
Propensity score matched survival analysis of octogenarians with muscle-invasive bladder cancer: chemoradiation compared to radical cystectomy

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Introduction: Radical cystectomy (RC) is an effective curative treatment option for muscle-invasive bladder cancer (MIBC). However, chemoradiation (CRT) is an evolving bladder preservation protocol alternative to RC. With the increase in life expectancy, it is essential to understand the survival outcomes among octogenarians treated with RC and CRT. In this study, we use the National Cancer Database (NCDB) to compare the survival outcomes between RC and CRT in octogenarians.

Materials and methods: We collected the data of patients treated for bladder cancer between 2004 to 2018 from the NCDB. Our primary analytic cohort included patients with MIBC (cT2-T4N0M0). We identified the octogenarians and categorized them into RC and CRT

arms. The RC arm included those who received RC. The CRT arm included those who received chemotherapy within 90 days of curative radiation therapy. After 1:1 propensity score matching, overall survival (OS) outcomes were compared between both arms.

Results: Among the octogenarians, the median OS for patients treated with RC was 26.1 months (95% CI, 23.9-28.2), and CRT was 28.7 months (95% CI, 26.8-30.6). Our covariate analyses showed that academic institutions performed more RC (49% RC and 29.7% CRT) and community programs served more CRT (45.7% CRT and 24.2% RC). A multivariate Cox regression analysis showed that the mortality risk increased as the Charlson-Deyo comorbidity score and T stage increased.

Conclusion: Octogenarians treated with RC and CRT had similar OS. As life expectancy increases, it is essential to individualize the treatment strategy based on risk assessment and its potential benefits.

Key Words: octogenarian, radical cystectomy, chemoradiation, muscle invasive bladder cancer

Introduction

Bladder cancer is often associated with increased morbidity and mortality. At diagnosis, approximately

25%-30% of bladder cancers are muscle-invasive bladder cancer (MIBC).¹ In 2020, global cancer statistics reported 573,278 new cases and 212,536 deaths due to bladder cancer, contributing to 3% and 2% of all malignancies.² In 2022, the National Comprehensive Cancer Network estimated 81,180 new cases and 17,100 deaths due to bladder cancer in the United States, making it the sixth most common cancer.³

According to the Centers for Disease Control and Prevention, in the United States, the overall average life expectancy has increased over the past few decades.

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The current average life expectancy at birth is 76.4 years. Men have an average life expectancy of 73.5 years, and women have an average of 79.3 years. At 65 years of age, the life expectancy of men is 18.4 years, and women are 19.7 years.⁴ In recent years, more octogenarian patients have been undergoing major surgeries such as radical cystectomy (RC) because of the increase in life expectancy and advances in healthcare.

RC is an effective curative treatment for MIBC.⁵ However, due to its high morbidity, bladder preservation protocols emerged aiming to improve the functional outcome and its effect on the patient's quality of life (QoL).⁶ Bladder preservation protocols included transurethral resection of bladder tumor (TURBT), radiation or chemotherapy as a monotherapy, and TURBT in combination with chemoradiation (trimodality treatment). Several studies have compared RC and chemoradiation (CRT), but the results are varied. Studies have shown that following RC, the 5-year cancer-specific survival (CSS) was 83 %, and the overall survival (OS) was 72%. Similarly, following trimodality treatment, the 5-year CSS was 85%, and 10-year OS was 77%.⁷ RC, and its outcome needs further evaluation in octogenarians due to the advances in healthcare.⁸ Only a few studies are available on the treatment modalities for MIBC and its survival outcomes in octogenarians. This study uses the National Cancer Database (NCDB) to analyze the survival outcomes among octogenarians undergoing CRT and RC.

Materials and methods

Patient selection

The NCDB is a nationwide data repository that houses information on 70% of all newly diagnosed cancers across the United States.⁹ Retrospective data from 2004 to 2018 were used for our study. Our primary analytic cohort included patients with localized MIBC (cT2-T4N0M0). Patients included in our study were those aged 80 years or more. The survival outcomes of the two treatment modalities, RC and CRT, were compared. The RC arm was defined as those patients who received RC as the definitive surgery (coded as radical/total cystectomy with urinary diversion). The RC arm also included patients who received neoadjuvant and adjuvant chemotherapy. The CRT arm was defined as patients receiving chemotherapy and radiation within 90 days of each other.

Statistical analyses

Sociodemographic (gender, race, ethnicity, treatment facility type, median income, and insurance type) and clinical (comorbidity score, histology, tumor grade,

and clinical stage) variables were compared between cohorts. Race and ethnicity were simplified to white, black, other/unknown, and Hispanic or non-Hispanic, respectively. This was because of the small amount of representation among the other listed categories. The sociodemographic and clinical variables were tabulated using Chi-square analysis and contingency tables. Following this, a 1:1 propensity score matching (greedy-matching algorithm) with a matching caliper width of 0.01 among the octogenarians was done to minimize confounding between the two treatment cohorts. Gender, race, ethnicity, facility type, comorbidity score, histology, tumor grade, and clinical T stage were the variables used for matching. The 1:1 propensity-matched cohort generated 2,648 patients each in the RC and CRT arms. Kaplan-Meier survival curves with log-rank test and Cox regression analyses were used to compare the survival outcomes between both treatment modalities. Statistical significance was defined as a p value of < 0.05 across all analyses. The statistical software used to perform these analyses was IBM SPSS Statistics, version 28.0.

Results

The NCDB reported 671,462 patients with bladder cancer between 2004 and 2018. Out of which, 95,543 patients had clinical stage T2-T4N0M0. Among these patients, 36,289 had undergone RC, and 7,645 had received CRT. We then identified the study population of 6,960 octogenarians who received either RC or CRT. In our octogenarian cohort, 4,146 patients underwent RC, and 2,814 received CRT. In the univariate analysis, among the patients who underwent RC, Table 1, 2,032 (49%) were treated in academic institutions and 1,231 (29.7%) in community programs ($p < 0.001$). While for patients who received CRT, 1,285 (45.7%) underwent CRT in a community program center and 681 (24.2%) in academic centers ($p < 0.001$). In patients with a comorbidity score of 0, 2,706 (59.5%) underwent RC, and 1,842 (40.5%) received CRT. Also, among those treated with RC and CRT, a comorbidity score of 2 or more was noted in 10.4% and 12.6% ($p < 0.001$), respectively, Table 1. However, race, ethnicity, income, histology, and clinical stage had no statistically significant difference.

In the multivariate analysis, Table 2, the mortality risk among RC and CRT increased as the Charlson-Deyo comorbidity index increased. Patients with a comorbidity index ≥ 3 had a hazard ratio (HR) of 1.42 ($p < 0.001$) within the CRT arm and HR of 1.45 ($p < 0.94$) within the RC arm. Similarly, the mortality risk increased as the patient's tumor stage increased.

TABLE 1. Demographics for chemoradiation vs. radical cystectomy for localized muscle-invasive bladder cancer (T2-T4N0M0) unmatched octogenarian population

Variables		Unmatched			Matched		
		RC	CRT	p value	RC	CRT	p value
Total n (%)		4146 (59.6)	2814 (40.4)		2648 (50)	2648 (50)	
Sex	Male, n (%)	2980 (71.9)	2038 (72.4)	0.617	1927 (72.8)	1903 (71.9)	0.461
	Female, n (%)	1166 (28.1)	776 (27.6)		721 (27.2)	745 (28.1)	
Race	White, n (%)	3892 (93.9)	2614 (92.9)	0.039	2482 (93.7)	2470 (93.3)	0.648
	Black, n (%)	141 (3.4)	129 (4.6)		110 (4.2)	112 (4.2)	
	Other/Unknown, n (%)	113 (2.7)	71 (2.5)		56 (2.1)	66 (2.5)	
Ethnicity	Non-Hispanic, n (%)	3892 (93.9)	2633 (93.6)	0.666	2506 (94.6)	2477 (93.5)	0.147
	Hispanic, n (%)	90 (2.2)	58 (2.1)		36 (1.4)	52 (2)	
	Unknown, n (%)	164 (4)	123 (4.4)		106 (4)	119 (4.5)	
Facility type	Community program	188 (4.5)	249 (8.8)	< 0.001			
	Comprehensive community program	1231 (29.7)	1285 (45.7)				
	Academic program	2032 (49)	681 (24.2)				
	Integrated network cancer program	695 (16.8)	599 (21.3)				
Median income	< \$40,227	496 (13.2)	340 (13.2)	0.771	328 (13.5)	306 (12.6)	0.195
	\$40,228-\$50,353	864 (23)	572 (22.1)		578 (23.8)	541 (22.3)	
	\$50,354-\$63,332	947 (25.2)	646 (25)		617 (25.4)	610 (25.1)	
	>=\$63,333	1444 (38.5)	1025 (39.7)		903 (37.2)	974 (40.1)	
Insurance	Not insured, n (%)	15 (0.4)	2 (0.1)	0.006	9 (0.3)	2 (0.1)	0.035
	Private, n (%)	332 (8)	232 (8.2)		224 (8.5)	219 (8.3)	
	Medicaid, n (%)	42 (1)	17 (0.6)		24 (0.9)	17 (0.6)	
	Medicare, n (%)	3690 (89)	2496 (88.7)		2351 (88.8)	2349 (88.7)	
	Other government, n (%)	26 (0.6)	34 (1.2)		14 (0.5)	30 (1.1)	
	Unknown, n (%)	41 (1)	33 (1.2)		26 (1)	31 (1.2)	
Comorbidity score	0	2706 (65.3)	1842 (65.5)	0.002	1756 (66.3)	1732 (65.4)	0.881
	1	1008 (24.3)	615 (21.9)		593 (22.4)	601 (22.7)	
	2	307 (7.4)	232 (8.2)		207 (7.8)	216 (8.2)	
	>=3	125 (3)	125 (4.4)		92 (3.5)	99 (3.7)	
Histology	Urothelial	3792 (91.5)	2601 (92.4)	0.147	194 (7.3)	204 (7.7)	0.602
	Non-urothelial	354 (8.5)	213 (7.6)		2454 (92.7)	2444 (92.3)	
Grade	1	27 (0.7)	18 (0.6)	0.003	16 (0.6)	18 (0.7)	0.775
	2	197 (4.8)	95 (3.4)		85 (3.2)	94 (3.5)	
	3	1478 (35.6)	1031 (36.6)		997 (37.7)	976 (36.9)	
	4	2030 (49)	1329 (47.2)		1276 (48.2)	1263 (47.7)	
	Unknown	414 (10)	341 (12.1)		274 (10.3)	297 (11.2)	
Clinical stage	cT2	3391 (81.8)	2319 (82.4)	0.120	2215 (83.6)	2169 (81.9)	0.246
	cT3	506 (12.2)	305 (10.8)		270 (10.2)	298 (11.3)	
	cT4	249 (6)	190 (6.8)		163 (6.2)	181 (6.8)	

RC = radical cystectomy

CRT = chemoradiation therapy

TABLE 2. Multivariate Cox regression for propensity-matched octogenarians

Variable	CRT		RC	
	HR (95% CI)	p value	HR (95% CI)	p value
Treatment modality	0.996 (0.934-1.061)	0.895	Ref	
Comorbidity index				
0	Ref.		Ref.	
1	1.117 (1.002-1.245)	0.046	1.241 (1.114-1.383)	< 0.001
2	1.235 (1.048-1.455)	0.012	1.472 (1.253-1.730)	< 0.001
>=3	1.419 (1.109-1.815)	0.005	1.448 (1.131-1.853)	0.003
Clinical stage				
T2	Ref.		Ref.	
T3	1.205 (1.047-1.386)	0.009	1.125 (0.973-1.300)	0.112
T4	1.618 (1.370-1.911)	< 0.001	1.622 (1.353-1.945)	< 0.001

RC = radical cystectomy; CRT = chemoradiation therapy

Patients with clinical-stage T4 had an HR of 1.62 ($p < 0.001$) within the CRT arm and an HR of 1.62 ($p < 0.001$) within the RC arm. A Kaplan-Meier survival analysis showed that among propensity-matched octogenarians, RC and CRT had similar OS, Figure 1. The median OS for the RC arm was 26.1 months (95% CI, 23.9-28.2), and for the CRT arm was 28.7 months (95% CI, 26.8-30.6).

Discussion

Our study compared the survival outcomes between RC and CRT in octogenarians with localized MIBC from the NCDB. We observed that octogenarians treated with RC had comparable OS to those treated with CRT (26.1 months vs. 28.7 months). In addition, our covariate analyses showed that academic

institutions performed more RC (49% RC and 29.7% CRT) and community programs served more CRT (45.7% CRT and 24.2% RC). In the propensity-matched octogenarian cohort treated with RC or CRT, the risk of mortality increased as the comorbidity score and clinical stage increased.

In a study by Ritch et al, the median 5-year OS for all ages was better with RC than with CRT (38% vs. 30%, $p < 0.004$). They noted an increase in age and comorbidity scores were significantly associated with decreased OS.¹⁰ We also noted that an increased comorbidity score was associated with decreased OS. They also found that urothelial histology predicted reduced OS.¹⁰ Similar to their study, we included both urothelial and non-urothelial histology. Even though urothelial histology was more predominant, we did not observe its influence on OS. Lin et al, in their NCDB study, showed that those treated with neoadjuvant chemotherapy followed by RC in all ages had better OS compared to those who received CRT after matching with the analytic stage. This benefit was no longer seen when the clinical stage was used for propensity matching or when less stringent criteria were used.¹¹

Cahn et al conducted a study that showed OS for all ages was increased in patients who underwent RC compared to any bladder preservation therapy (BPT). Notably, patients receiving CRT were likely to have more than two comorbid conditions and were treated at community or lower-volume centers. When more stringent definitions and rigorous statistical methods were used to control confounders, the extent of OS benefit was reduced between the RC and CRT. Their study also observed that continuous or split-dosing CRT is becoming increasingly popular in BPT, and 4.6%

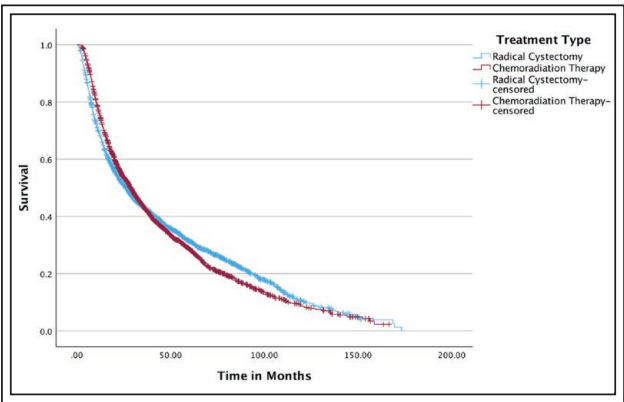


Figure 1. Propensity-matched octogenarian survival curve (RC vs. CRT).

of their BPT cohort had definitive CRT.¹² Similarly, our study also showed CRT was performed more in community centers, but OS was comparable between RC and CRT.

A case-control study by Gofrit et al found that although the comorbidity index was significantly higher in patients treated with CRT, the OS was similar among all ages in both RC and CRT arms. The 5 years OS for RC and CRT were 54.8% and 56.6%, respectively. The mean radiation was 62 Gy, and gemcitabine, cisplatin, and carboplatin were used for chemotherapy.¹³ Similar survival outcomes were noted in both arms of our cohort, although chemotherapy details were unavailable.

Kaushik et al found that RC patients had better 5-year OS than those who received CRT. However, in patients of age 70 years and above, this difference was not appreciated. When age was matched, there was no difference in OS for those over 70 years ($p = 0.52$).¹⁴ In our study on 2,814 octogenarians pairs, the median overall survival for RC was similar to CRT. A study focused on octogenarians conducted by Fischer-Valuck et al, using the NCDB, showed that CRT had increased OS compared to RC but was not statistically significant. Also, RC with chemotherapy had better median survival over CRT.¹⁵ On the other hand, Boustani et al, in their study on 164 octogenarians, showed no significant difference in OS between RC and CRT.¹⁶ As the results are variable, assessing QoL in octogenarians following RC and CRT would be essential to contemplate the treatment options. Evaluation of QoL includes assessment of physical, psychological, and functional health.¹⁷

There is little research on survival and oncological outcomes of RC in octogenarians. A comparative study on survival outcomes of RC and CRT showed RC had decreased survival in the initial period compared to CRT but better long term results.¹⁰ These results are not particular to octogenarians. This highlights the need to determine life expectancy, treatment goals, and prognosis when considering treatment options for patients. For patients opting for surgical management, neoadjuvant chemotherapy with RC has shown better results which need further research in octogenarians.¹¹

We observed that a higher percentage of octogenarians (40.4%) are treated with CRT. Elshabrawy et al studied the refusal of RC despite being recommended as a first-line treatment. Those patients who refused surgery were mostly elderly, with comorbidities like those pursuing radical cystectomy.¹⁸ Patients refusing surgery could have been a possible reason for the increased percentage of octogenarians receiving CRT. However, the need

for follow up salvage cystectomy among those who refused RC is not evaluated. Schuettfort et al conducted a meta-analysis on salvage RC and found a pooled non-response rate of 15.5% for bladder-sparing therapy, and the local recurrence after such therapy was 28.7%. In addition, there was a higher overall complication rate for salvage RC compared to primary RC.¹⁹ Our study lacks data on the recurrence rates, details of salvage RC, and QoL following the interventions. This information could help facilitate informed and shared decision-making.

Although TURBT as a monotherapy is not an alternative to RC, it is considered a viable treatment option, considering the patient's age and general condition. Zheng et al, in a study from Surveillance, Epidemiology, and End Results program, noted that 90.9% of patients with age > 85 years underwent TURBT. Also, the 5-year OS for TURBT was reduced compared to RC (28.7% vs. 64.9%).²⁰ In a study by Rehme et al, RC had a better OS in octogenarians than TURBT (18.9% vs. 15.2%; $p = 0.036$). Interestingly they observed that the median percentage change in QoL at 6 months was better with the RC cohort than the TURBT cohort (22.9% and 2.3%; $p < 0.0001$).²¹ As life expectancy increases and more patients undergo major surgeries, exploring the potential of RC among octogenarians is essential.

Our results showed RC and CRT had similar OS, but more prospective studies in the future, including QoL, will be needed to help inform patients about the treatment options. Kaushik et al used screening logs from the recruitment phase and found that only 5 of 62 patients were candidates for either RC or CRT. Eventually, they underwent RC due to the extensive tumor nature.²² The complexity associated with tumor burden and tumor upstaging makes conducting randomized trials challenging.

An inherent limitation of this study is its retrospective design. Although propensity matching can minimize the effect of confounding factors and selection bias, it still cannot eliminate it. In addition, many other factors, like depth of TURBT and its effect as a monotherapy, type of chemotherapy and its complications, post-radical cystectomy follow up complications, complications post radiation therapy, QoL, and recurrence-free survival, are unavailable in the NCDB. Future studies conducted to assess the interventions in terms of QoL, complications, treatment failure, and impact on survival would help to individualize treatment for octogenarians. Also, this could aid in improving shared decision-making in healthier elderly patients who are better candidates for surgery.

Conclusion

Octogenarians treated with RC had similar OS compared to CRT. With the increase in life expectancy, it is essential to tailor the treatment options to each individual. In addition, octogenarians encompass a wide range of individuals with varying health conditions. Hence personalizing the treatment based on the risk assessment and potential benefits would be advisable. Future prospective studies focusing on the long term outcomes, including disease-specific survival and QoL in octogenarians following RC, CRT, and other bladder preservation protocols, will provide valuable insight. This will empower shared decision-making and balance the QoL in octogenarians. □

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