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RESEARCH ARTICLE

Effect of Intravesical Chemotherapy on the Survival of Patients with Non-Muscle-Invasive Bladder Cancer Undergoing Transurethral Resection: A Retrospective Cohort Study Among Older Adults

Ashis K. Das[1,*], Devi K. Mishra[2] and Saji S. Gopalan[3]

[1]*Department of Health Nutrition and Population, The World Bank Group, WashingtonDC, USA*
[2]*Department of Community Medicine, Hitech Medical College, Rourkela, India*
[3]*Department of Human Development, The World Bank, WashingtonDC, USA*

Abstract:

Background:

The average age of diagnosis for bladder cancer is 73 and about 75 percent of all bladder cancers are non-muscle invasive at initial diagnosis. It is recommended that non-muscle invasive bladder cancers (NMIBC) should be treated with transurethral resection of the bladder tumor (TURBT) followed by chemotherapy. However, there is no large-scale study from real-world databases to show the effectiveness of chemotherapy on the survival of older adults with NMIBC that have undergone TURBT. This study aimed to investigate the effects of chemotherapy on survival among older NMIBC patients with TURBT.

Methods:

Using the Surveillance, Epidemiology, and End Results (SEER) database (2010-2015), we performed analyses of cancer-specific mortality and overall mortality comparing chemotherapy *versus* no chemotherapy after TURBT. Coarsened exact matching was performed to balance the baseline patient characteristics. Cox proportional hazards and Kaplan-Meir analyses were used to evaluate survival outcomes.

Results:

A total of 3,222 matched patients with 1,611 in each arm (chemotherapy and no chemotherapy) were included in our study. After adjusting for covariates, multivariable Cox regression analyses show chemotherapy was associated with lower cancer-specific mortality (HR 0.63; 95% CI 0.42-0.94; p value 0.024). However, chemotherapy did not have any effect on overall mortality (HR 0.84; 95% CI 0.65-1.07; p value 0.159). The Kaplan-Meier curves show the protective effects of chemotherapy on cancer specific survival (p=0.032), but not on overall survival (p=0.34).

Conclusion:

Chemotherapy improved cancer specific survival among older patients with non-muscle invasive bladder cancer undergoing TURBT surgery, but it had no effect on overall survival. There is a need for more granular level real-world data on chemotherapy regimens and dosage to effectively investigate the effects of chemotherapy on the survival of older patients with NMIBC that have undergone TURBT.

Keywords: Bladder cancer, Cancer survival, Chemotherapy, TURBT, Comparative effectiveness, Real-world databases.

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1. INTRODUCTION

Bladder cancer is the most common cancer of the urinary system among the American population, and an estimated 83,730 new cases of bladder cancer and 17,200 deaths are expected to occur in the United States in 2021 [1]. It is the fourth most common cancer among men. The average age of diagnosis for bladder cancer is 73 and about 90 percent of patients are above 55 years [2]. About 75 percent of all bladder cancers are non-invasive at initial diagnosis [3]. The non-muscle invasive bladder cancers (NMIBC) include papillary tumors (Ta), carcinoma *in situ* (CIS or Tis) and tumors invading the subepithelial connective tissue (T1). The 5-year relative survival rate for bladder cancer is 77% overall, whereas it can be up to 96% for patients with NMIBC. Though

* Address correspondence to this author at Department of Health Nutrition and Population, The World Bank Group, Washington DC, USA;
Email: adas8@worldbank.org

patients with NMIBC have higher survival rates, they have a high chance of recurrence or progression even with therapies [3]. Depending on the clinical and pathological characteristics, NMIBCs have been further risk-stratified as low-, intermediate- and high-risk groups. The recent guidelines recommend that low- and intermediate-risk NMIBC should be treated with transurethral resection of the bladder tumor (TURBT) followed by a single postoperative instillation of intravesical chemotherapy within 24 hours of TURBT [4].

While the guidelines recommend and clinical trials have shown the benefits, there is no large-scale study from real-world databases to show the effectiveness of chemotherapy on the survival of older adults with NMIBC that have undergone TURBT [4 - 7]. Therefore, the aim of this study was to estimate the additional benefit of intervascular chemotherapy on survival of older adults with NMIBC that have undergone TURBT.

2. MATERIALS AND METHODS

2.1. Study Population

In this retrospective cohort study, we selected patients from the Surveillance Epidemiology and End Result (SEER) 21 databases [8]. SEER database has a completeness rate of 98% and all patients were followed up for 10 years after routine treatment until death or loss to follow-up [9]. Patient details such as demographic background, tumor features, and survival are available from these databases. We included patients in our study if they met the following criteria: (a) year of diagnosis 2010 to 2015; (b) adults of 65 years or older age; (c) non-muscle invasive bladder cancer (T1, Ta and Tis); (d) positive histology; and (e) undergone transurethral resection of bladder tumor (TURBT). We excluded patients if they had: (a) radiation therapy; (b) missing socio-demographic characteristics – age, sex, race; (c) missing survival time; (d) missing/unknown cause of death classification; (e) missing tumor characteristics – tumor size, number of malignant tumors, (f) tumor with lymph node involvement; (g) high-risk NMIBC as defined by American Urological Association; and (h) metastatic tumor.

2.2. Variables Definition

The outcome variables for our study were cancer-specific (CSM) and overall mortality (OM). Censoring was applied to patients that died of other causes or were still alive at the end of the follow-up period. Chemotherapy was coded as either administered or not administered according to the SEER classification. Covariates were patient level demographic and tumor specific variables as well as the year of diagnosis. Demographic covariates were sex (male, female), age at diagnosis (categorized by years 65-70, 71-75, 76-80, >80), and race (Black, White, others). Tumor specific covariates were grade (I, II, III, IV and unknown), site (trigone, lateral wall, posterior wall, overlapping lesion of bladder, bladder NOS and others), tumor size (up to 10 mm, 11-20 mm, 21-30 mm, 31-40 mm, 41-50 mm and above 50 mm), and a number of *in-situ* tumors (solitary, multiple). In the SEER database, tumor grade is defined as follows – well differentiated or Grade I, moderately differentiated or Grade II, poorly differentiated or Grade III, undifferentiated/anaplastic or Grade IV, and unknown.

2.3. Statistical Analyses

Frequencies and proportions of categorical variables constituted descriptive statistics. Differences in proportions for categorical variables were compared by the chi-square test. There were baseline imbalances among the covariates. So, a matching technique known as coarsened exact matching was used to create a balanced sample [10]. The cancer specific survival and overall survival curves were created by the Kaplan-Meier method with the log-rank test to compare survival between groups. Multivariable Cox regressions were performed to estimate the impact of chemotherapy on prognosis. The results of the regressions were presented as hazard ratios (HR) with their 95% confidence intervals (CI). The statistical analyses were performed using R programming language (version 3.6.3) and Stata (version 15). All reported P-values were two-tailed with a level of significance at $P < 0.05$.

3. RESULTS

3.1. Descriptive Analysis

Applying the inclusion and exclusion criteria, information of 10,318 patients was extracted from the database. As shown in Table **2**, there were statistically significant differences among the baseline characteristics between patients who received chemotherapy versus those did not. Unbalanced characteristics were age group ($p < 0.001$), year of diagnosis ($p<0.001$), tumor grade ($p=0.001$), size ($p<0.001$) and number of *in-situ,* tumors ($p<0.001$). The five-year survival rate was 96.8 percent. After implementing the coarsened exact matching, there were no significant differences in the covariates. The matched sample consisted of 3,222 patients with 1,611 in each arm (chemotherapy and no chemotherapy). Most patients were men (84.4%), White (97.6%) with solitary *in-situ* tumors (97.3%). More than a third had the tumor on the lateral wall (34%), grade IV tumors (35.6%) and sizes of 21-30 mm (33.3%).

3.2. Survival Analysis

After matching and adjusting for covariates, multivariable Cox regression analyses (Table **2**) showed chemotherapy was associated with lower cancer-specific mortality (HR 0.63; 95% CI 0.42-0.94; p value 0.024). However, chemotherapy did not have any effect on overall mortality (HR 0.84; 95% CI 0.65-1.07; p value 0.159). Patients that are above 75 years and with multiple *in-situ* tumors had higher cancer specific and overall mortality. In addition, patients with grade IV tumors had higher cancer specific mortality. On the contrary, patients diagnosed in the year 2015 had significantly lower cancer-specific and overall mortality. Similar to the regression analyses, the Kaplan-Meier curves Fig. (**1**) show the protective effects of chemotherapy on cancer specific survival ($p=0.032$) but not on overall survival ($p=0.34$).

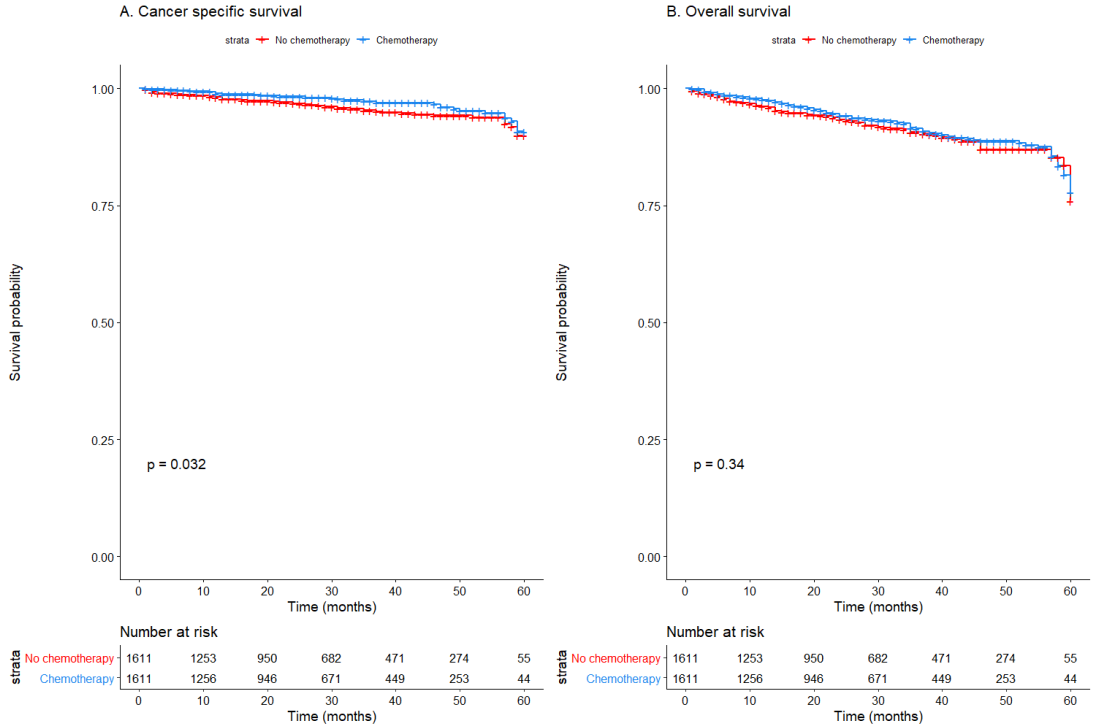

Fig. (1). Effect of chemotherapy on cancer specific survival (**A**) and overall survival (**B**) in NMIBC patients undergoing TURBT.

Table 1. Clinical and pathological characteristics of patients by receipt of chemotherapy.

	Unmatched Sample (n=10,318)			Matched Sample (n=3,222)		
	CHT (n=2,645)	No CHT (n=7,673)	P value	CHT (n=1,611)	No CHT (n=1,611)	P Value
Sex						
Male	2,038 (77.1)	5,831 (76)	0.270	1,360 (84.4)	1,360 (84.4)	1.000
Female	607 (22.9)	1,842 (24)		251 (15.6)	251 (15.6)	
Age Group						
65-70	844 (31.9)	2,301 (30)	<0.001	538 (33.4)	538 (33.4)	1.000
71-75	643 (24.3)	1,634 (21.3)		365 (22.7)	365 (22.7)	
76-80	501 (18.9)	1,502 (19.6)		287 (17.8)	287 (17.8)	
>80	657 (24.8)	2,236 (29.1)		421 (26.1)	421 (26.1)	
Race						
White	2,389 (90.3)	6,939 (90.4)	0.071	1,573 (97.6)	1,573 (97.6)	1.000
Black	92 (3.5)	324 (4.2)		8 (0.5)	8 (0.5)	
Others	164 (6.2)	410 (5.3)		30 (1.9)	30 (1.9)	
Diagnosis Year						
2011	360 (13.6)	1,454 (19)	<0.001	203 (12.6)	203 (12.6)	1.000
2012	454 (17.2)	1,463 (19.1)		265 (16.5)	265 (16.5)	
2013	546 (20.6)	1,459 (19)		304 (18.9)	304 (18.9)	
2014	584 (22.1)	1,629 (21.2)		363 (22.5)	363 (22.5)	
2015	701 (26.5)	1,668 (21.7)		476 (29.6)	476 (29.6)	
Grade						
I	319 (12.1)	1,074 (14)	0.001	151 (9.4)	151 (9.4)	1.000
II	698 (26.4)	2,033 (26.5)		464 (28.8)	464 (28.8)	
III	135 (5.1)	353 (4.6)		45 (2.8)	45 (2.8)	
IV	894 (33.8)	2,301 (30)		573 (35.6)	573 (35.6)	
Unknown	599 (22.7)	1,912 (24.9)		378 (23.5)	378 (23.5)	
Tumor Site						

	Unmatched Sample (n=10,318)			Matched Sample (n=3,222)		
	CHT (n=2,645)	No CHT (n=7,673)	P value	CHT (n=1,611)	No CHT (n=1,611)	P Value
Trigone	175 (6.6)	575 (7.5)	0.310	65 (4.0)	65 (4.0)	1.000
Lateral wall	756 (28.6)	2,165 (28.2)		547 (34.0)	547 (34.0)	
Posterior wall	329 (12.4)	906 (11.8)		167 (10.4)	167 (10.4)	
Overlapping lesion	247 (9.3)	687 (9)		110 (6.8)	110 (6.8)	
Bladder, NOS	760 (28.7)	2,318 (30.2)		520 (32.3)	520 (32.3)	
Others	378 (14.3)	1,022 (13.3)		202 (12.5)	202 (12.5)	
Tumor Size						
Up to 10 mm	280 (10.6)	973 (12.7)	<0.001	153 (9.5)	153 (9.5)	1.000
11-20 mm	690 (26.1)	1,826 (23.8)		436 (27.1)	436 (27.1)	
21-30 mm	740 (28)	2,185 (28.5)		536 (33.3)	536 (33.3)	
31-40 mm	382 (14.4)	942 (12.3)		190 (11.8)	190 (11.8)	
41-50 mm	317 (12)	902 (11.8)		181 (11.2)	181 (11.2)	
> 50 mm	236 (8.9)	845 (11)		115 (7.1)	115 (7.1)	
Number of *in-situ* Tumors						
Solitary	2,445 (92.4)	6,898 (89.9)	<0.001	1,568 (97.3)	1,568 (97.3)	1.000
Multiple	200 (7.6)	775 (10.1)		43 (2.7)	43 (2.7)	

Table 2. Cox regression models predicting cancer specific and overall mortality after matching (n=3,222).

	Cancer Specific Mortality			Overall Mortality		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Chemotherapy						
No	Reference			Reference		
Yes	0.63	0.42-0.94	0.024	0.84	0.65-1.07	0.159
Sex						
Male	Reference			Reference		
Female	1.59	0.95-2.66	0.075	0.70	0.47-1.06	0.09
Age Group						
65-70	Reference			Reference		
71-75	1.06	0.40-2.81	0.91	2.16	1.36-3.43	0.001
76-80	3.40	1.55-7.47	0.002	2.52	1.58-4.02	<0.001
>80	6.76	3.40-13.44	<0.001	5.42	3.67-8.02	<0.001
Race						
White	Reference			Reference		
Black	1.91	0.25-14.62	0.534	.	.	.
Others	0.98	0.23-4.12	0.977	1.20	0.49-2.96	0.694
Diagnosis Year						
2011	Reference			Reference		
2012	1.45	0.83-2.53	0.188	1.22	0.86-1.73	0.258
2013	0.78	0.40-1.53	0.471	1.20	0.81-1.78	0.352
2014	0.44	0.19-1.04	0.061	0.89	0.56-1.41	0.61
2015	0.13	0.06-0.29	<0.001	0.12	0.07-0.21	<0.001
Grade						
I	Reference			Reference		
II	1.37	0.43-4.36	0.595	0.92	0.55-1.53	0.747
III	2.18	0.39-12.33	0.378	0.74	0.28-1.97	0.546
IV	3.40	1.19-9.77	0.023	0.95	0.58-1.55	0.827
Unknown	1.24	0.42-3.69	0.702	1.01	0.62-1.65	0.962
Tumor Site						
Trigone	Reference			Reference		
Lateral wall	0.48	0.14-1.65	0.246	0.69	0.34-1.39	0.303
Posterior wall	0.30	0.07-1.31	0.11	0.80	0.37-1.70	0.558

	Cancer Specific Mortality			Overall Mortality		
	Hazard Ratio	**95% CI**	**P Value**	**Hazard Ratio**	**95% CI**	**P Value**
Overlapping lesion	1.06	0.29-3.90	0.929	0.67	0.28-1.60	0.367
Bladder, NOS	0.77	0.23-2.57	0.669	0.73	0.36-1.47	0.375
Others	0.45	0.12-1.76	0.254	0.74	0.35-1.58	0.442
Tumor Size						
Up to 10 mm	Reference			Reference		
11-20 mm	1.45	0.48-4.36	0.505	1.17	0.72-1.91	0.521
21-30 mm	1.80	0.62-5.19	0.279	1.20	0.75-1.94	0.452
31-40 mm	2.45	0.81-7.35	0.111	1.01	0.58-1.76	0.977
41-50 mm	2.32	0.76-7.09	0.139	1.26	0.72-2.21	0.419
> 50 mm	3.06	0.97-9.65	0.056	0.95	0.47-1.91	0.891
Number of *in-situ* tumors						
Solitary	Reference			Reference		
Multiple	4.53	2.35-8.72	<0.001	2.10	1.32-3.32	0.002

4. DISCUSSION

In this study, we used the SEER database to retrospectively investigate the impact of additional chemotherapy on older patients with non-muscle invasive bladder cancer undergoing TURBT surgery. Chemotherapy improved cancer specific survival among the patients, but it had no effect on overall survival. To the best of our knowledge, this is the first large scale population-based real-world study to investigate the impact of chemotherapy on older patients with NMIBC undergoing TURBT surgery.

There could be two reasons for chemotherapy having no effect on overall survival. First, while meta-analyses prove the benefits of chemotherapy in NMIBC undergoing TURBT surgery [6, 11] a few clinical trials have shown beneficial effects of chemotherapy on preventing recurrences of NMIBC in the short run (12 to 24 months) [12, 13]. Beyond 24 months, the protective effect of chemotherapy on recurrences was statistically not significant versus the control group. For instance, a trial by El-Ghobashy *et al*. shows that the recurrence was 18.7% in the control group versus 3.2% in the chemotherapy group by 12 months [13]. However, at 24 months, it was 28.6% in control versus 26.9% in chemotherapy. Therefore, we could postulate that chemotherapy does not have any impact on long-term mortality in NMIBC patients. Secondly, overall survival could be influenced by non-cancer related co-morbid conditions [14]. Our study findings on higher mortality among older patients and those with grade IV and multiple *in-situ* tumors align with the current evidence [15, 16]. Literature shows that older patients are less likely to receive intravesical therapy [16]. Contrary to some earlier studies, race was not significantly associated with mortality in our study [17]. Lower mortality among the patients that were diagnosed in 2015 could reflect higher adherence to the current treatment guidelines on administering chemotherapy as well as recent advances in bladder cancer therapies [18 - 20].

There are several limitations to our study. First, retrospective databases have the inherent selection bias even though we tried to control for confounders with matching. Second, SEER database does not contain the details of the chemotherapy regimens, their dosage nor the time of administration, *e.g.* adjuvant or neo-adjuvant. The database also does not have information on patients' genetic constitution that might influence survival. Finally, our model did not include key socio-demographic features such as geographic location, household education and economic status, insurance as well as co-morbidities that might have an impact on the disease outcome.

CONCLUSION

Chemotherapy improved cancer specific survival among older patients with non-muscle invasive bladder cancer undergoing TURBT surgery, but it had no effect on overall survival. There is a need for more granular level real-world data on chemotherapy regimens and dosage to effectively investigate the effects of chemotherapy on survival of older patients with NMIBC that have undergone TURBT.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

STROBE guidelines and methodologies were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

The data supporting findings of this study is present within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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