Bladder | **2018** | Vol. 5(4) | e37
DOI: 10.14440/bladder. 2018.785

ARTICLE

Outcomes of patients undergoing radiation therapy for bladder cancer

Salman Hasan[1], Eva Mercedes Galvan[2], Courtney Shaver[3], Michael Hermans[4], Chul Soo Ha[2], Gregory P. Swanson[1]*

[1]Department of Radiation Oncology, Baylor Scott & White Health, Temple, TX 76502, USA
[2]Department of Radiation Oncology, UT Health San Antonio Mays Cancer Clinic, San Antonio, TX 78229, USA
[3]Department of Biostatistics, Baylor Scott & White Health, Temple, TX 76502, USA
[4]Department of Urology, Central Texas Veterans Health Care System, Temple, TX 76504, USA

*Corresponding author: Gregory P. Swanson, Email: swansong@uthscsa.edu

Competing interests: The authors have declared that no competing interests exist.

Abbreviations used: AACCI, age-adjusted Charlson comorbidity index; AR, aggressive radiation; CCR, concurrent chemoradiation; CMT, combined modality therapy; CTCAE, common terminology criteria for adverse events; GI, gastrointestinal; GU, genitourinary; NCDB, National Cancer Data Base; PR, palliative radiation; RT, radiation treatment; SCC, squamous cell carcinoma

Received June 11, 2018; Revision received September 11, 2018; Accepted September 22, 2018; Published December 31, 2018

ABSTRACT

OBJECTIVES: To review our two institutional experiences regarding the historical referral patterns of bladder cancer patients to receive radiation therapy, characteristics of these referred patients, and their treatment outcomes.

METHODS: A retrospective review was performed analyzing patients who underwent radiation therapy for bladder cancer from 2005 to 2015 (*n* = 69) at two regional referral institutions. The age-adjusted Charlson comorbidity index (AACCI) was calculated for each patient. Patients were divided into three groups: definitive concurrent chemoradiation (CCR), aggressive radiation (AR) alone ≥ 50 Gy, or palliative radiation alone (PR) < 50 Gy. Gastrointestinal (GI) and genitourinary (GU) acute toxicities were recorded.

RESULTS: The median overall AACCI score was 7, which correlates to a two-year expected survival of 55% ± 11%. Thirty-five (50.7%) patients received CCR, 19 (27.5%) received AR, and 15 (21.7%) received PR. Patients presented with hematuria (*n* = 43, 62%), pain (*n* = 18, 26%), or obstruction (*n* = 12, 17%). Of symptomatic patients, treatment improved hematuria in 86%, pain in 75%, and obstruction in 42%. Twenty-two recurrences (32%) were identified at follow-up. Local, regional, and distant recurrences developed in 20%, 14%, and 17% of patients who received CCR. There were two grade 3 GU toxicities and one grade 3 GI toxicity; all grade 3 toxicities were in patients receiving CCR.

CONCLUSIONS: Bladder preservation is possible with chemoradiation therapy; however, urologists rarely refer patients for consideration of chemoradiation. The limited patients who are referred for radiation generally have limited life expectancy, significant comorbidities, or have advanced disease amenable only to palliation. Palliative radiation improves symptoms with minimal toxicity.

Keywords: bladder cancer, combined-modality therapy, palliative care, radiation therapy

INTRODUCTION

Nearly 81000 new cases of urinary bladder cancer are diagnosed each year in the United States, making it the sixth most common cancer [1]. Bladder cancer is broadly categorized as non-muscle-invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). Nearly 30% of newly-detected cases are MIBC. NMIBC may be managed with transurethral resection of the bladder tumor, followed by Bacillus Calmette-Guerin or intravesical chemotherapy. In the United States, for patients with MIBC, urologists typically recommend radical cystectomy (RC) as the standard of care, with consideration of neoadjuvant chemotherapy.

Cystectomy is associated with significant perioperative complications in the range of 25%–57%, with in-hospital mortality rates of approxi-

How to cite this article: Hasan S, Galvan EV, Shaver C, Hermans M, Ha CS, Swanson GP. Outcomes of patients undergoing radiation therapy for bladder cancer. *Bladder* 2018;5(4):e37. DOI: 10.14440/bladder.2018.785

mately 3% [2,3]. The most common complications include issues with intestinal anastomosis, hepatic failure, wound healing, and cardiac complications [2]. Medical co-morbidities, significant smoking history, and advanced age often preclude patients from undergoing surgery. Bladder preservation with combined-modality therapy (CMT) using chemotherapy and radiation is a reasonable option for patients unfit for surgery or for patients who are interested in exploring alternatives to surgery. The SPARE trial attempted to compare bladder preserving CMT with RC, but was closed due to poor accrual [4]. A pooled analysis of six bladder preservation studies with CMT demonstrated a complete response rate of 69% with comparable long-term disease-specific survival when compared to modern cystectomy studies [5,6]. In addition, a recent meta-analysis comparing over 9000 MIBC patients who had either RC or CMT showed no difference in overall survival or disease-free survival at 5–10 years, but with high rates of major complications in the RC group [7].For some patients who are not candidates for chemotherapy, radiation alone has been shown to be effective for palliation of symptoms associated with bladder cancer [8-10].

Recent population database analyses have shown that bladder-preserving CMT has been underutilized in the United States compared to other countries. Nearly a quarter of patients undergo no treatment if they are not candidates for surgery [11,12]. Our perception is that our radiation oncology departments rarely see patients for whom surgery is not an option, but who may be candidates for CMT. Therefore, we reviewed our own experience to ascertain the characteristics of patients actually seen in our radiation departments and their treatment outcomes.

PATIENTS AND METHODS

After IRB approval, a bi-institutional retrospective review was performed analyzing patients who underwent radiation therapy for bladder cancer between 2005 and 2015 at the Baylor Scott and White Vasicek Cancer Center, Temple, Texas and UT Health San Antonio Mays Cancer Center, San Antonio, Texas (total of 18 referring urologists). The two practices represent the largest referring medical centers in Central Texas. Both are teaching institutions with residency training programs in both urology and radiation oncology. Though this study only accounts for internal referrals, the charts for all patients with bladder cancer who received radiation were reviewed and no significant mention of external referrals were noted.

Sixty-nine patients were considered for analysis (**Table 1**). Patients included had been deemed unfit for surgical management or had refused surgery. Patients with bladder cancer that received palliative radiation for distant metastases but not to the bladder itself were excluded.

Each patient was initially evaluated by a urologist and then seen by a radiation oncologist. Pathologic diagnosis of bladder cancer was required. The American Joint Committee on Cancer staging manual 7th edition was used for staging classification. The age-adjusted Charlson comorbidity index (AACCI) was calculated for each patient to assess the risk of mortality (**Table 2** and **Table 3**) [13,14].Gastrointestinal (GI) and genitourinary (GU) toxicities were recorded and toxicities were reported using the common terminology criteria for adverse events (CTCAE) version 4 [15].

External beam radiation was performed with high-energy photons with either 3D-conformal technique (3DCRT) or intensity-modulated radiation therapy (IMRT), with or without concurrent chemotherapy. Radiation to the lymph nodes was allowed. Patients were divided into three groups: definitive concurrent chemoradiation (CCR), aggressive radiation (AR) alone ≥ 50 Gy, or palliative radiation alone (PR) < 50 Gy.

Symptom control was considered successful if it had improved or resolved after radiation treatment. Follow-up time was calculated from date of last radiation treatment to date of last follow-up appointment or death. Patients with no follow-up appointments were excluded for survival analysis but were included in symptom control response. A significant number of patients (n = 12) had no to minimal disease-specific follow-up because they were managed with end-of-life care (including hospice). Recurrence was calculated from date of last radiation treatment to the identification of the recurrence, which was noted on either cystoscopy or imaging.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., North Carolina, USA). Kaplan-Meier curves were used to describe survival and recurrence. A Cox regression model was used to test for association between variables and recurrence or survival.

RESULTS

Sixty-nine patients were evaluated. The median patient age was 73 (range: 37–98). Seventy-one percent of patients were male. Seventy-two percent of our patients reported a smoking history, with an average of 42 pack-year equivalents. The distribution of patients with stage I, II, III, and IV disease were 4.4%, 52.2%, 15% and 28.4% respectively. Thirty-five (50.7%) patients received CCR, 19 (27.5%) received AR, and 15 (21.7%) received PR. The median ages of patients receiving CCR, AR, and PR were 72, 75, and 73, respectively. The median follow-up time for all patients was 6.0 months (range: 0–92 months). Median AACCI scores for patients receiving CCR, AR, or PR were 6, 7, and 8, respectively.

The median radiation dose was 5940 cGy (range: 600–7000 cGy) in 32 fractions (range: 2–37). For those receiving CCR, the median dose was 6100 cGy in 33 fractions (range: 2200–6800 cGy). The patient who received 2200 cGy had been planned for 6400 cGy, but died of cardiac arrest before completing treatment. For those receiving AR, the median dose was 6060 cGy in 33 fractions (range: 5000–7000 cGy). The median dose of radiation for those receiving PR was 3000 cGy in 10 fractions (range: 600–4000 cGy). The patient who received 600 cGy had been planned for 3000 cGy, but was discharged to hospice prior to completing treatment. Chemotherapy was given to 58% of patients either pre-RT, concurrently, or post-RT.

Patients presented with symptoms including hematuria (62%, n = 43), pain (26%, n = 18), obstruction (17%, n = 12). Of symptomatic patients, treatment improved hematuria in 86%, pain in 75%, and obstructive symptoms in 42%. Among the different treatment groups, symptoms improved in 73% of patients receiving CCR, 78% of patients receiving AR, and 100% of patients receiving PR. Specifically, hematuria improvement was noted in 90% of patients receiving CCR, 71% receiving AR, and 100% receiving PR.

The median overall survival from treatment completion was 7.4 months. The median survival in months for those receiving CCR, AR, and PR were 11.3 (range: 1–67), 9.2 (range: 0–92), and 4.1 (range: 0–17), respectively (**Fig. 1**). Thirty-two percent of patients (n = 22) developed a recurrence at follow-up. Local, regional, and distant recurrences developed in 20%, 14%, and 17% of patients who received

CCR. The median times to recurrence for those undergoing CCR and AR were 14 months and 8.5 months (**Fig. 2**). There were two grade 3 GU toxicities and one grade 3 GI toxicity; all grade 3 toxicities were in patients receiving CCR.

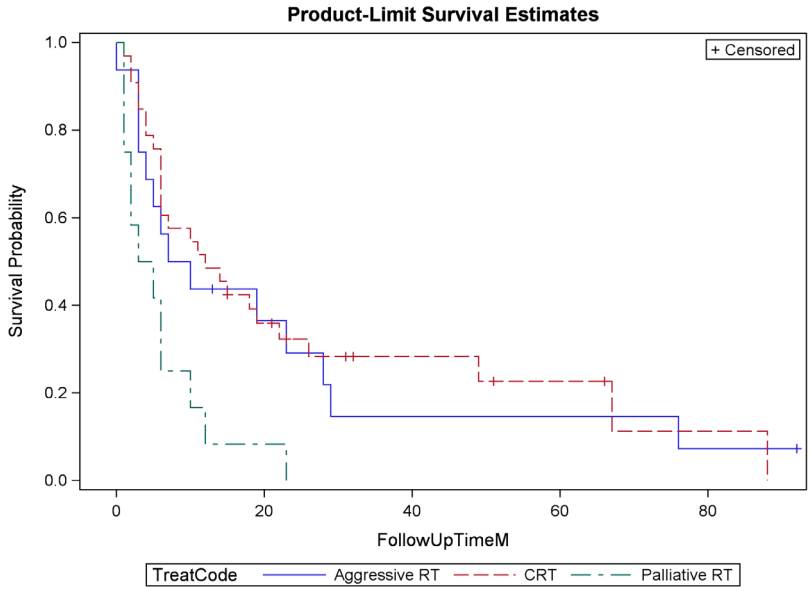

Figure 1. Overall survival.

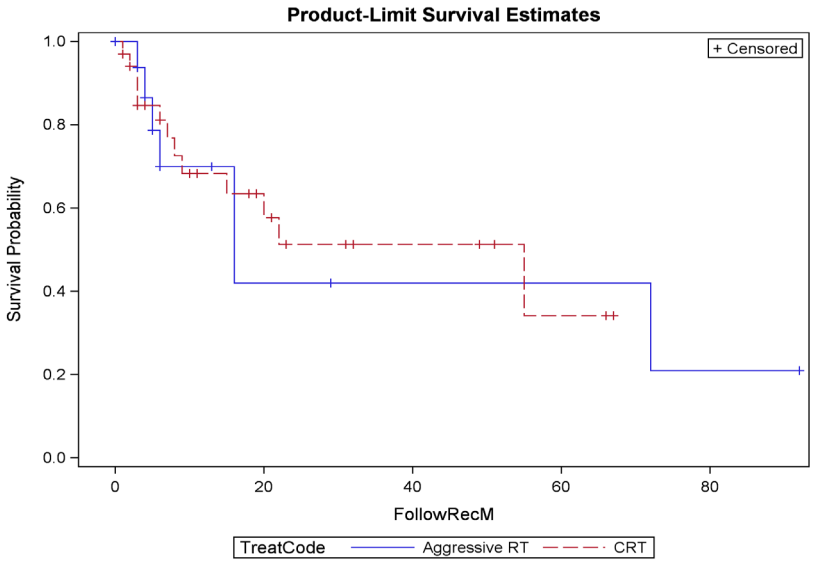

Figure 2. Recurrence free survival.

At one of the institutions, we queried our cancer database for patients who underwent cystectomy for bladder cancer during this time period. Ninety one patients had adequate records for review and Urology consultation/progress notes were reviewed. After reviewing the notes 72.5% (66/91) of patients did not have radiation treatment mentioned as an option and 24.2% (22/91) discussed radiation but no consultation with radiation oncology was made to discuss the option. Only 3.3% (3/91) of patients who went for cystectomy actually had a consultation with radiation oncology to discuss bladder preservation.

DISCUSSION

In the United States, the incidence of bladder cancer has remained relatively stable over the last 20 years, despite a decreased trend in smoking, which is a significant risk factor for developing bladder cancer [16]. Mortality rates attributed to bladder cancer have also remained similar. The median age at diagnosis is 73, with increasing incidence as age increases; up to 45% of cases are diagnosed in patients over the age of 75 [17]. At these advanced ages, patients often have multiple medical co-morbidities along with a significant smoking history, which precludes some patients from surgical management with RC.

Table 1. Patient demographics and disease characteristics.

Characteristic		Total patients (*N* = 69)
Age, median (range)	73 (37–98)	
Sex, *N* (%)		
	Male	49 (71)
	Female	20 (29)
Smoking history (%)		
	Yes	50 (72)
	No	17 (25)
	Missing data	2 (3)
	Pack years, average (range)	41.8 (0–175)
AACCI, *N* (%)		
	3–5	12 (17)
	6–7	28 (41)
	> 7	29 (42)
Stage, *N* (%)		
	Stage I	3 (4)
	Stage II	35 (52)
	Stage III	10 (15)
	Stage IV	19 (28)
T stage, *N* (%)		
	T1	4 (6)
	T2	43 (67)
	T3	10 (16)
	T4	7 (11)
Regional nodal status, *N* (%)		
	Positive	12 (18)
	Negative	53 (82)
Distant metastasis, *N* (%)		
	Positive	15 (22)
	Negative	52 (78)
Histology, *N* (%)		
	Urothelial	53 (80)
	Squamous	5 (8)
	Adenocarcinoma	3 (5)
	Neuroendocrine	1 (2)
	Mixed	4 (6)
Hydronephrosis, *N* (%)		
	Present	29 (44)
	Negative	37 (56)
Treatment		
	Definitive (CCR)	35 (51)
	Aggressive radiation	19 (28)
	Palliative radiation	15 (22)

Alternatively, CMT with chemotherapy and radiation has been proven an effective treatment regimen with outcomes comparable to RC. In our 10-year bi-institutional review, only 69 patients with MIBC were treated with radiation therapy for the bladder itself, which correlates to only about three cases per year per institution. Among these 69 patients, 15 were treated with palliative intent further emphasizing the limited number of patients being treated with definitive intent CMT.

These low referral rates of MIBC patients to radiation oncologists are consistent with a National Cancer Data Base (NCDB) study by Gray *et al*., which demonstrated that, among 28691 MIBC patients,

only 7.6% of patients were offered definitive CMT or radiation therapy, while 25.9% were offered only observation [11]. An additional NCDB analysis by Haque *et al*. reported that in patients with abdominal or pelvic wall invasion (T4b disease), the percentage of patients receiving chemotherapy alone were 20.6%, CMT 8.9%, RC 18.9%, other treatments 24.7%, or observation alone 27.8% [12]. In the Haque analysis, outcomes in patients treated with CMT were superior to observation or chemotherapy alone, and CMT outcomes were statistically similar to RC outcomes [12]. These observations indicate that nearly a quarter of patients with MIBC are offered no treatment, and that CMT is underutilized.

Table 2. Age adjusted Charlson comorbidity index.

Weight	Comorbid condition
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebral vascular disease
	Dementia
	Chronic obstructive pulmonary disease
	Connective tissue disorder
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate/severe renal disease
	Diabetes with endo organ damage
	Any tumor
	Leukemia
	Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumor
	AIDS
1	For each decade over the age 40 years

The patients that our radiation oncology departments did evaluate typically presented with significant symptoms from their cancer such as hematuria, pain, or urinary obstruction. We found that a majority of patients reported symptom improvement with radiation treatment. Hematuria was the most likely symptom to improve after radiation, with nearly 90% of patients presenting with hematuria reporting improvement. We were not able to identify a threshold dose at which hematuria was best controlled, but a randomized study by Duchesne *et al*. showed that either 35 Gy in 10 fractions or 21 Gy in 3 fractions resulted in symptomatic improvement in 68% of patients with no evidence of significant toxicity [8]. Another study compared 30 Gy in 10 daily fractions and 20 Gy in 4 once-weekly fractions; in this review, 69% of patients reported improvement in symptoms at two weeks, although 69% of patients also had relapse bleeding at 6 months [9].CMT is a reasonable treatment option that should be discussed, but judicious candidate selection is recommended, along with a thorough review of potential treatment-related toxicities. The NCCN reports reserving bladder preservation approaches for those with solitary tumors, negative nodes, no carcinoma *in situ* and good pre-treatment bladder function [18]. In addition, in patients undergoing CMT, inferior outcomes were noted in those with hydronephrosis [19]. There have been mixed reports of patients with inflammatory bowel disease (IBD) being at increased risk of GI toxicities with radiation therapy, but a report by Gestaut *et al*. reviewed patients over a 23 year period in patients with IBD and prostate cancer who underwent radiation therapy and found minimal GI toxicity in the IMRT era [20]. Therefore, just as surgery requires preoperative evaluation, review of patient candidacy for CMT is warranted as well.

In our study, there were a total of 3 (4.3%) grade three GU or GI toxicities, which were all among patients undergoing concurrent chemoradiation. Regarding toxicities associated with concurrent chemoradiation, late GU and GI toxicities were assessed by Efstathiou *et al*., who demonstrated 21.7%, 10.2%, and 7% risk of grade 1, 2, and 3 late GI/GU toxicities, respectively, with GU complications being more common. The late grade 3 toxicities included severe frequency, frequent hematuria, and bowel obstruction. A median time to late grade 3 toxicities was 22 months with a median duration of toxicities of 7.1 months before decreasing in severity [21].

Approximately 90% of carcinomas of the bladder are of the urothelial subtype; in our study, this histology represented the majority of cases as well (80%) [18]. Squamous cell carcinoma (SCC) accounts for 3%–5% of cases in the United States and is more common in areas where Schistosoma haematobium infection is endemic such as Egypt. Management options of SCC typically consist of cystectomy with similar control rates to urothelial carcinoma. Bladder preservation with CMT has been explored in patients with SCC of the bladder: two studies out of Egypt have demonstrated similar overall survival rates and pCR rates with CMT in comparison to RC [22,23].

Table 3. 2-year estimated expected survival.

Total score	2-year estimated expected survival
3–5	80%–95%
6–7	55%
> 7	< 35%

Our study was limited by typical weaknesses of a retrospective review. Follow-up data were limited, as many patients proceeded to hospice during or soon after radiation treatment. This high rate of subsequent hospice enrollment is a reflection of the poor overall health of the population of patients that we are referred for consideration of radiation for bladder cancer. For this reason we stratified treatment outcomes into three groups: CCR, AR, PR. In addition, tracking of the duration of symptom control was limited due the aforementioned constraint.

A recent SEER analysis by Williams *et al*. in 2018 demonstrated decreased survival and increased costs with CMT in comparison to RC, suggesting these findings should be incorporated in decision-making when reviewing treatment options [24]. Though bias between the two groups was attempted to be mitigated by undergoing propensity-matched analysis, some of the patients who underwent RC also underwent adjuvant radiation. It was noted that, in the patients who received CMT, those receiving < 18 fractions had worse survival in contrast to those receiving > 18 fractions. Typical definitive courses of radiation range

from 20–36 fractions, which brings to question the intensity of radiation treatment in this analysis being less than what would typically be recommended. Such retrospective studies are hypothesis-generating, but only a randomized study will be able to appropriately answer the question.

In 2017, the American Urological Association and American Society for Radiation Oncology released guidelines for the treatment of non-metastatic MIBC. This report recommends that urologists and radiation oncologists discuss bladder preservation approaches with CMT with patients who decline surgery or are otherwise unfit for surgery [25]. Our hope is that, with these new guidelines, future referral patterns will change to allow patients to consider the less invasive, but equally effective, technique of CMT.

Though the overall prognosis for MIBC has not changed over the last 30 years, future developments in enhanced detection of bladder cancer cells and the introduction of immunotherapeutic agents may further provide improvements in cancer control in conjunction with CMT.

In conclusion, accumulating data demonstrate bladder preservation with CMT in MIBC patients has outcomes equivalent to those of RC. The reality in our two tertiary referral institutions is that patients are rarely given the option of bladder preservation and undergo RC. Patients referred for primary radiation therapy are either unfit for surgery or have significant disease amenable only to palliation, and many patients have a limited 2-year overall survival related to their other medical comorbidities, therefore limiting our long-term data regarding outcomes of CMT. Fortunately, in symptomatic patients, radiation was often successful in controlling the cancer and in alleviating symptoms for the remainder of our patients' lives with minimal associated radiation-induced toxicity.

Acknowledgments

None.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68: 7-30. doi: 10.3322/caac.21442. PMID: 29313949
2. Konety BR, Allareddy V, Herr H (2006) Complications after radical cystectomy: analysis of population-based data. Urology 68: 58-64. doi: 10.1016/j.urology.2006.01.051. PMID: 16806414
3. Donat SM, Shabsigh A, Savage C, Cronin AM, Bochner BH, et al. (2008) Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol 55: 177-185. doi: 10.1016/j.eururo.2008.07.018. PMID: 18640770
4. Huddart RA, Hall E, Lewis R, Birtle A (2010) Life and death of spare (selective bladder preservation against radical excision): reflections on why the spare trial closed. BJU Int 106: 753-755. doi: 10.1111/j.1464-410X.2010.09537.x. PMID: 20707796
5. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, et al. (2012) Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 366: 1477-1488. doi: 10.1056/NEJMoa1106106. PMID: 22512481
6. Mak RH, Hunt D, Shipley WU, Efstathiou JA, Tester WJ, et al. (2014) Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. J Clin Oncol 32: 3801-3809. doi: 10.1200/JCO.2014.57.5548. PMID: 25366678
7. Vashistha V, Wang H, Mazzone A, Liss MA, Svatek RS, et al. (2016) Radical Cystectomy Compared to Combined Modality Treatment for Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. Int J Radiat Oncol Biol Phys 97: 1002-1020. doi: 10.1016/j.ijrobp.2016.11.056. PMID: 28332983
8. Duchesne GM, Bolger JJ, Griffiths GO, Trevor Roberts J, Graham JD, et al. (2000) A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. Int J Radiat Oncol Biol Phys 47: 379-388. doi: 10.1016/S0360-3016(00)00430-2. PMID: 10802363
9. McLaren DB, Morrey D, Mason MD (1997) Hypofractionated radiotherapy for muscle invasive bladder cancer in the elderly. Radiother Oncol 43: 171-174. PMID: 9192963
10. Lacarrière E, Smaali C, Benyoucef A, Pfister C, Grise P (2013) The efficacy of hemostatic radiotherapy for bladder cancer-related hematuria in patients unfit for surgery. Int Braz J Urol 39: 808-816. doi: 10.1590/S1677-5538.IBJU.2013.06.06. PMID: 24456773
11. Gray PJ, Fedewa SA, Shipley WU, Efstathiou JA, Lin CC, et al. (2013) Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. European Urology 63: 823-829. doi: 10.1016/j.eururo.2012.11.015. PMID: 23200811
12. Haque W, Verma V, Butler EB, Teh BS (2017) National practice patterns and outcomes for T4b urothelial cancer of the bladder. Clin Genitourin Cancer doi: 10.1016/j.clgc.2017.08.013. PMID: 28958674
13. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML (2000) A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. Am J Med 108: 609-613. doi: 10.1016/S0002-9343(00)00371-5. PMID: 10856407
14. Koppie TM, Serio AM, Vickers AJ, Vora K, Dalbagni G, et al. (2008) Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. Cancer 112: 2384-2392. doi: 10.1002/cncr.23462. PMID: 18404699
15. National Institutes of Health. National Cancer Institute (2018) Common terminology criteria for adverse events (CTCAE). Cited on May 24, 2018. Available from: https://ctep.cancer.gov.
16. Centers for Disease Control (2018) Smoking & Tobacco Use. Cited on May 24, 2018. Available from: https://www.cdc.gov/tobacco.
17. National Institutes of Health, National Cancer Institute (2018) SEER Cancer Stat Facts. Cited on May 24, 2018. Available from: https://seer.cancer.gov/statfacts. Cited on May 24:
18. National Comprehensive Cancer Network (2018) Evidence-Based Cancer Guidelines. Available from: https://www.nccn.org/.
19. Shipley WU, Kaufman DS, Zehr E, Heney NM, Lane SC, et al. (2002) Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. Urology 60: 62-67. PMID: 12100923
20. Gestaut MM, Swanson GP (2016) Long term clinical toxicity of radiation therapy in prostate cancer patients with Inflammatory Bowel Disease. Rep Pract Oncol Radiother 22: 77-82. doi: 10.1016/j.rpor.2016.10.005. PMID: 27920612
21. Efstathiou JA, Bae K, Shipley WU, Kaufman DS, Hagan MP, et al. (2009) Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89-03, 95-06, 97-06, 99-06. J Clin Oncol 27: 4055-4061. doi: 10.1200/JCO.2008.19.5776. PMID: 19636019
22. Zaghloul MS (2012) Bladder cancer and schistosomiasis. J Egypt Natl Canc Inst 24: 151-159. doi: 10.1016/j.jnci.2012.08.002. PMID: 23159285
23. Sabaa MA, El-Gamal OM, Abo-Elenen M, Khanam A (2008) Combined modality treatment with bladder preservation for muscle invasive bladder cancer. Urol Oncol 28: 14-20. doi: 10.1016/j.urolonc.2008.07.005. PMID: 18818110
24. Williams SB, Shan Y, Jazzar U, Mehta HB, Baillargeon JG, et al. (2018) Comparing Survival Outcomes and Costs Associated With Radical Cystectomy and Trimodal Therapy for Older Adults With Muscle-Invasive Bladder Cancer. JAMA Surg 153: 881-889. doi: 10.1001/jamasurg.2018.1680. PMID: 29955780
25. Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, et al. (2017) Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol 198: 552-559. doi: 10.1016/j.juro.2017.04.086. PMID: 28456635

This work is licensed under a Creative Commons Attribution-Non-Commercial-ShareAlike 4.0 International License: http://creativecommons.org/licenses/by-nc-sa/4.0