. For the indicated reasons, according to European Association of Urology guidelines, multimodal therapy is only recommended for “informed, and compliant patients in whom cystectomy is not considered for clinical, and personal reasons.”^[37]

Retrospective design of our study is one of the most important factors which restricted our investigation. Other restricted factor is scarce number of our patient population over 70 years of age. Prospective, randomized, and large-scale studies are needed.

In conclusion, we have detected that in our study, radical cystectomies performed with the indication of bladder tumour in elderly patients yielded results similar to those obtained in young people as for oncologic outcomes, mortality, and complication rates. Therefore, we think that age of the patient should not constitute a contraindication *per se*, and in selected cases radical cystectomy can be performed safely.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İzmir Atatürk Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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