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Bladder preservation for localized muscle-invasive bladder cancer: the survival impact of local utilization rates of definitive radiotherapy

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Abstract

Purpose—This study examines the management and outcomes of muscle-invasive bladder cancer in the U.S.

Methods and Materials—Patients with muscle-invasive bladder cancer diagnosed between 1988 and 2006 were identified in the Surveillance, Epidemiology, and End Results (SEER) database. Patients were classified according to three mutually exclusive treatment categories based on the primary initial treatment: no local management, radiotherapy, or surgery. Overall survival was assessed with Kaplan-Meier analysis and Cox models based on multiple factors including treatment utilization patterns.

Results—The study population consisted of 26,851 patients. Age, sex, race, tumor grade, histology and geographic location were associated with differences in treatment (all $P < 0.01$). Patients receiving definitive radiotherapy tended to be older and have less differentiated tumors than patients undergoing surgery (RT: median age 78 years and 90.6% grade 3/4 tumors; surgery: median age 71 years and 77.1% grade 3/4 tumors). No large shifts in treatment were seen over time, with the vast majority of patients managed with surgical resection (86.3% for overall study population). Significant survival differences were observed according to initial treatment: median survival 14 months with no definitive local treatment, 17 months with radiotherapy, and 43 months for surgery. On multivariate analysis, differences in local utilization rates of definitive radiotherapy did not demonstrate a significant effect on overall survival (H.R. = 1.002 (95% C.I. 0.999–1.005)).

Conclusions—Multiple factors influence the initial treatment strategy for muscle-invasive bladder cancer but definitive radiotherapy continues to be uncommonly employed. Although patients who undergo surgery fare better, a multivariable model that accounted for patient and tumor characteristics found no survival detriment to the utilization of definitive radiotherapy. These results support continued research into bladder-preservation strategies and suggest that

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definitive radiotherapy represents a viable initial treatment strategy for those who wish to attempt to preserve their native bladder.

Keywords

SEER; chemoradiation; bladder cancer; organ preservation

Introduction

Bladder cancer is the second most common genitourinary malignancy with greater than 70,000 new cases diagnosed in the U.S. each year(1). Approximately 70% of patients present with superficial disease, which can be a recurrent problem but is not life-threatening(2). Muscle-invasive disease, on the other hand, represents a potentially grave threat, with long-term survival of approximately 50%(3–5). In recent decades, surgical resection has typically been preferred for such patients if they are medically operable. This approach was bolstered when reports of outcomes with radiotherapy alone were considered suboptimal(6–8). Both chemotherapy and radiotherapy have been added to surgery, however, to attempt to improve surgical results. There appears to be increasing data supporting a role for neoadjuvant chemotherapy for muscle-invasive disease(9). In contrast, no randomized data support the routine use of adjuvant radiotherapy though it is considered in certain cases(10).

Surgical advances have improved the outcomes of urinary diversion necessary after cystectomy, but this approach can nevertheless negatively impact subsequent quality of life(5, 11, 12). Partial cystectomy in highly selected patients may preserve the native bladder, and urinary function, but few patients are felt to be appropriate for this approach(2). Additional bladder-sparing options include aggressive endoscopic transurethral resection or radiotherapy (RT), both of which can be performed with or without chemotherapy. No consensus exists regarding the appropriateness of these approaches to muscle-invasive disease and only the combination of radiotherapy and chemotherapy has been subjected to prospective randomized study.

Multiple institutions and cooperative groups have played a role in developing and refining the modern approach to radiotherapy-based bladder preservation(2, 13). The general approach in the U.S. has typically been maximal safe transurethral resection followed by induction chemoradiotherapy. Tumor response is then evaluated, with patients proceeding to early cystectomy if a complete response has not been achieved. Otherwise, patients proceed to consolidative chemoradiotherapy followed by long-term close follow-up to monitor for recurrence. Data from prospective trials indicate that 5 year overall survival rates have generally been 45% to 60%, and approximately three-quarters of surviving patients are able to maintain their native bladder(14). These survival rates are comparable to those published for similarly staged patients undergoing cystectomy(5, 15–19). Unfortunately, no randomized data is available that directly compares chemoradiotherapy to surgery. Oncologists therefore have little guidance to tailor treatment in an evidence-based manner, and it remains unclear to what degree bladder preserving approaches have been adopted in the community. The current study uses the SEER database of the National Cancer Institute to evaluate the use of radiotherapy-based bladder preservation in the U.S. Patterns of care data are analyzed to determine to what extent, and in which patients, definitive external beam radiotherapy is used. County-level data is then used to determine the survival impact, if any, of local utilization rates of bladder preservation.

Methods

Study Population

The SEER-17 registries data set of the US National Cancer Institute (April 2009 release) was used to identify patients diagnosed with non-metastatic, muscle-invasive bladder cancers between January 1, 1988, to December 31, 2006(20). Inclusion criteria consisted of known age, sex, race, histology, treatment and county. Additionally, only patients aged greater than 20 years at the time of diagnosis who were diagnosed with their first malignancy were included, and histologies were limited to transitional cell carcinomas, squamous cell carcinomas, and adenocarcinomas. The cohort was further limited to counties with at least 25 cases. Patients were defined as having undergone no definitive treatment (no surgery or external beam radiotherapy), definitive radiotherapy (external beam radiotherapy with or without a local resection (i.e. TURBT)), or definitive surgery (surgical resection alone or cystectomy plus radiotherapy). For the latter category, any surgical resection is considered definitive local management of the tumor in the absence of radiotherapy: i.e. cystectomy, partial cystectomy or trans-urethral resection. A total of 26,851 patients met the inclusion criteria.

Statistical Analyses

Both univariate and multivariate methods were used to evaluate the study population. The Chi-square coefficient was used to evaluate differences in treatment by patient characteristics, with values < 0.05 deemed statistically significant. Multivariable logistic regression analyses were used to analyze treatment trends by patient characteristics. Each variable of interest was used for the overall model and $P = 0.05$ was used to assign possible significance to each variable. Overall survival was evaluated using Kaplan-Meier survival analyses. Patients were censored at either death or date of last follow-up. Two-sided Mantel-Cox log-rank tests were used to assess the significance of differences between survival curves. Both univariable and multivariable Cox proportional hazards models were also used to evaluate the possible survival impact of each variable of interest. The primary survival analysis used county-level data to determine the utilization rate of each treatment modality (definitive surgery, definitive RT, or neither), and this was used as a continuous variable to ascertain the possible survival impact of each of these treatments. This analysis represents an implicit use of the instrumental variable analysis, an econometric method to assess treatment effect while attempting to remove hidden bias in observational studies(21). Local variability in the utilization of different treatments therefore represents a form of “natural randomization” that allows an examination of possible treatment effects(22). Whereas a randomized trial imparts a probability of either 0 or 100% to each patient regarding possible treatment options, the current study uses intermediate likelihoods of each treatment to evaluate treatment outcomes.

SEER*STAT software version 6.4.4 (Surveillance Research Program, NCI, Bethesda, MD) was used to extract case level data from the SEER public-use database. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS, V14.0).

Results

The study population consisted of 26,851 patients with non-metastatic, muscle-invasive bladder cancer. The patient and tumor characteristics as well as treatment for this population are shown in Table 1. The median age of the study population was 72 years, and most of the patients were male (72.5%) and white (89.5%). Almost all of the tumors were transitional cell carcinomas (93.8%), and 78.2% of the tumors were poorly differentiated or undifferentiated. The study population was characterized according to three mutually

exclusive treatment categories: 1) definitive surgery (surgical resection alone, or cystectomy plus radiotherapy) ; 2) definitive radiotherapy (external beam radiotherapy with or without a local resection such as a TURBT); or 3) no definitive local treatment (neither of the prior two categories). As shown in Table 1, the vast majority of the patients (86.3%) received definitive surgery, whereas only 10.9% of patients were treated with external beam RT in the absence of a cystectomy.

Table 1 also shows the type of treatment performed based on patient and tumor characteristics of interest. Groups of patients treated more frequently with definitive radiotherapy included older patients, females, and patients with squamous cell carcinomas or poorly differentiated tumors ($P < 0.001$ except histology ($P = 0.008$)). Geographic location (by registry) also significantly affected the use of different treatment strategies on univariate analysis ($P < 0.001$, data not shown). Figure 1 shows the use of each treatment strategy by year of diagnosis. The use of definitive radiotherapy stayed within a fairly narrow range, varying from a low of 8.1% of patients in 1993 to a high of 13.1% in 2004. A multinomial logistic regression model was constructed to determine what variables remained significant independent predictors of treatment. This model is shown in Table 2, with the reference treatment category being definitive surgery. Age, grade, race, and geographic location remained significant predictors of treatment received on multivariable analysis (all $P < 0.001$) for the overall model (although not necessarily significant for each patient category individually), as did sex ($p = 0.03$), and histology ($p = 0.01$). Notably, year of diagnosis was not a significant predictor of treatment in this model ($p = 0.704$).

Kaplan-Meier survival curves for patients receiving each type of treatment are shown in Figure 2. For the entire study population, treatment type was significantly associated with overall survival ($P < 0.001$). The median survival was 14 months for no definitive local treatment, 17 months for definitive radiotherapy, and 43 months for definitive surgery. Due to heterogeneity in the no treatment group, the long-term survival rate for these patients was intermediate between surgery and radiotherapy. Multiple factors may have contributed to this finding. The median age of those dying within the first 2 years was 78 years, for instance, versus 69 years for those surviving greater than 2 years.

A univariable Cox model was developed to further quantify the differences in overall survival between the various treatment groups. Table 3 shows that patients for whom no definitive local treatment is given suffer a 63.3% increase in risk of death as compared to surgical management (H.R. = 1.633, 95% C.I. 1.499–1.779). According to the Cox model, the associated risk of death is even greater when definitive radiotherapy is the initial treatment (H.R. = 1.788, 95% C.I. 1.709–1.870). Because patient and tumor characteristics significantly influence the initial treatment strategy, as shown in Table 2, subsets of patients were further examined according to additional non-treatment variables. The impact of stratifying patients by these additional variables is further shown in Table 3. Relatively little difference is seen for the no treatment group of patients. For patients undergoing definitive radiotherapy, accounting for additional variables had a greater effect. This was particularly noticeable when patients were stratified by age, resulting in a decreased hazard ratio of 1.387 (95% C.I. 1.325–1.452). In no case did the hazard ratio increase for patients treated with radiotherapy when additional information was taken into account. Failure to account for non-treatment factors may therefore impact the discrepancies in survival seen between the various groups of patients, particularly with respect to patients undergoing radiotherapy.

To estimate the effect of treatment strategy on survival, independent of other factors, a multivariable analysis was conducted using county-level data of the utilization rates of the various treatment categories. As shown in Table 4, utilization of definitive radiotherapy is not significantly associated with a difference in survival as compared to definitive surgery

(H.R. = 1.002, 95% C.I. 0.999–1.005). For such an analysis, the hazard ratio indicates the associated survival effect for each percentage increase in the use of each treatment. In contrast, increased use of no treatment was associated with a statistically significant detriment in survival (H.R. = 1.011, 95% C.I. 1.003–1.018). The robustness of these results to possible hidden bias was then explored using a variable deletion method in which each variable was omitted from the final multivariable model and the results compared to the full model. In this fashion, the impact of artificially missing data can be ascertained as a way to probe the possible impact of data that is not available from the SEER database. Table 5 demonstrates the results of such an analysis for the associated survival impact of definitive RT and no treatment. For RT, only the deletion of tumor grade yielded a result demonstrating a significant effect of RT ($P = 0.003$). All other effects were non-significant ($P > 0.05$). Little change was also seen for the no treatment category.

Discussion

Despite considerable effort to improve outcomes for patients with muscle-invasive bladder cancer, there is a dearth of randomized data to guide oncologists. Outcomes are progressively worse for higher stage disease, and long-term survival approaches 50% for all patients with nonmetastatic, muscle invasive disease(3–5). The rationale for organ preservation strategies has been to improve quality of life while achieving comparable long-term survival. Such an approach, reserving radical surgery only for salvage in the presence of persistent or recurrent disease, has been successful for an array of malignancies. Despite an intensive international effort to develop a similar approach to bladder cancer using chemoradiotherapy, it has not been fully embraced for medically operable patients. One goal of this study was to quantitatively evaluate the patterns of care of muscle-invasive disease. The number of patients receiving bladder preservation was low in our cohort, and significant changes in the patterns of care were not seen over time (Figure 1). However, certain patients were more likely to undergo such treatment. One dramatic difference was the increased use of definitive RT among older patients. Medical operability could not be directly evaluated using this data set, but trends such as that seen with patient age suggest to us that the utilization rates of definitive RT for operable patients is even lower than that which we observe for our overall patient population. Given the effort expended on bladder preservation trials over the last 20 years, it is striking that year of diagnosis was not an independent variable predicting the use of bladder preservation. The publication of multiple prospective trials attempting to optimize such an approach, all without a cystectomy treatment arm for comparison, have not markedly increased its utilization in the U.S.

The possibility of improved quality of life with bladder preservation has been less controversial than the issue of a possible survival effect. Despite advances in surgical techniques, with both incontinent and continent urinary diversions possible, most patients would prefer to maintain their native bladder if oncologic outcomes were uncompromised. Genitourinary complaints besides incontinence are also reported such as impotence. On the other hand, radiotherapy-based approaches have yielded relatively encouraging results. Approximately three-quarters of surviving patients were able to maintain their native bladder in prospective trials(14). Studies have demonstrated good urinary function overall after radiotherapy. One study demonstrated normal bladder function on functional urodynamic studies in the majority of patients(23), whereas another reported that 10% of patients reported some degree of incontinence or increased micturition(18). In a review of toxicity data from multiple RTOG protocols, no treatment-related deaths or cystectomy for RT-complications were seen(24). Data comparing quality of life after cystectomy or RT is limited, but one study reported improved sexual function after radiotherapy compared to cystectomy with similar gastrointestinal complaints(25). Consequently, improved quality of life with organ preservation appears to be a valid consideration.

The possible impact of bladder preservation on survival is in many ways the current fundamental question regarding this approach. Comparisons of survival rates from surgical series with RT series have led many to conclude that the survival rates from these modalities are similar. For example, Munro and colleagues recently reported comparable 10-year overall survival with radical radiotherapy compared to cystectomy among 458 patients with (predominantly) muscle invasive bladder cancer(26). Differences in study populations, however, can confound such conclusions. Such differences can also bias results from traditional Cox models that can account for differences in known variables but cannot address hidden bias. The SEER database, for instance, lacks information on comorbidities and performance status. Such patient characteristics can confound estimates of treatment effects by influencing both treatment selection and endpoints of interest such as survival. We therefore used an alternative analysis in which local utilization of different treatment strategies (using county-level data) was used as the key variable of interest rather than the employed treatment strategy itself. This approach is analogous to the use of instrumental variables which has been shown to better handle hidden bias in certain circumstances(22). County of residence is the instrument used in our model to capitalize on the natural “randomization” in local patterns of care that is evident in our cohort. The results of our final model were indeed robust to missing data (Table 5). Basic demographic information and tumor grade were also utilized in our model, but detailed staging was not used. This avoids an additional possible source of bias because clinical and pathologic staging for bladder cancer has been shown to significantly differ in many cases(27–29). Through this analysis, our study suggests that increased utilization of definitive RT for bladder preservation is not independently associated with a detriment in overall survival. This finding, based on a multivariable analysis of patterns of care and outcomes in the U.S. over nearly two decades, supports the belief that modern definitive RT represents a viable treatment option for patients who are motivated to maintain their native bladder.

It is important to note the limitations of the study. Patient characteristics such as performance status and comorbidities are not available in the SEER database. Detailed tumor staging is available but was not included in the model because patients undergoing cystectomy are pathologically staged whereas nonsurgical treatment strategies involve clinical staging. Inclusion of such information would be expected to bias the results in favor of cystectomy because pathologically staged patients may be upstaged at the time of surgery. The use of chemotherapy is also not included in the SEER database. It is assumed that many patients receiving definitive radiotherapy and surgery (and possibly neither modality) also received chemotherapy based on a benefit seen in studies evaluating this issue(9, 30). The treatment categories analyzed in this study were chosen such that the use of chemotherapy would not alter the treatment category assigned to each patient. Knowledge of chemotherapy use would not have affected the major findings regarding the use and survival effect associated with each treatment category, but it would allow the treatment received by patients in each treatment category to be better defined.

The present study suggests that definitive radiotherapy for muscle-invasive bladder cancer has been infrequently used in the U.S. over the last 20 years. There has been a persistent reluctance to use bladder preservation despite multiple prospective trials designed to determine the feasibility of such an approach and to improve outcomes. Current efforts in the U.S. include further alterations to the chemoradiotherapy scheme and the inclusion of targeted agents(2). It is not clear, however, that anything short of a large phase III trial directly comparing bladder preservation and cystectomy will yield a significant change in patterns of care in the U.S. The SPARE trial by the Medical Research Council in the U.K. was designed to test the feasibility of just such a trial, but this was recently closed due to poor accrual (just 45 patients in 30 months)(31). While many factors are surmised to have led to this unfortunate outcome, it is noteworthy that most patients who declined enrollment

did so because they preferred radiotherapy. Meanwhile, strongly held preconceived views regarding treatment efficacy coupled with the dramatic differences in treatment have been felt to preclude an attempt at a similar trial in the U.S.(32) For the foreseeable future, it appears, there will not be a well-powered phase III study assessing the potential equivalence of bladder preservation techniques and surgical management. The corollary of this is that there will also remain a lack of randomized data demonstrating the supposed superiority of the historical “gold-standard” of cystectomy over modern bladder-preservation approaches. It will therefore be incumbent upon oncologists to make individualized treatment recommendations in light of various factors, including informed patient treatment preference. The current study, having demonstrated no survival decrement with increased use of bladder preservation on multivariable analysis, suggests that this approach should be discussed with appropriate patients and represents a viable, well-investigated treatment option for patients who wish to attempt to maintain their native bladder while undergoing curative treatment for muscle-invasive bladder cancer.

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Figure 1. Utilization of different treatment strategies over time. Squares, no treatment; triangles, radiotherapy; diamonds, surgery.

Figure 2. Overall survival of patients receiving different treatments for bladder cancer. Thin solid line, no treatment; dotted line, radiotherapy; thick solid line, surgery.

Table 1

Treatment by patient and tumor characteristics.

	No. patients (%)	No treatment	Definitive XRT	Definitive surgery	P value [*]
Total	26,851 (100)				
Age (years)					< 0.001
21–50	1619 (6.0)	3.2	4.0	92.8	
51–70	10,396 (38.7)	2.4	6.6	91.0	
71–80	8698 (32.4)	2.6	12.0	85.4	
>80	6138 (22.9)	3.8	18.5	77.7	
Sex					< 0.001
Male	19,469 (72.5)	2.6	10.5	86.9	
Female	7382 (27.5)	3.5	12.0	84.5	
Race					< 0.001
White	24,023 (89.5)	2.7	10.7	86.6	
Black	1670 (6.2)	4.9	14.0	81.1	
Asian/Pacific Islander	1118 (4.2)	2.5	11.3	86.2	
American Indian	40 (0.1)	0.0	12.5	87.5	
Tumor grade					< 0.001
Well differentiated	1361 (5.1)	7.3	2.4	90.4	
Moderately differentiated	4473 (16.7)	3.5	5.4	91.0	
Poorly differentiated	13,302 (49.5)	2.5	12.2	85.2	
Undifferentiated	7715 (28.7)	2.1	13.3	84.6	
Histology					0.008
Transitional cell carcinoma	25,193 (93.8)	2.8	10.9	86.3	

	No. patients (%)	No treatment	Definitive XRT	Definitive surgery	P value*
Squamous cell carcinoma	1105 (4.1)	4.3	12.1	83.6	
Adenocarcinoma	553 (2.1)	3.1	8.7	88.2	
Treatment, total no. (%)		757 (2.8)	2932 (10.9)	23,162 (86.3)	

* Treatment was characterized according to 3 mutually exclusive categories based on the initial treatment given. Treatment is typically defined by SEER based on a 4 month period of time after diagnosis. Details of each category are provided in the Methods section.

† Chi-square value regarding treatment and variable of interest.

Table 2

Multinomial logistic regression model of treatment.*

	Coefficient	P value
No treatment		
Age (years) [†]	1.021	< 0.001
Sex		
Male	0.813	0.01
Female	1.00 (ref)	
Race ^{††}		
White	0.853	0.47
Black	1.450	0.14
Asian/ Pacific Islander	1.00 (ref)	
Tumor grade		
Well differentiated	3.047	< 0.001
Moderately differentiated	1.488	0.001
Poorly differentiated	1.089	0.39
Undifferentiated	1.00 (ref)	
Histology		
Transitional cell carcinoma	0.954	0.85
Squamous cell carcinoma	1.186	0.56
Adenocarcinoma	1.00 (ref)	
Year of diagnosis**	1.006	0.46
Definitive radiotherapy		
Age (years) [†]	1.046	< 0.001
Sex		
Male	1.030	0.50
Female	1.00 (ref)	
Race ^{††}		
White	0.886	0.28
Black	1.426	0.007

	Coefficient	P value
Asian/Pacific islander	1.00 (ref)	
Tumor grade		
Well differentiated	0.199	< 0.001
Moderately differentiated	0.414	< 0.001
Poorly differentiated	0.939	0.17
Undifferentiated	1.00 (ref)	
Histology		
Transitional cell carcinoma	1.113	0.49
Squamous cell carcinoma	1.557	0.02
Adenocarcinoma	1.00 (ref)	
Year of diagnosis	1.002	0.69

* The reference category for treatment is definitive surgery. All coefficients therefore refer to the likelihood of either no treatment or definitive radiotherapy being given to each patient, according to each variable of interest. The *P* value of each variable of interest, based on its inclusion or omission from the final model, is as follows: age ($P<0.001$), year of diagnosis ($P=0.704$), sex ($P=0.029$), tumor grade ($P<0.001$), race ($P<0.001$), and histology (0.013). Geographic location (SEER registry) was also included in the model (data not shown) and this variable was also a significant predictor of treatment ($P<0.001$).

[†] Age and year of diagnosis were analyzed as continuous variables.

^{††} For convergence of the model, it was necessary to omit American Indian patients ($n=40$).

Table 3

Univariable Cox models of overall survival based on initial treatment.

	No treatment		Radiotherapy	
	HR (95% C.I.) [*]	P value	HR (95% C.I.) [*]	P value
Basic model (no stratification)	1.633 (1.499–1.779)	<0.001	1.788 (1.709–1.870)	<0.001
Stratified variable [†]				
Age	1.638 (1.504–1.785)	<0.001	1.387 (1.325–1.452)	<0.001
Sex	1.625 (1.492–1.771)	<0.001	1.774 (1.695–1.856)	<0.001
Race	1.620 (1.487–1.764)	<0.001	1.783 (1.704–1.865)	<0.001
Tumor grade	1.906 (1.535–1.680)	<0.001	1.606 (1.535–1.680)	<0.001
Histology	1.627 (1.493–1.772)	<0.001	1.785 (1.706–1.867)	<0.001
Year of diagnosis	1.622 (1.489–1.767)	<0.001	1.748 (1.670–1.829)	<0.001
Urban code	1.641 (1.506–1.788)	<0.001	1.786 (1.707–1.868)	<0.001

^{*} The hazard ratio shown describes the associated impact of initial treatment versus definitive surgery (HR for surgery equals 1.000 by definition).

[†] The categories for each variable are as follows: age (21–50 years, 51–70 years, 71–80 years, >80 years), sex (male, female), race (white, black, Asian/ Pacific Islander, American Indian), tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated), histology (transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma), year of diagnosis (by individual year), urban code (metropolitan > 1 million, metropolitan 250K – 1 million, metropolitan <250K, non-metropolitan >25K, non-metropolitan 2.5K – 25K, non-metropolitan <2.5K).

Table 4

Multivariable Cox model of overall survival

	Hazard ratio (95% C.I.)	P value
Age (years) *	1.048 (1.046–1.050)	< 0.001
Sex		0.221
Male	1.000 (ref)	
Female	1.021 (0.987–1.056)	
Race		< 0.001
White	1.000 (ref)	
Black	1.333 (1.254–1.418)	
Asian/Pacific Islander	0.818 (0.755–0.886)	
Native American	2.038 (1.432–2.902)	
Tumor grade		< 0.001
Well differentiated	1.000 (ref)	
Moderately differentiated	1.223 (1.126–1.329)	
Poorly differentiated	2.007 (1.857–2.169)	
Undifferentiated	2.051 (1.891–2.225)	
Histology		< 0.001
Transitional cell carcinoma	1.000 (ref)	
Squamous cell carcinoma	1.622 (1.508–1.746)	
Adenocarcinoma	1.342 (1.211–1.488)	
Year of diagnosis *	1.012 (1.009–1.016)	< 0.001
Urban code		0.099
Metropolitan > 1 million	1.000 (ref)	
Metropolitan 250K – 1 million	1.018 (0.979–1.058)	
Metropolitan < 250K	0.995 (0.934–1.060)	
Non-metropolitan > 25K	1.020 (0.950–1.095)	
Non-metropolitan 2.5K – 25K	1.039 (0.962–1.122)	
Non-metropolitan < 2.5K	1.289 (1.078–1.542)	
Treatment		
No treatment	1.011 (1.003–1.018)	0.005

	Hazard ratio (95% C.I.)	P value
Radiotherapy	1.002 (0.999–1.005)	0.184
Surgery	1.000 (ref)	

* Age and year of diagnosis were analyzed as continuous variables.

Table 5

Impact of omitting specific variables on survival hazard ratio from the multivariable Cox model.

	No treatment		Radiotherapy	
	HR (95% C.I.) [*]	P value [†]	HR (95% C.I.) [*]	P value [†]
Full model ^{††}	1.011 (1.003–1.018)	0.005	1.002 (0.999–1.005)	0.184
Omitted variable [§]				
Age (years)	1.011 (1.003–1.018)	0.004	1.001 (0.998–1.004)	0.516
Sex	1.011 (1.003–1.018)	0.005	1.011 (1.003–1.018)	0.180
Race	1.015 (1.007–1.022)	< 0.001	1.002 (0.999–1.005)	0.141
Tumor grade	1.005 (0.997–1.013)	0.204	1.005 (1.002–1.008)	0.003
Histology	1.010 (1.003–1.018)	0.009	1.002 (0.999–1.005)	0.149
Year of diagnosis	1.012 (1.004–1.019)	0.002	1.002 (0.999–1.006)	0.111
Urban code	1.010 (1.002–1.017)	0.011	1.002 (0.999–1.005)	0.210

^{*} The hazard ratio shown describes the associated survival impact of increasing the county-level utilization rate of the treatment of interest by one percentage point.

[†] Describes the statistical significance of the hazard ratio associated with either no definitive treatment or radiotherapy for the model of interest.

^{††} The full model consists of each available variable: initial treatment, age, sex, race, tumor grade, histology, year of diagnosis, and urban code.

[§] For each corresponding model, all of the variables from the full model are used except for the variable shown.