Original Article

Survival Analysis of the Treatment of Muscle Invasive Bladder Cancer in Octogenarians

Jakrapong Jirasiritham MD[1], Charoen Leenanupunth MD[1], Chinnakhet Ketsuwan MD[1], Wisoot Kongchareonsombat MD[1], Kittinut Kijvikai MD[1], Wachira Kochakarn MD[1], Premsant Sangkum MD[1]

[1] Division of Urology, Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: Radical cystectomy is a major surgical procedure that may be associated with perioperative complications, especially in patients of advanced age.

Objective: To evaluate survival and complication rates and compare outcomes after treatment of muscle invasive bladder cancer in octogenarian patients in Ramathibodi Hospital.

Materials and Methods: A retrospective analysis was performed after approval by the institutional ethical committee. Data from 807 bladder cancer patients between 2006 and 2016 were collected. Of these, 154 patients had muscle invasive bladder cancer, and 97 of these had adequate data for analyses. The primary outcome was overall survival. The log rank test was used to compare the treatments and outcomes of each age group. Cox regression analysis was used to predict factors related to survival outcome and presented with a Kaplan-Meier curve.

Results: Of the 97 patients, 86 were treated by radical cystectomy and 11 were given non-surgical treatment. The five-year survival rate for the surgical treatment group was 66.51% (95% CI 46.86 to 80.29). The median survival time in the radical cystectomy group showed a longer median survival time than in the non-surgical treatment group, at 68 and 24 months, respectively. Patients that received radical cystectomy at age of 80 years or older had overall five-year survival time of 44.44% (95% CI 6.62 to 78.49). The median survival length of patients aged of 80 years or older in the radical cystectomy group and the non-surgical therapy group were 36 and 20 months, respectively. There was no statistically significant difference by hazard risk ratio (HR) 2.99 (p=0.106) between patients that received radical cystectomy in both age groups of less than 80 and 80 years or older. Elderly patients were more prone to have minor postoperative complications than younger patients, however, the major complication rates were similar in all ages.

Conclusion: Radical cystectomy demonstrated better outcomes in median and five-year survival than the non-surgical treatment group. Octogenarian patients benefited from radical cystectomy, as did their younger counterparts. Radical cystectomy in the octogenarian group should be performed in well-selected patients and preoperative care should be improved to decrease the rate of complications.

Keywords: Bladder cancer; Muscle invasive bladder cancer; Octogenarian; Elderly; Radical cystectomy

Correspondence to:

Sangkum P.

Division of Urology, Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Toong Phayathai, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-2011315, **Fax**: +66-2-2011316

Email: Charoen.lee@mahidol.ac.th

Bladder cancer is among the top ten most common cancer types in the world, with 549,393 new cases in 2017[1]. In Thailand, records from 1990 to 2017 showed 1,487 people died from bladder cancer[2]. The most common presenting symptom of bladder cancer is painless hematuria, both gross and microscopic[3]. Another symptom that can lead patients to hospital is irritative voiding symptoms. Bladder cancer can be divided into non-muscle invasive and muscle invasive bladder cancers. Approximately 20% to 30% of patients present with muscle invasive bladder cancer at the time of initial presentation[4].

Treatment of muscle invasive bladder cancer is challenging. Radical cystectomy with bilateral pelvic lymph node dissection with urinary diversion is still the standard treatment[5]. Radical cystectomy provides excellent oncological outcomes with disease recurrence rates as low as 4% in patients who are lymph node negative[6].

However, radical cystectomy and urinary diversion are considered major surgeries that have potential intra-operative and post-operative complications. Furthermore, many bladder cancer patients are very old, and may have comorbidities, which mean that they are not fit for major surgery.

Optimizing the treatment outcomes in this population is a challenging issue for urologists. The objective of the present study was to evaluate the treatment outcomes of muscle invasive bladder cancer in octogenarian patients in Ramathibodi Hospital. The outcomes of various treatment options in this population were also compared.

Materials and Methods

The present study was conducted in agreement with the ethical principles of the Declaration of Helsinki and ethical approval for the research was permitted from the Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital (COA MURA 2018/482).

A retrospective study was conducted after receiving the approval. The inclusion criteria specified patients diagnosed with muscle invasive bladder cancer in Ramathibodi Hospital between 2006 and 2016. The exclusion criteria were inadequate data or pathology reports that were not detailed enough to study. Baseline demographic data such as age, body weight, underlying conditions, and staging were recorded. From the Ramathibodi Cancer Center database, there were 807 bladder cancer patients between 2006 and 2016. One hundred fifty-four patients had muscle invasive bladder cancer, and 97 of those patients had adequate data for further analyses.

Radical cystectomy with urinary diversion was the first treatment option for muscle invasive bladder cancer patients in Ramathibodi Hospital. If the patients did not agree to have the surgery or were unfit for surgery, external beam radiation and adjuvant chemotherapy were the second option. For the patients who opted for radical surgery, the surgical approach, which were open or laparoscopic or robotic radical cystectomy, depended on the patients' and doctors' preferences. Urinary diversion using an ileal conduit or orthotopic ileal neobladder was used if there were no contraindications.

The primary outcomes were the overall survival and median survival of each treatment group. The secondary outcome was the comparison of overall survival in the radical cystectomy group between the octogenarian group and the non-octogenarian group, a factor related to survival outcomes and postoperative complications.

The log rank test was used to compare the treatments and outcomes of each age group. Cox regression analysis was used to predict factors related to survival outcome and presented by Kaplan-Meier curve. Univariate and multivariate binary logistic regression were used to examine the association of factor-related mortality. Stata, version 14.1 (StataCorp LP, College Station, TX, USA; Licensed to: Section for clinical epidemiology and biostatistics Ramathibodi Hospital) was utilized.

Results
Demographic, clinical, and pathologic characteristics

Ninety-seven muscle invasive bladder cancer patients were identified between 2006 and 2016. Eighty-six patients were treated by radical cystectomy (88.65%), and 11 patients were given non-surgical treatment (11.34%). Of all patients who received surgical treatment, 14 (16.28%) were in the octogenarian group or aged 80 years or older, and 72 (83.72%) were in the non-octogenarian group or younger than 80 years old.

In the surgical therapy group, the median body mass index (BMI) was 23.24. Most patients had ECOG status 1, with seven patients at ECOG 0, 33 at ECOG 1, 17 at ECOG 2, four at ECOG 3, one at ECOG 4, and , none at ECOG 5. The most common underlying diseases in patients received surgical treatment were hypertension with 50 patients, and dyslipidemia with 48 patients. The pathological stage was T2 in 35 patients, T3 in 32 patients, and T4 in 15 patients, as shown in Table 1.

Clinical and survival outcomes

Table 2 shows the overall survival at one, three, and five years in the patients that received radical cystectomy or non-surgical therapy. The radical cystectomy group had overall survival at five years of 66.51% (95% CI 46.86 to 80.29), while the non-radical cystectomy group had overall survival at five years of 42.86% (95% CI 5.83 to 77.86). Median survival times of non-surgical therapy and radical cystectomy were 24 and 68 months, respectively. Cox regression was used to analyze associations between patients that received radical cystectomy in all ages, and mortality end point events were not significantly associated with hazard risk ratio (HR) 0.41 (95% CI 0.11 to 1.49, p=0.178) as shown in Figure 1.

The association between age and survival outcome was interpreted in Table 3. Patients that received a radical cystectomy at age of 80 years or older had overall five-year survival of 44.44% (95% CI 6.62 to 78.49), and there were no patients that received non-surgical therapy at ages of 80 years or older who survived at three and five years (Table 3). The median survival rates of patients aged 80 years

Table 1. Demographic and baseline clinical characteristics of the included patients

Demographic	Radical cystectomy; n (%)		Non-surgical treatment; n (%)		p-value
	<80 years	≥80 years	<80 years	≥80 years	
No. of patients	72 (100)	14 (100)	7 (100)	4 (100)	0.107
Sex					
Male	55 (76.39)	11 (78.57)	4 (57.14)	1 (25.00)	
Female	17 (23.61)	3 (21.43)	3 (42.85)	3 (75.00)	
BMI (kg/m^2); median	24.48	22.00	25.63	21.41	0.724
BMI <25	37 (51.39)	11 (78.51)	5 (71.43)	0 (0.00)	
BMI ≥25	35 (48.61)	3 (21.43)	2 (28.57)	4 (100)	
ECOG status					0.053
ECOG 0	5 (6.94)	2 (14.28)	1 (14.29)	1 (25.00)	
ECOG 1	29 (40.28)	4 (28.57)	2 (28.57)	0 (0.00)	
ECOG 2	16 (22.22)	1 (7.14)	2 (28.57)	2 (50.00)	
ECOG 3	1 (1.39)	3 (21.43)	2 (28.57)	0 (0.00)	
ECOG 4	1 (1.39)	0 (0.00)	0 (0.00)	1 (25.00)	
ECOG 5	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
ASA classification					0.476
ASA class 1	4 (5.56)	1 (7.14)	0 (0.00)	0 (0.00)	
ASA class 2	29 (20.28)	2 (14.29)	2 (28.57)	0 (0.00)	
ASA class 3	34 (47.22)	9 (64.29)	5 (71.43)	4 (100)	
ASA class 4	5 (6.94)	2 (14.29)	0 (0.00)	0 (0.00)	
Underlying disease					
Diabetes mellitus	20 (27.78)	5 (35.71)	2 (28.57)	2 (50.00)	0.572
Hypertension	40 (55.56)	10 (71.43)	5 (71.43)	2 (50.00)	0.299
Dyslipidemia	33 (45.83)	9 (64.29)	3 (42.86)	2(50.00)	0.178
COPD	4 (5.56)	2 (14.29)	0 (0.00)	0 (0.00)	0.290
Heart disease	5 (6.94)	3 (21.43)	1 (14.29)	0 (0.00)	0.748
Cerebrovascular disease	3 (4.17)	0 (0.00)	0 (0.00)	0 (0.00)	0.464
Chronic kidney disease	15 (20.83)	7 (50.00)	2 (28.57)	2 (50.00)	0.898
Operation technique					
Open	63 (87.5)	12 (85.71)			
Laparoscopic	5 (6.94)	2 (14.29)			
Robotic	4 (5.56)	0 (0.00)			
Type of urinary diversion					
Ileal conduit	50 (69.44)	14 (100)			
Orthotopic neobladder	22 (30.56)	0 (0.00)			
Pathological finding					
T stage					
• T stage 2	29 (40.28)	6 (42.86)			
• T stage 3	28 (38.89)	4 (28.57)			
• T stage 4	11 (15.28)	4 (28.57)			
Lymph node status					
• Positive	22 (30.56)	3 (21.43)			
• Negative	50 (69.44)	11 (78.57)			
Surgical margin					
• Positive	5 (6.94)	0 (0.00)			
• Negative	67 (93.06)	14 (100)			
Lymphovascular invasion					
• Positive	27 (37.5)	7 (50.00)			
• Negative	45 (62.5)	7 (50.00)			
Histologic type					
• Urothelial cell carcinoma	60 (83.33)	11 (78.57)			
• Non-urothelial cell carcinoma	12 (16.67)	3 (21.43)			

BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; ASA=American Society of Anesthesiologists; COPD=chronic obstructive pulmonary disease

Table 2. Overall survival in all age ages group between surgical treatment and non-surgical treatment

Time	Overall function (%)	95% confidence interval
Radical cystectomy		
1 years	95.24	82.27 to 98.79
3 years	74.82	56.88 to 86.14
5 years	66.51	46.86 to 80.29
Non-surgical therapy		
1 years	85.71	33.41 to 97.86
3 years	42.86	5.83 to 77.68
5 years	42.86	5.83 to 77.68

Table 3. Overall survival function stratified by ages

Variable	Age	Time	Overall survival (%)	95% confidence interval
Radical cystectomy	<80 years	1 years	100	-
		3 years	80.09	60.79 to 90.57
		5 years	70.08	48.00 to 84.18
	≥80 years	1 years	66.67	19.46 to 90.44
		3 years	44.44	6.62 to 78.49
		5 years	44.44	6.62 to 78.49
Non-surgical therapy	<80 years	1 years	75.00	12.79 to 96.05
		3 years	75.00	12.79 to 96.05
		5 years	75.00	12.79 to 96.05
	≥80 years	1 years	100	-
		3 years	-	-
		5 years	-	-

Number at risk

Non-radical cystectomy	8	5	3	2	1
Radical cystectomy	42	32	20	10	1

- - - Non-radical cystectomy —— Radical cystectomy

Figure 1. Kaplan-Meier curve of survival stratified by treatment (p=0.178).

Number at risk

Age < 80	36	29	18	8	1
Age ≥ 80	6	3	2	2	0

—— Age < 80   - - - Age ≥ 80
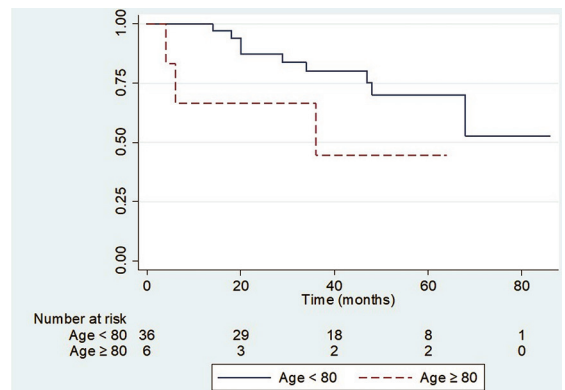
Figure 2. Kaplan-Meier curve of survival stratified by ages in the radical cystectomy group (p=0.106).

or older in the radical cystectomy group and non-surgical therapy group were 36 and 20 months, respectively. Cox regression analysis between patients aged 80 years or older or less than 80 years who received radical cystectomy showed no statistically significant difference by HR 2.99 (95% CI 0.79 to 11.31, p=0.106), as shown in Figure 2.

Postoperative complications related to age

Postoperative complications were stratified by an age group of 80 years or older and less than 80 years old. Early postoperative complications were defined as complications that occurred in the period after radical cystectomy until discharge from hospital. Late complications were defined by any complications that related to the radical cystectomy operation and occurred after discharge or from outpatient department follow-up. Minor complications included Clavien-Dindo classification below grade 2 and major co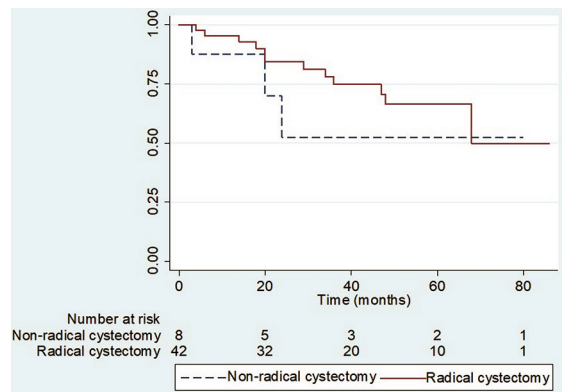mplications were more than grade 3. In the early postoperative complications, patients in age group of 80 years or older had complications reported by 12 from 14 patients (85.71%), and those in the age group younger than 80 years old had complications in 25 from 72 patients (34.72%). The most common early complication was Clavien-Dindo classification 3 in both groups. In the late postoperative stages, patients 80 years or older had complications in 9 out of 14 patients (64.28%), and patients younger than 80 years old had complications in 44 out of 72 patients (61.11%), as shown in Table 4. The most common late complication was infection in both groups.

Discussion

The present study endeavored to explore the survival outcomes after treatment of muscle invasive bladder cancer patients in both octogenarian and non-octogenarian age groups and attempted to identify the factors that might relate to the survival outcomes and complications after surgery in the octogenarian group.

Table 4. Postoperative complication (complications stratified by ages)

Variables	Age ≥80 years; n (%)	Age <80 years; n (%)
Radical cystectomy	14 (100)	72 (100)
Clavian-Dindo classifications		
Grade 2	5 (35.71)	9 (12.5)
Grade 3	5 (35.71)	12 (16.67)
Grade 4	0 (0.00)	2 (9.72)
Grade 5	2 (14.28)	2 (9.72)
Early postoperative complication	12 (85.71)	25 (34.72)
Late postoperative complication	9 (64.28)	44 (61.11)

The present study showed that patients who received radical cystectomy had an overall survival of up to five years better than the non-surgical treatment group at 66.51% and 42.86%, respectively. However, this was not a statistically significant difference (p=0.178). Similarly, the median survival time in the radical cystectomy group was longer than in the non-surgical treatment group at 68 and 24 months, respectively. Again, this was not a statistically significant difference. The authors still believe that radical cystectomy provides better cancer control and better oncological outcomes for muscle invasive bladder cancer patients. From the present study findings, patients who had radical cystectomy could live 44 months longer than the non-surgical treatment group. Most patients in the non-surgical group had unfit or unsuitable conditions for surgery, such as underlying disease or frailty, which led them to have shorter life spans. However, the authors could not find a statistically significant difference because of the very small number of patients in the non-surgical treatment group. Therefore, this might have caused a deviation in the statistical analysis results.

Similarly, in the analysis of age and treatment associated with mortality rates, the present study showed that overall survival in the non-surgical treatment group with an age of 80 years or older still had an inferior outcome when compared to the radical cystectomy group of the same age. The radical cystectomy group with age 80 years or older had an HR of 2.99 to mortality events, but it was not significant (p=0.106). This result imply that the octogenarian group still benefited from radical cystectomy like younger patients of less than 80 years.

In a systematic review by Fonteyne et al[7], they found that overall survival decreased in elderly patients and worsened for patients aged older than 80 years. Cancer-specific survival and perioperative mortality were also worse in the group of elderly patients than for younger patients. From 12 trials included, 10 were interpreted as increasing age was associated with worse survival for patients older than 70 years compared with patients younger than 70 years old with reported hazard ratios between 1.34 to 1.46. Risk of dying also increases in patients older than 80 years compared with patients younger than 70 years with reported hazard ratios between 1.63 to 3.22. Old age, or older than 80 years, is a significant factor for cancer-specific survival, with hazard ratios between 1.56 and 2.54. Patients older than 80 years have a 4.61 to 6.25-fold increased risk of perioperative mortality.

Standard therapy for muscle invasive bladder cancer patients is radical cystectomy with pelvic lymph node dissection. More than half of those that undergo definitive therapy receive radical cystectomy[5]. Although radical cystectomy is an aggressive treatment for elderly patients, it may improve survival rate. Hollenbeck et al[8] reported that radical cystectomy in bladder cancer patients who were 80 or older reduced the risk of death from cancer (hazard ratio 0.3). Similarly, Chamie et al[9] found that radical cystectomy with standard pelvic lymphadenectomy in the octogenarian group showed an increased rate of cancer-specific survival, but not overall survival.

It is challenging to distinguish the cut-off age between young and elderly patients. Most studies, including a systematic review, defined elderly patients as those who were 70 years of age or older[7]. However, the cut-off for old age cannot be defined exactly because the concept does not share the same meaning in all societies and may differ in each patient or country. Some elderly patients may have a better health status than younger patients. Age should not be a factor or criterion for treating patients. Nevertheless, the comorbidity of patients is crucial for planning treatment options for each patient[10]. Some comorbidities can develop along with aging, such as cardiovascular disease, renal impairment, hypertension, and dyslipidemia. Preoperative or pretreatment planning and good preparation for patients can potentially reduce the risk of morbidity and complications.

Perioperative and postoperative complications in the elderly are prone to occur more than in younger patients. In a large current series of octogenarians from the Memorial Sloan-Kettering Cancer Center, the elderly tended to have a higher complication rate

than younger patients at 72% versus 64% (p=0.08), whereas major complication rates were similar in both groups at 17% versus 13% (p=0.3)[11]. Several studies have demonstrated that elderly patients have a mortality rate higher than younger patients but a similar rate of postoperative complications, even in patients older than 80 years[12,13].

In the present study, the authors found that postoperative complications occurred more frequently in the elderly group. In elderly patients, they were more prone to have comorbidities than younger patients. However, most of these complications were minor. Major complications were similar in all age groups. Regarding the present study data, good preparation, well-selected patients, and good perioperative care could significantly decrease the complication rate in elderly patients.

As described previously, elderly patients are prone to comorbidity, which can also relate to having poorer American Society of Anesthesiologists physical status classification compared to younger patients[14]. Despite good preoperative or perioperative care, elderly patients can still have more perioperative complications and mortality compared to younger patients. Postoperative mortality is reduced when elderly patients are treated in high-volume centers[15]. High-volume centers have a better prognosis for five-year disease-specific survival when compared to low-volume centers. However, some elderly patients cannot tolerate receiving surgical treatment due to frailty or severe comorbidity. Therapy options must be considered in this patient group and should be balanced between risk and outcome. External beam radiotherapy alone can be considered as an alternative treatment option for elderly patients who are unfit for surgery or cannot tolerate other treatments[16]. Some articles have proposed short radiotherapy regimens rather than longer radiotherapy schedules to reduce the toxicity of radiation[17]. The toxicity of radiation is a topic that physician should advise and discuss with patients before treatment. Gastrointestinal toxicity, genitourinary toxicity, hematuria, and dysuria may occur after radiation therapy, and some side effects can improve or worsen over time[18].

The present study had several limitations. First, it was a retrospective study. Radical cystectomy and pelvic lymphadenectomy are considered standard treatments for this condition, so it is unethical to conduct a randomized study to compare outcomes between surgical and non-surgical treatments. Second, the number of patients in the non-surgical treatment group was small, which led to the difference in the baseline patient characteristics. This was limited by its retrospective nature. Further large-scale clinical studies are needed to confirm the present study findings.

Conclusion

In summary, the present study analyses showed that radical cystectomy provided longer median survival than non-surgical treatment. In terms of five-year survival, the radical cystectomy group still had a better outcome, even in patients of 80 years or older. This can result in better oncologic control from radical cystectomy. Radical cystectomy was still beneficial in well-selected octogenarian patients, no difference from younger patients. Even though the elderly patients were more prone to minor complications, the major complication rates were the same in both groups. Therefore, radical cystectomy in the octogenarian group should be performed in well-selected patients with good preoperative and postoperative care to decrease the rate of complications. Health status and underlying conditions of elderly patients should be carefully considered and discussed with patients to select the most suitable treatment for them. Further large-scale prospective studies may confirm factors related to clinical and survival outcomes.

What is already known on this topic?

Radical cystectomy with pelvic lymphadenectomy was the standard therapy for muscle invasive bladder cancer, but this major operative surgery may be associated with perioperative complications, especially in patients of advanced age. Well-selected patients with good preoperative and postoperative care can decrease the rate of complications.

What this study adds?

This study showed that radical cystectomy with pelvic lymphadenectomy provided a longer survival rate than non-surgical treatment in octogenarians and no statistically significant difference between octogenarian patients and younger patients.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

2. Roser M, Ritchie H. Cancer. Our World in Data [Internet] 2015 [cited 2020 Feb 21]. Available from: https://ourworldindata.org/cancer.

3. Tan WS, Feber A, Sarpong R, Khetrapal P, Rodney S, Jalil R, et al. Who should be investigated for haematuria? Results of a contemporary prospective observational study of 3556 patients. Eur Urol 2018;74:10-4.

4. Prout GR, Marshall VF. The prognosis with untreated bladder tumors. Cancer 1956;9:551-8.

5. Bekelman JE, Handorf EA, Guzzo T, Evan Pollack C, Christodouleas J, Resnick MJ, et al. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification biasin cancer observational comparative effectiveness research. Value Health 2013;16:610-8.

6. Morris DS, Weizer AZ, Ye Z, Dunn RL, Montie JE, Hollenbeck BK. Understanding bladder cancer death: tumor biology versus physician practice. Cancer 2009;115:1011-20.

7. Fonteyne V, Ost P, Bellmunt J, Droz JP, Mongiat-Artus P, Inman B, et al. Curative treatment for muscle invasive bladder cancer in elderly patients: A systematic review. Eur Urol 2018;73:40-50.

8. Hollenbeck BK, Miller DC, Taub D, Dunn RL, Underwood W, 3rd, Montie JE, et al. Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older. Urology 2004;64:292-7.

9. Chamie K, Hu B, Devere White RW, Ellison LM. Cystectomy in the elderly: does the survival benefit in younger patients translate to the octogenarians? BJU Int 2008;102:284-90.

10. Takao T, Tsujimura A, Kiuchi H, Komori K, Fujita K, Miyagawa Y, et al. Urological surgery in patients aged 80 years and older: a 30-year retrospective clinical study. Int J Urol 2008;15:789-93.

11. Froehner M, Brausi MA, Herr HW, Muto G, Studer UE. Complications following radical cystectomy for bladder cancer in the elderly. Eur Urol 2009;56:443-54.

12. Knap MM, Lundbeck F, Overgaard J. Early and late treatment-related morbidity following radical cystectomy. Scand J Urol Nephrol 2004;38:153-60.

13. Yamanaka K, Miyake H, Hara I, Inoue TA, Fujisawa M. Significance of radical cystectomy for bladder cancer in patients over 80 years old. Int Urol Nephrol 2007;39:209-14.

14. Prout GR Jr, Wesley MN, Yancik R, Ries LA, Havlik RJ, Edwards BK. Age and comorbidity impact surgical therapy in older bladder carcinoma patients: a population-based study. Cancer 2005;104:1638-47.

15. Patel MI, Bang A, Gillatt D, Smith DP. Contemporary radical cystectomy outcomes in patients with invasive bladder cancer: a population-based study. BJU Int 2015;116 Suppl 3:18-25.

16. Bellmunt J, Orsola A, Maldonado X, Kataja V. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v134-6.

17. Kouloulias V, Mosa E, Tolia M, Kantzou I, Koliarakis N, Platoni K, et al. Evaluation of efficacy and toxicity in two different hypofractionated 3D-conformal external beam radiotherapy schedules in localised muscle invasive bladder cancer. J BUON 2013;18:942-8.

18. Kouloulias V, Tolia M, Kolliarakis N, Siatelis A, Kelekis N. Evaluation of acute toxicity and symptoms palliation in a hypofractionated weekly schedule of external radiotherapy for elderly patients with muscular invasive bladder cancer. Int Braz J Urol 2013;39:77-82.