Trends of Muscle Invasive Bladder Cancer: Evidence from the SEER Database, 1988 to 2013

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Abstract

Background: Guidelines for Muscle-Invasive Bladder cancer (MIBC) recommends that patients receive neoadjuvant chemotherapy with radical cystectomy or chemoradiotherapy, as treatment over radical cystectomy alone. Though trends and practice patterns of MIBC have been defined using the National Cancer Database, data using the Surveillance, Epidemiology, and End Results (SEER) have been poorly described.

Methods: Using the SEER database, we collected data of MIBC according to the AJCC (American Joint Commission on Cancer). We considered differences in patient demographics and tumor characteristics based on three treatment groups: chemotherapy with radical cystectomy, radical cystectomy alone, and chemoradiotherapy. Multinomial logistic regression was performed to compare likelihood ratios. Temporal trends of each treatment were compared.

Results: Of 16,728 patients, 10,468 patients received radical cystectomy alone, 3,236 received radical cystectomy plus chemotherapy, and 3,024 received chemotherapy plus radiation. Patients who received chemoradiotherapy tended to be older and African American compared to radical cystectomy alone ($<.001$); stage III patients tended to be divorced ($<.001$). Patients who received chemotherapy with radical cystectomy tended to be males ($<.001$); stage II patients were less likely to be Asian than White ($<.001$). Stage III patients were less likely to receive chemoradiotherapy as a treatment option than stage II ($<.001$). Chemotherapy with radical cystectomy and chemoradiotherapy are both used less frequently as treatment, though increasingly utilized ($<.001$).

Conclusion: Radical cystectomy alone is still the most commonly used treatment for muscle-invasive bladder cancer based on temporal trends. Significant disparities exist in those who receive chemoradiotherapy over radical cystectomy for treatment.

Background

In the United States for 2019, Bladder cancer (BC) is expected to account for 80,470 new cancer cases according to the National Cancer Institute.¹ BC based on the TNM stage system can be described into three chief groups: non-muscle-invasive bladder cancer, muscle-invasive bladder cancer, and metastatic bladder cancer. Non-muscle-invasive bladder cancer is classified as stage I (Ta, Tis, T1) and accounts for approximately 75% of cases.²⁻³ The rest of cases are either considered muscle-invasive bladder cancer (MIBC), classified as stage II to III, or metastatic bladder cancer, classified as stage IV.³⁻⁴ Primary treatments for MIBC, based on NCCN guidelines, differs based on stage. For stage II tumors, treatment consists of: 1) NAC plus radical cystectomy 2) NAC plus partial cystectomy (for highly selected patients) 3) radical cystectomy and 4) concurrent chemoradiotherapy.¹ For stage III, NCCN lists treatment guidelines as: 1) NAC plus radical cystectomy and 2) concurrent chemoradiotherapy.¹

NAC plus radical cystectomy become the standard treatment for MIBC over radical cystectomy alone. The first study of NAC plus radical cystectomy was conducted by the Medical Research Council/European Organisation for Research and Treatment of Cancer in 1999.⁵ In this phase III trial, roughly half of the 976 patients with high grade T2-T4a, N0-NX, M0 urothelial carcinoma were selected for either radical cystectomy alone or three cycles of neoadjuvant chemotherapy (CMV: cisplatin, methotrexate, and vinblastine, with folinic acid rescue) plus radical cystectomy and/or radiation therapy.⁵ An 8-year follow up showed a statistically significant 16% improvement in survival outcome.⁶ In a 2003 randomized phase III trial from the Southwest Oncology Group (SWOG), 317 patients considered to have muscle-invasive bladder cancer (stage T2-T4a) were randomly assigned to either radical cystectomy alone or three cycles of neoadjuvant chemotherapy (MVAC: methotrexate, vinblastine, doxorubicin, and cisplatin) followed by radical cystectomy.⁷ Compared to NAC plus radical cystectomy, patients who received radical cystectomy alone were associated with a 33 percent greater risk of death (hazard ratio, 1.33; 95% CI).⁷ Despite CMV and MVAC being used in the phase III trials, healthcare providers have preferred the combination of gemcitabine and cisplatin (GC) in clinical setting due to its better tolerability and similar efficacy.⁸ A non-randomized retrospective study comparing GC to MVAC has shown similar likelihood of downstaging primary tumors and eliminating muscle-invasive disease while also showing less toxicity.⁹

Bladder preservation therapy that consists of chemoradiation therapy has traditionally been considered a regimen for highly-selected patients with MIBC who are poor candidates for radical cystectomy or for quality of life purposes (ie those who prefer to preserve their native bladder).¹⁰ While no randomized trials of patients with MIBC have directly compared radical cystectomy and bladder preservation therapy, meta-analysis has shown similar overall 5-year and 10-year survival rates.¹¹

The purpose of our study is to compare trends in three major options of care for MIBC using SEER: radical cystectomy alone, radical cystectomy plus chemotherapy, and chemoradiotherapy with and without TURBT. Previous studies have investigated, using the National Cancer Database (NCDB), tumor characteristics and patient demographic in NAC in combination with radical cystectomy.¹²⁻¹⁷ This the first study to our knowledge to use SEER, a more appropriate database for considering sociodemographic disparities.¹⁸ This is the largest study to directly compare utilization of radical cystectomy with or without chemotherapy to a bladder-preservation approach for MIBC, though the second largest to look at tumor characteristics and patient demographics between these two groups.^{19,20} We hypothesize that the use of radical cystectomy alone will decline in lieu of the rise in popularity of alternative treatments.

Methods

SEER is a national cancer database in the United States, a part of the National Cancer Institute, that provides cancer incidence and survival. SEER contains information not available in other national registries including stage of cancer.²¹

Our study was based on incident cases of bladder cancer diagnosed among patients of 18 geographic regions, which included the chemotherapy recode, covered by the SEER program (November 2015 submission). Eligible bladder cancer cases were identified using the International Classification of Diseases for Oncology (ICD-O-3) topography code C67.0-C67.9.

Patients with AJCC clinically staged T2-T4a, N0, M0 were included in the study and considered to have muscle-invasive bladder cancer. Cases of T4b MIBC were excluded due to metastasis. Cancers of unknown stage were excluded. Patients who underwent radical cystectomy without radiation therapy were included in the study based on the 2-Digit Site-Specific Surgery codes from 1973–1997 listed as 40, 50, and 70. The SEER 2003 + Site-Specific Surgery of Primary Site Codes listed as 50, 60, and 70 were also included. Additionally, patients who received solely chemotherapy plus radiation with or without transurethral resection of bladder tumor (TURBT) were also included in the study. For 1973–1997 the 2-Digit Site-Specific Surgery Codes are listed under 10 and for SEER 2003 + listed as 20.

Descriptive statistics were compiled using the statistical package for the social sciences (SPSS) in order to summarize patient demographics, TNM stage and grade, and treatment characteristics. Associations of cases were compared using chi-squared as well as multinomial logistic regression, due to more than two sample groups. Usage rate was compared using 5-year intervals in order to better group the data.

Results

Between the years 1988 and 2013, there were 360,559 cases of bladder cancer in the SEER program that were initially queried for our study. Within each group there resulted in 10,468 radical cystectomy cases, 3,236 radical cystectomy plus chemotherapy cases, and 3,024 chemotherapy plus radiation cases for a total of 16,728 cases that met selection criteria (Fig. 1). Patients were stratified based on stage in order to control for progression of the cancer. The SEER program does not provide a specific patient age, but instead provides age ranges of 5-years. To calculate median ages of each treatment, averages were created for each patient. After separating by stage, there were significant differences between the groups according to patient demographics and tumor characteristics (Tables 1 & 2). Patients were also compared based on the treatment groups between stage II and III (Table 3). Patients in both stage II and III who received chemoradiotherapy were older (median age: stage II were 72.1 years old and stage III were 71.9 years old) compared to radical cystectomy (median age: stage II were 66.2 years old and stage III 68.9 years old) or radical cystectomy plus chemotherapy (median age: stage II were 63.8 years old and stage III were 65.5 years old) with highly significant p-values ($< .001$). There was also a difference in the number of patients who received chemoradiotherapy. Although 2,443 stage II cases (26.4%) received chemoradiotherapy for treatment of MIBC, only 581 stage III cases (7.8%) received the same treatment. The values of chemoradiotherapy as a treatment option between stage II and III showed high levels of significance ($< .001$).

A multinomial logistic regression for each stage was performed in order to compare likelihood of patient demographic or tumor characteristic listed to receive any of three treatments (Table 3). Compared to the

reference category of radical cystectomy alone, patients who received chemoradiotherapy had 1.32 higher odds of being African American than White for stage II tumors (95% CI 1.086–1.63) and 1.59 higher odds for stage III tumors (95% CI 1.17–2.15). Stage II showed a higher level of significance (stage II: $\leq .001$; compared to stage III: $< .05$). Stage II patients who received chemoradiotherapy had 8.67 higher odds of being 75–85 years old compared to the reference age of 55–65 (95% CI 7.05–10.65). Stage III patients who received chemoradiotherapy had 1.37 higher likelihood of being divorced rather than married (95% CI 1.03–1.82). For the treatment group of radical cystectomy plus chemotherapy, patients of both stage II and III groups had lower likelihood of being female, compared to radical cystectomy alone, with highly significant values ($< .001$). The stage II group of chemotherapy plus radical cystectomy had a lower likelihood of being Asian than White ($< .001$). Compared to the reference group, both radical cystectomy and chemoradiotherapy have higher likelihood of being poorly or undifferentiated grade tumors ($< .001$).

Practice trends were calculated for each treatment option based on the year of diagnosis and separated based on stage (Figs. 2 and 3). Based on stage II cases from 1988–1992, the usage of radical cystectomy plus chemotherapy (7.61%) initially dropped and then began rising in 2003–2007 (12.43%) and 2008–2013 (26.47%). Compared to 1988–1992, the usage of chemotherapy plus radiation (11.93%) initially stayed the same in 1993–1997 and then has consistently risen over the years to 2008–2013 (32.11%). In contrast, the usage of radical cystectomy alone based has dropped over the years compared to the other treatment options. For 2003, the percentage of patients elected for radical cystectomy plus chemotherapy showed a jump (9.30% based on 344 cases) compared to the previous year (6.79% based on 324 cases).

For stage III cases from 1988–1992, the usage of radical cystectomy plus chemotherapy (11.76%) initially dropped in 1993–1997 (10.34%) and then began rising each 5-year increment to 2008–2013 (33.61%). For stage III cases of chemotherapy plus radiation, the usage rate was rising till 2003–2007 when the usage dropped slightly (8.87%). In contrast, Stage III cases of radical cystectomy alone slightly rose in 1993–1997 (82.76%) and then the rate has been dropping into 2008–2013 (57.16%). Again for 2003, the percentage of patients elected for each treatment option was obtained. In 2003, there was an increase in radical cystectomy plus chemotherapy (13.76% based on 465 cases) compared to the previous year (11.72% based on 418 cases).

Discussion

The purpose of this study was to compare practice trends in patients with clinically staged T2-T4a, N0, M0 MIBC treated in the United States with three major treatment options from 1988–2013 using the SEER database. Although chemotherapy with radical cystectomy and chemoradiotherapy are both category 1 treatment options for MIBC according to NCCN guidelines, our results show that both groups are used less frequent as treatment than radical cystectomy alone over each time interval ($< .001$).

Despite practice patterns having changed in the last two decades, clinicians have continued to use the previously standard treatment of radical cystectomy for MIBC. The landmark article published in 2003 from Grossman et al. has made an immediate impact on the usage of NAC with radical cystectomy though.⁷ Our results reflect this change in clinical knowledge. In 2003–2007, the use of radical cystectomy plus chemotherapy doubled for both stage II and stage III data compared to the previous interval. For 2003 specifically, the use of radical cystectomy plus chemotherapy as a treatment option increased for both stages.

Studies looking at chemotherapy with radical cystectomy show results comparable to our own with some caveats. Zaid et al. looked at trends of 5,692 patients who received either radical or partial cystectomy alone combined with NAC for MIBC in the NCDB from 2006 to 2010.¹⁷ Duplisea et al. identified 18,188 patients who underwent either radical or partial cystectomy combined with NAC using NCDB from 2006 to 2014.¹³ The current study looked solely at radical cystectomy. Reardon et al. looked at 5,692 patients with MIBC treated with radical cystectomy alone or with perioperative chemotherapy in the same timeframe.¹⁶ Our study similar to Zaid et al., Reardon et al., and Duplisea et al. all showed an increase in chemotherapy with radical cystectomy after clinical guidelines changed.^{13,16,17} While Zaid et al. and Duplisea et al. showed that neither patient sex or race were associated with NAC, our study showed that patients who received chemotherapy with radical cystectomy were less likely to be female or Asian compared to radical cystectomy alone.^{13,17} Compared to Zaid et al. and Reardon et al., our study included more patients in each treatment group.^{16,17} Duplisea et al. included more patients in each treatment group than our own.¹³ Compared to studies that looked at chemotherapy with radical cystectomy, our study covered the longest timeframe.

Chemoradiotherapy overall has shown increased utilization. We suggest that chemotherapy and radiation have greatly improved when it comes to not only targeting the cancer, but also reducing the amount of side effects leading to increased usage for otherwise difficult to manage MIBC cases, especially older patients who would have poorer quality of life after a radical cystectomy surgery. Trenta et al. suggests that clinical treatment of MIBC using chemotherapy has made great strides from using the single platinum agent cisplatin to the development of effective drug combinations that improve safety profiles and thus survival.²² Along with this, Sandler et al. suggests that radiotherapy has also improved and led to better outcomes in the treatment of MIBC through an improved understanding of fractionation and tumor response.²³ The continued improvement in chemoradiotherapy may help explain its increased utilization. However, our results have shown a significant difference in the number of patients who have received chemoradiotherapy for stage II compared to III ($< .001$). While chemoradiotherapy for both stages of MIBC is suggested, it is less likely to be utilized for stage III. We also considered patient demographics based on each treatment group. Our findings suggest that clinicians are more likely to choose one treatment over another based on a variety of factors. Patients who were more likely to receive chemoradiotherapy were more commonly African American and aged 75–85 years old, compared to the radical cystectomy reference group. According to a phase II study that evaluated 31 elderly patients

treated with bladder preservation therapy for MIBC, treatment showed acceptable toxicity with good survival and response rate.²⁴

Previous studies have shown results similar for chemoradiotherapy utilization. In comparing 15,510 cases that received radical cystectomy to 1,450 cases that received chemoradiotherapy for MIBC between 2004–2013, patients who underwent chemoradiotherapy tended to be older, female, and African American.¹⁴ This is in line with results from the current study. Our study, however, found that when you controlled for stage that stage III patients tended to be more likely to be male rather than female. Unlike their study, ours also compared bladder preservation therapy to chemotherapy plus radical cystectomy as separate treatment options for MIBC. To go along with ours and the Haque et al. studies that showed patients who received chemoradiotherapy for MIBC tended to be African American, the Gray et al. and Fedeli et al. studies found that the rate of cystectomy decreased with age and among ethnic/racial minorities.¹⁴ The Gray et al. study looked at 28,691 patients from the NCDB between 2003 to 2008 who received aggressive therapy that included radical cystectomy or partial cystectomy, chemotherapy, or radiotherapy as treatment options for MIBC.^{23,28} Although their study included more patients who received treatment for MIBC, ours had larger pools of data for treatment of radical cystectomy or chemoradiotherapy. Fedeli et al. looked at 40,388 patients from the NCDB between 2003 to 2007 who received either cystectomy, chemoradiotherapy, or no treatment for MIBC.²⁸ Their study similar to our own showed an increase in chemotherapy for radical cystectomy due to NAC.²⁸ Although their study considered many similar patient demographics as the present study and included more patients, our own study controlled for stage when considering patient demographics.²⁸ In the Cahn et al. study, the authors looked at contemporary use trends between radical cystectomy and bladder preservation therapy for MIBC that included 32,300 from the NCDB between 2004 to 2013.¹³ Their study included more patients in radical cystectomy and bladder preservation therapy, when looking at patient and tumor characteristics. Cahn et al., however, did not include a group for chemotherapy with radical cystectomy or control by stage.^{13,20,25} Compared to all previous studies, ours looked at greater temporal trends in using data from 1988–2013. Our study uniquely found a drop in chemoradiotherapy in stage III tumors.

While NAC with radical cystectomy is the preferred treatment for MIBC, a significant portion of the bladder cancer population may be ineligible to receive chemotherapy. Several retrospective studies have shown that approximately 40% of patients who received radical cystectomy were ineligible to receive cisplatin chemotherapy treatment due to poor renal function.^{26,27} Other co-morbidities including hearing loss and cardiac dysfunction may similarly prevent patients from receiving standard cisplatin-based chemotherapy.²⁸ The usage of a bladder-preservation approach with chemoradiotherapy for MIBC may be used less frequent for the same reason. Moreover, data has identified basal and luminal subgroups of MIBC based on survival and chemotherapy response.²⁹ A study has shown that the basal subtype of MIBC derive the most benefit from NAC while luminal nonimmune infiltrated may not derive any benefit.³⁰ The identification of molecular markers in these subtypes of MIBC may pave the way for neoadjuvant immunotherapies with radical cystectomy and in the future more personalized medicine.

Limitations

As an analysis of a national oncologic registry, our study has several limitations that extends to all cohort studies. Our study is limited in the patients that are recorded in the registry. The SEER database itself has several limitations especially on radiotherapy and chemotherapy information. Data stemming from radiotherapy and chemotherapy treatment can be underreported. As both radiotherapy and chemotherapy are commonly administered in outpatient settings, the SEER database may not capture all data especially being driven by hospital-based registries. The SEER database also lacks radiotherapy doses and intent of treatment as either curative or palliative regimens. Data submitted to SEER in terms of chemotherapy options are limited, being listed solely as either “yes” or “no-unknown.”²¹ While there is confidence that a patient received chemotherapy after the box was marked as “yes,” there is less confidence that a patient who was marked as “no-unknown” did not actually receive chemotherapy. For this reason, the data for radical cystectomy alone would be most affected as the patients may actually have received chemotherapy. We are unable to know whether a patient received neoadjuvant compared to adjuvant chemotherapy.

Conclusions

Although considered the standard treatment prior to 2003, radical cystectomy is still the most commonly utilized treatment for MIBC. NAC with radical cystectomy and chemoradiotherapy are still used less frequently as treatment despite category 1 evidence. Differences in chemoradiotherapy as a treatment option were especially noticeable between stage II and III tumors, with stage III cases less likely to receive this treatment. Significant disparities exist in those who receive chemoradiotherapy over radical cystectomy for treatment especially age and race. More research is still needed to understand what treatment delivers better survival outcomes.

Declarations

No conflict of interest exists in the submission of this manuscript, and the manuscript has been approved by all authors for publication. The work described herein is original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part. All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria, and all agree to the terms of the BioMed Central License Agreement and Open Data Policy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR'S CONTRIBUTIONS

VC made substantial contributions to conception and design of the study; acquisition, analysis and interpretation of data; and drafted and revised the manuscript. MLB and HZ analysis and interpretation of data; assisted with drafting and revising the manuscript. PS contributed to conception and design of the study and acquisition of data; conception and design of the study; analysis and interpretation of data; assisted with drafting and revised the manuscript critically for important intellectual content.

NOTES

Ethics approval and consent to participate

The study was not primary research involving humans or animals but was instead a secondary analysis of human subject data available in the public domain.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

BC	Bladder Cancer
TNM	Tumor, Nodes, Metastasis
MIBC	Muscle-invasive bladder cancer
NAC	Neoadjuvant Chemotherapy
AJCC	American Joint Commission on Cancer
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base
SEER	Surveillance, Epidemiology, and End Results
TURBT	Transurethral Resection of Bladder Tumor
CHEMO	Chemotherapy
RAD	Radiation
BC	Bladder Cancer
TNM	Tumor, Nodes, Metastasis
MIBC	Muscle-invasive bladder cancer
NAC	Neoadjuvant Chemotherapy
AJCC	American Joint Commission on Cancer
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base
SEER	Surveillance, Epidemiology, and End Results

References

1. PDQ Adult Treatment Editorial Board: Bladder Cancer Treatment (PDQ®). January 17, 2019. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK65962/>. Accessed July 10, 2019.
2. Pasin E, Josephson D, Mitra A et al: Superficial Bladder Cancer: an Update on Etiology, Molecular Development, Classification, and Natural History. Rev Urol 2008; **10**:
3. Anastasiadis A and de Reijke T: Best Practice in the Treatment of Nonmuscle Invasive Bladder Cancer. Ther Adv Urol 2012; **4**:
4. Burger M, Catto JW, Dalbagni G et al: Epidemiology and Risk Factors of Urothelial Bladder Cancer. Eur Urol 2013; **63**:
5. Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: a Randomised Controlled Trial. International Collaboration of Trialists. Lancet 1999; **354**:

6. International Collaboration of Trialists et al: International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial. *J Clin Oncol* 2011; **29**:
7. Grossman HB, Natale RB, Tangen CM et al: Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer. *N Engl J Med* 2003; **349**:
8. Meleis L, Moore R, Inman BA et al: Retrospective Analysis of the Efficacy and Safety of Neoadjuvant Gemcitabine and Cisplatin in Muscle-Invasive Bladder Cancer. *J Oncol Pharm Pract* 2019.
9. Vashistha V, Wang H, Mazzone A et al: Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. *Int J Radiat Oncol Biol Phys* 2017; **97**:
10. Premo C, Apolo AB, Agarwal PK et al: Trimodality Therapy in Bladder Cancer: Who, What, and When? *Urol Clin North Am* 2019; **42**:
11. Shipley WU, Kaufman DS, Zehr E et al: Selective Bladder Preservation by Combined Modality Protocol Treatment: Long-Term Outcomes of 190 Patients with Invasive Bladder Cancer. *Urology* 2002; **60**:
12. Cahn DB, Handorf EA, Ghiraldi EM et al: Contemporary Use Trends and Survival Outcomes in Patients Undergoing Radical Cystectomy or Bladder-Preservation Therapy for Muscle-Invasive Bladder Cancer. *Cancer* 2017; **123**:
13. Duplisea JJ, Mason RJ, Reichard CA et al: Trends and Disparities in the Use of Neoadjuvant Chemotherapy for Muscle-Invasive Urothelial Carcinoma. *Can Urol Assoc J* 2019; **13**:
14. Haque W, Verma V, Butler EB et al: Radical Cystectomy Versus Chemoradiation for Muscle-Invasive Bladder Cancer: Impact of Treatment Facility and Sociodemographics. *Anticancer Research* 2017; **37**:
15. Martini T, Gilfrich C, Mayr R et al: The Use of Neoadjuvant Chemotherapy in Patients With Urothelial Carcinoma of the Bladder: Current Practice Among Clinicians. *Clin Genitourin Cancer* 2017; **15**:
16. Reardon ZD, Patel SG, Zaid HB et al: Trends in the Use of Perioperative Chemotherapy for Localized and Locally Advanced Muscle-Invasive Bladder Cancer: a Sign of Changing Tides. *Eur Urology* 2015; **67**:
17. Zaid HB, Patel SG, Stimson CJ et al: Trends in the Utilization of Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer: Results from the National Cancer Database. *Urology* 2014; **83**:
18. Joshi SS, Handorf ER, Smaldone MC et al: What Can the National Cancer Database Tell Us about Disparities in Advanced Bladder Cancer Outcomes? *Transl Androl Urol* 2018; **7**:
19. Audenet F, Waingankar N, Ferket BS et al: Effectiveness of Transurethral Resection plus Systemic Chemotherapy as Definitive Treatment for Muscle Invasive Bladder Cancer in Population Level Data. *J Urol* 2018; **200**:
20. Gray PJ, Fedewa SA, Shipley WU et al: Use of Potentially Curative Therapies for Muscle-Invasive Bladder Cancer in the United States: Results from the National Cancer Data Base. *Eur Urol* 2013; **63**:

21. National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Available at: <https://seer.cancer.gov/>. Accessed July 13, 2019.
22. Trenta P, Calabrò F, Cerbone L et al: Chemotherapy for Muscle-Invasive Bladder Cancer. *Curr Treat Options Oncol* 2016; **17**:
23. Sandler HM and Mirhadi AJ et al: Current Role of Radiation Therapy for Bladder Cancer. *Semin Oncol* 2012; **39**:
24. Mohamed HAH, Salem MA, Elnagger MS et al: Trimodalities for Bladder Cancer in Elderly: Transurethral Resection, Hypofractionated Radiotherapy and Gemcitabine. *Cancer Radiother* 2018; **22**:
25. Fedeli U, Fedewa SA, Ward EM et al: Treatment of Muscle Invasive Bladder Cancer: Evidence from the National Cancer Database, 2003 to 2007. *J Urol* 2011; **185**:
26. Canter D, Viterbo R, Kutikov A et al: Baseline renal function status limits patient eligibility to receive perioperative chemotherapy for invasive bladder cancer and is minimally affected by radical cystectomy. *Urology* 2011; **77**:
27. Dash A, Galsky MD, Vickers AJ et al: Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006; **107**:
28. Apolo AB, Grossman HB, Bajorin D et al: Practical Use of Perioperative Chemotherapy for Muscle-Invasive Bladder Cancer: Summary of Session at the Society of Urologic Oncology Annual Meeting. *Urol Oncol* 2012; **30**:
29. Lindgren D, Frigyesi A, Gudjonsson S et al. Combined gene expression and genomic profiling define two intrinsic molecular subtypes of urothelial carcinoma and gene signatures for molecular grading and outcome. *Cancer Res* 2010; **70**: 3463-72.
30. Seiler R, Ashab HAD, Erho N et al: Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy. *Eur Urol* 2017; **72**:

Tables

Table 1: Patient demographics and tumor characteristics based on treatment groups for stage II. Groups were removed that had less than 50 values or provided no information (ie of unknown status). P-values evaluated level of significance between treatment and patient demographic/tumor characteristic.

(STAGE II)	TREATMENT:	Radical Cystectomy	Radical Cystectomy + Chemotherapy	Chemotherapy + Radiation	<i>P</i>
	Total n=9,243	n=5185 (56.0)	n=1615 (17.5)	n=2443 (26.4)	
Age at Diagnosis (yrs)		66.22	63.85	72.08	<.001
	85+ years old	165 (29.2)	15 (2.7)	384 (68.1)	<.001
Sex	Male	3918 (56.2)	1264 (18.1)	1785 (25.6)	≤.001
	Female	1267 (55.7)	351 (15.4)	658 (28.9)	
Race	White	4663 (56.0)	1482 (17.8)	2179 (26.2)	≤.001
	Asian or Pacific Islander	221 (63.0)	48 (13.7)	82 (23.3)	
	Black	275 (53.0)	74 (14.3)	170 (32.7)	
Marital	Married	3382 (57.6)	1108 (18.9)	1383 (23.5)	<.001
	Widowed	613 (48.4)	122 (9.6)	532 (42.0)	
	Divorced	460 (56.2)	147 (18)	211 (25.8)	
	Single	510 (57.8)	163 (18.5)	209 (23.7)	
Primary Site	Trigone of Bladder	329 (55.3)	89 (15.0)	177 (29.7)	<.05
	Dome of Bladder	194 (50.9)	63 (16.5)	124 (32.6)	
	Bladder Wall	1607 (54.3)	505 (17.1)	847 (28.6)	
	Overlapping Lesion of Bladder	881 (57.4)	278 (18.1)	375 (24.5)	
Grade	Moderately Differentiated	387 (72.7)	51 (9.6)	94 (17.7)	<.001
	Poorly Diff/Undifferentiated	4553 (55.6)	1450 (17.7)	2187 (26.7)	

Table 2: Patient demographics and tumor characteristics based on treatment groups for stage III. Groups were removed that had less than 50 values or provided no information (ie of unknown status). P-values evaluated level of significance between treatment and patient demographic/tumor characteristic. NS indicates no significance.

(STAGE III)	TREATMENT:	Radical Cystectomy	Radical Cystectomy + Chemotherapy	Chemotherapy + Radiation	<i>P</i>
	Total n=7,485	n=5283 (70.6)	n=1621 (21.7)	n=581 (7.8)	
Age at Diagnosis (yrs)		68.98	65.55	71.85	<.001
	85+ years old	229 (70.0)	20 (6.1)	78 (23.9)	<.001
Sex	Male	3707 (69.1)	1216 (22.7)	438 (8.2)	≤.001
	Female	1576 (74.2)	405 (19.1)	143 (6.7)	
Race	White	4728 (70.7)	1462 (21.9)	499 (7.4)	<.05
	Asian or Pacific Islander	214 (69.7)	66 (21.5)	27 (8.8)	
	Black	317 (69.8)	84 (18.5)	53 (11.7)	
Marital	Married	3275 (69.6)	1104 (23.5)	325 (6.9)	<.001
	Widowed	870 (76.5)	146 (12.8)	122 (10.7)	
	Divorced	471 (70.4)	134 (20.0)	64 (9.6)	
	Single	487 (68.6)	174 (24.5)	49 (6.9)	
Primary Site	Trigone of Bladder	317 (68.3)	105 (22.6)	42 (9.1)	NS
	Dome of Bladder	263 (76.0)	67 (19.4)	16 (4.6)	
	Bladder Wall	147 (7.0)	1509 (71.3)	459 (21.7)	
	Overlapping Lesion of Bladder	1146 (71.6)	343 (21.5)	111 (6.9)	
Grade	Moderately Differentiated	362 (79.0)	73 (16.0)	23 (5.0)	<.001
	Poorly Diff/Undifferentiated	510 (7.6)	4700 (70.3)	1479 (22.1)	

Table 3: Treatment groups were separated into stage II or III. P-values evaluated level of significance between a treatment and a stage. NS indicates no significance.

Treatment:		Radical Cystectomy	Radical Cystectomy + Chemotherapy	Chemotherapy + Radiation	Total:
Stage:	II	5185 (56.0)	1615 (17.5)	2443 (26.4)	9,243
	III	5283 (70.6)	1621 (21.7)	581 (7.8)	7,485
P-value:		NS	NS	<.001	

Table 4: Multinomial logistic regression indicating likelihood of group receiving either radical cystectomy plus chemotherapy or chemotherapy plus radiation compared to reference radical cystectomy group. 85 year olds who had stage II tumors were used as a reference group compared to stage III tumors. P-values measure significance between patient or tumor characteristic and treatment. Separate statistical analysis was performed by stage. LR indicates likelihood ratio; 95% CI indicates 95% confidence interval; Radical Cyst indicates radical cystectomy; Chemo indicates chemotherapy; Rad indicates radiation.

LR:						
Stage:		II		III		II/III
Treatment:		Radical Cyst + Chemo	Chemo + Rad	Radical Cyst + Chemo	Chemo + Rad	
Sex:	P-value:	≤.001		<.001		
Male		++++	++++	++++	++++	
95% CI:						
Female:		0.859	1.140	0.783	0.768	
95% CI:		0.751-0.982	1.022- 1.272	0.690-0.889	0.630- 0.936	
Age:	P-value:	<.001		<.001		
55-65		++++	++++	++++	++++	
95% CI:						
65-75		1.074	1.971	0.736	1.060	
95% CI:		0.936-1.233	1.635- 2.375	0.637-0.851	0.794- 1.417	
75-85		2.287	8.665	0.423	1.963	
95% CI:		1.925-2.718	7.047- 10.653	0.359-0.498	1.498- 2.574	P- value:
85+		++++	++++	0.961	0.146	<.001
95% CI:				0.478-1.932	0.107- 0.201	
Race:	P-value:	≤.001		<.05		
White:		++++	++++	++++	++++	
95% CI:						
Asian:		0.684	0.794	0.999	1.198	
95% CI:		0.498-0.940	0.613- 1.029	0.753-1.324	0.794- 1.806	
Black:		0.848	1.323	0.858	1.587	
95% CI:		0.652-1.103	1.086- 1.613	0.670-1.099	1.170- 2.154	

Marital:	P-value:	<.001		<.001	
Married:		++++	++++	++++	++++
95% CI:					
Divorced:		0.943	0.986	0.844	1.369
95% CI:		0.783-1.136	0.720-1.352	0.688-1.035	1.030-1.821
Grade:	P-value:	<.001		<.001	
Moderately Differentiated:		++++	++++	++++	++++
95% CI:					
Poorly/ Undifferentiated:		2.433	1.978	1.560	1.708
95% CI:		1.806-3.278	1.570-2.492	1.205-2.020	1.110-2.629

Figures

Figure 1

Case flow diagram.

Figure 2

Percentage of patients by treatment group treated for stage II MIBC from 1988-2013 based on 5-year intervals. For 1988-1992, n=399; 1993-1997, n=597; 1998-2002, n=1186; 2003-2007, n=2848; 2008-2013, n=4213 (Highly Significant P-values <.001). CHEMO indicates Chemotherapy; RAD indicates Radiation.

Figure 3

Percentage of patients by treatment treated for stage III MIBC from 1988-2013 based on 5-year intervals. For 1988-1992, n=478; 1993-1997, n=743; 1998-2002, n=1666; 2003-2007, n=2060; 2008-2013, n=2538 (Highly significant P-values <.001). CHEMO indicates Chemotherapy; RAD indicates Radiation.