International Journal of Radiation Oncology biology • physics

www.redjournal.org

Scientific Letter

Bladder-Preserving Therapy Patterns of Care: A Survey of US Radiation Oncologists

Abhishek A. Solanki, MD, MS,* Brendan Martin, MA,† Mark Korpics, BS,* Christina Small, MPH,* Matthew M. Harkenrider, MD,* and Timur Mitin, MD, PhD‡

**Department of Radiation Oncology, Stritch School of Medicine, and †Clinical Research Office, Health Sciences Division, Loyola University Chicago, Maywood, Illinois; and ‡Department of Radiation Medicine, Oregon Health and Science University, Portland, Oregon*

Received Aug 8, 2016, and in revised form Mar 21, 2017. Accepted for publication Apr 4, 2017.

Summary

Given the variable dose/fractionations, radiation therapy targets, and chemotherapy regimens of the key trials evaluating bladder-preserving chemoradiation therapy, we conducted an electronic survey of US radiation oncologists to explore clinicians' actual practice patterns. We found several areas of consistency, such as the use of conventional fractionation, and other areas of significant heterogeneity, such as the preferred radiation therapy target. Our findings identify areas in need of further investigation, education, and development of consensus within our field.

Purpose: Clinical trials have demonstrated the efficacy of bladder-preserving chemoradiation therapy (BPT) in muscle-invasive bladder cancer but have differed in the radiation therapy dose/fractionations, radiation therapy targets, and concurrent chemotherapy regimens used. No data exist on the technical and practical approaches actually used in clinical practice throughout the United States when delivering BPT. We performed a survey to explore radiation oncologists' practice patterns.

Methods and Materials: We conducted an electronic survey of US radiation oncologists regarding the management of patients with cT2-3N0M0 transitional cell muscle-invasive bladder cancer. The instrument included questions regarding the types of patients treated with BPT, as well as several aspects of treatment delivery. Descriptive statistics were reported for all responses. Pearson χ^2 tests were used for univariate analysis.

Results: In total, 277 physicians completed our survey. Most respondents (58%) stated that they only treated 1 to 3 patients in the prior year. Seventy-four percent of respondents primarily treated patients deemed unfit for cystectomy, while only 28% saw patients prior to cystectomy for consultation to discuss BPT. The majority of radiation oncologists used conventional fractionation (91%) instead of hypofractionation (7.6%), but more variability existed for radiation therapy targets. Sixty percent used a small pelvis field, 29% used a whole-pelvis field, and 12% treated the bladder only. There was increased use of hypofractionation (29%) and bladder-only radiation therapy (34%) in patients who were not candidates for cystectomy or chemotherapy ($P<.001$). Cisplatin-based concurrent chemotherapy was most commonly preferred (89%). In non-cisplatin candidates, most respondents preferred 5-fluorouracil plus mitomycin C (32%) or carboplatin (32%). Intensity modulated radiation therapy use and midtreatment cystoscopic re-evaluation were variable, while hyperfractionation use was low.

Reprint requests to: Abhishek A. Solanki, MD, MS, 2160 S First Ave, Maywood, IL 60153. Tel: (708) 216-2556; E-mail: abhishek.solanki@lumc.edu

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 99, No. 2, pp. 383–387, 2017
0360-3016/$ - see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ijrobp.2017.04.009

Conclusions: Our study describes radiation oncologists' practice patterns for patients undergoing BPT. Although there are areas of consistency, variability exists in many technical and practical aspects of treatment delivery. Further research and education are needed to determine the optimal radiation therapy target, dose/fractionation, and concurrent chemotherapy regimen. Published by Elsevier Inc.

Introduction

Multiple clinical trials have established bladder-preserving chemoradiation therapy (BPT) as an effective and safe alternative to radical cystectomy for patients with muscle-invasive bladder cancer (MIBC) (1-3). The key trials guiding management have used variable radiation therapy dose/fractionations, anatomic target regions, and concurrent chemotherapy agents. Yet, there are no data available describing the actual practice patterns of radiation oncologists (ROs) throughout the United States.

We performed a survey to describe the real-world technical and practical BPT practices of ROs. Driving this objective was an effort to identify areas that may be targets for focused clinical research, clinician education, and/or consensus development, as well as to identify ROs' practices to help with pragmatic clinical trial design for future BPT clinical trials.

Methods and Materials

We designed an electronic survey instrument focusing on cT2-3N0M0 transitional cell MIBC patients (Appendix E1; available online at www.redjournal.org). The instrument included questions regarding respondent demographic characteristics, patient selection, and various technical and practical factors of BPT delivery. The survey was e-mailed to 4057 US ROs on October 26, 2015, with 1 reminder emailed a week later. Descriptive statistics were reported for each item, and univariate analyses were conducted with Pearson χ^2 tests. $P<.05$ was considered statistically significant.

Results

In total, there were 277 evaluable responses. Table 1 describes the characteristics of the respondents and their clinical practice. Most respondents treated 1 to 3 patients over the prior year (58%), and even more primarily treated patients who were unfit for cystectomy (74%). Only 28% routinely saw MIBC patients prior to cystectomy to discuss radiation therapy options.

Table 2 depicts respondents' chemoradiation therapy practices. Most respondents (91%) used conventional fractionation as the preferred dose/fractionation, while only 7.6% preferred hypofractionation. However, for the group of patients who are unfit for both cystectomy and chemotherapy, more respondents used hypofractionation (29%, $P<.001$). The use of hyperfractionation was low, while intensity modulated radiation therapy use and cystoscopic re-evaluation after 40 to 45 Gy were variable.

Figure 1 depicts the preferred radiation therapy target based on different patient scenarios. Most respondents preferred a small-pelvis field (60%) as per the classic Radiation Therapy Oncology Group (RTOG) fields when treating patients who were candidates for both cystectomy and concurrent chemotherapy. A whole-pelvis volume was the second most preferred (29%), and the minority used bladder-only radiation therapy (12%). More respondents used bladder-only radiation therapy for patients who were unfit for cystectomy ($P<.001$) and even more for patients deemed unfit for both chemotherapy and cystectomy ($P<.001$).

Most respondents (89%) favored cisplatin-based concurrent chemotherapy regimens when possible, with 61% preferring single-agent cisplatin, 16% preferring 5-fluorouracil plus cisplatin, and 12% preferring cisplatin plus paclitaxel. For non-cisplatin candidates, single-agent carboplatin (32%) and 5-fluorouracil plus mitomycin C (32%) were the most commonly preferred regimens. Most respondents (64%) did not use adjuvant chemotherapy.

Discussion

We performed a survey of the practice patterns of US ROs regarding the practical and technical aspects of BPT delivery for patients with MIBC. In doing so, we identified several consistent paradigms, as well as areas of significant heterogeneity in practices.

In our study, over half of our respondents treat only 1 to 3 MIBC patients per year, fewer than one-third routinely evaluate patients prior to cystectomy, and three-quarters primarily treat patients who are unfit for cystectomy. These findings support the anecdotal experience that the MIBC patients who receive BPT in the United States are those who are unfit for cystectomy. This fact should be considered in trial design to improve generalizability.

We found that nearly all respondents use conventional fractionation when delivering BPT, and hypofractionation appears to be reserved for patients with poor performance status. Although there are some exceptions, most of the RTOG studies used a convention dose per fractionation (64.8 Gy at 1.8 Gy/fraction) (2). However, the Bladder Cancer 2001 (BC2001) trial used 2 dose/fractionation schemas per physician discretion: 64 Gy at

Table 1 Respondent clinical and demographic characteristics (N = 277)

Respondent characteristic	n (%)
No. of years in practice	
0-2	18 (7)
3-5	30 (11)
6-10	45 (16)
>10	156 (56)
In residency	28 (10)
Primary practice setting	
Veterans Health Administration hospital	6 (2)
Academic hospital	101 (36)
Community hospital or private practice	170 (61)
US census region	
Midwest	90 (32)
Northeast	54 (19)
South	80 (29)
West	53 (19)
Consultation clinic setting	
Single-specialty clinic as a referral from a physician from another specialty	225 (81)
Multidisciplinary clinic with physicians representing multiple specialties	52 (19)
No. of patients with nonmetastatic bladder cancer treated over the past year	
0	19 (7)
1-3	160 (58)
4-6	64 (23)
>6	34 (12)
Routinely see patients prior to cystectomy to discuss radiation therapy options	
Yes	77 (28)
No	200 (72)
Nonmetastatic bladder cancer patients most commonly treated	
Patients who are unfit for cystectomy	206 (74)
Patients who are fit for surgery but are unwilling to undergo cystectomy	31 (11)
Patients who are candidates for cystectomy and bladder-preserving therapy and are considering both	40 (14)
"When you see a patient who is a cystectomy candidate and is referred to you to discuss bladder preserving therapy, how do you counsel the patient regarding the oncologic outcomes?"	
Bladder preservation is equivalent to cystectomy	214 (77)
Bladder preservation is inferior to cystectomy	51 (18)
Bladder preservation is superior to cystectomy	12 (4)

2 Gy/fraction and a hypofractionated course of 55 Gy at 2.75 Gy/fraction (1). Although toxicity comparisons between groups have not been reported from BC2001, multiple older randomized trials have shown no difference in outcomes with conventional versus hypofractionated regimens (4, 5). Given our shift toward hypofractionation in the treatment of other malignancies, one could argue that hypofractionation should be investigated further in bladder cancer. The vehicle for this may be adaptive radiation therapy, which may optimize the therapeutic ratio.

Table 2 Respondent radiation therapy and chemotherapy practices (N = 277)

Radiation therapy and chemotherapy practice	n (%)
Dose/fractionation most commonly used*	
Conventional (1.8-2 Gy/fraction to 60-70 Gy)	251 (91)
Hypofractionated radiation therapy (>2-2.75 Gy/fraction to 50-55 Gy)	21 (7.6)
Other	4 (1.4)
Preferred dose/fractionation for patients unfit for cystectomy	
Conventional (1.8-2 Gy/fraction to 60-70 Gy)	254 (92)
Hypofractionated radiation therapy (>2-2.75 Gy/fraction to 50-55 Gy)	19 (7)
Other	4 (1)
Preferred dose/fractionation for patients unfit for cystectomy and chemotherapy	
Conventional (1.8-2 Gy/fraction to 60-70 Gy)	166 (60)
Hypofractionated radiation therapy (>2-2.75 Gy/fraction to 50-55 Gy)	80 (29)
Palliative regimen	24 (9)
Other	7 (3)
Cystoscopic re-evaluation during treatment for response after 40-45 Gy	
Almost never (<10% of patients)	86 (31)
In select cases (10%-50% of patients)	61 (22)
Frequently (51%-90% of patients)	47 (17)
Almost always (>90% of patients)	83 (30)
Use hyperfractionation	
Yes	33 (12)
No	244 (88)
IMRT use	
Almost never (<10% of patients)	64 (23)
In select cases (10%-50% of patients)	73 (26)
Frequently (51%-90% of patients)	67 (24)
Almost always (>90% of patients)	73 (26)
Preferred concurrent chemotherapy	
Cisplatin	168 (61)
5-Fluorouracil and cisplatin	45 (16)
Cisplatin and paclitaxel	32 (12)
5-Fluorouracil and mitomycin C	21 (8)
Gemcitabine	4 (1)
Paclitaxel	3 (1)
Carboplatin	4 (1)
Preferred concurrent chemotherapy if not cisplatin candidate	
5-Fluorouracil and mitomycin C	89 (32)
Carboplatin	89 (32)
Paclitaxel	35 (13)
Gemcitabine	32 (12)
No concurrent chemotherapy (radiation therapy monotherapy)	32 (12)
Adjuvant chemotherapy use	
Yes	100 (36)
No	177 (64)

Abbreviation: IMRT = intensity-modulated radiation therapy.
* There were 276 responses because 1 respondent did not answer this question.

There was more variability in the preferred radiation therapy target, although a similar trend of "de-escalation" was seen, as most respondents use a small pelvis field for patients who are candidates for cystectomy and/or

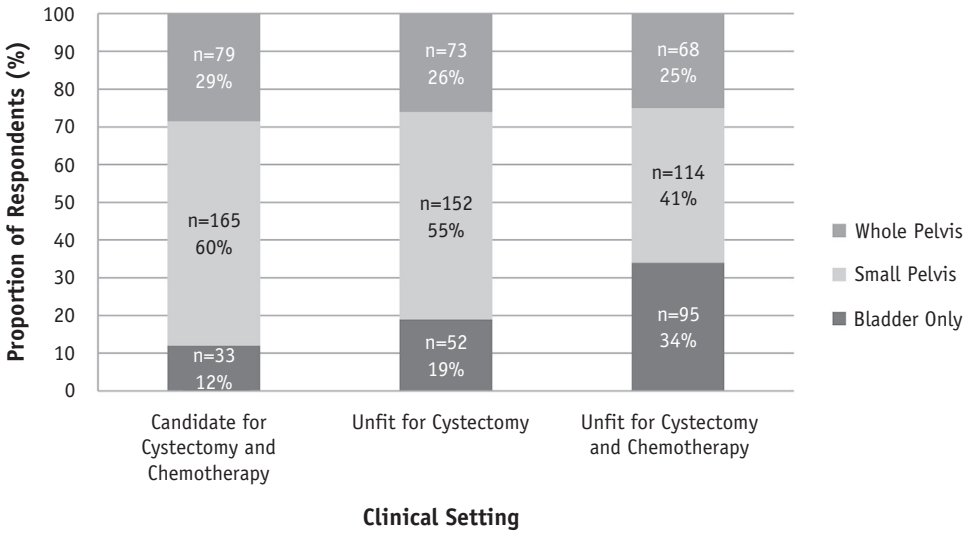

Fig. 1. Radiation therapy target based on patient clinical setting.

chemotherapy but increasingly prefer bladder-only radiation therapy for those who are not. Truly, the optimal radiation therapy target is unknown. Most RTOG studies used a small-pelvis volume, which encompasses the pelvic nodes up to the mid-sacrum, but pathologic studies from patients with extended lymph node dissections have suggested that even nodes outside of the standard small pelvis field may be microscopically involved, compelling some ROs to use whole-pelvis fields targeting the pelvic lymph nodes superiorly to L5/S1. However, the BC2001 trial treated the bladder plus margin only and had a risk of nodal failure of only approximately 5% (1), and a randomized trial comparing bladder-only with whole-pelvis radiation therapy found no benefit to nodal radiation therapy (6). These findings challenge the presumed benefit of more extensive elective nodal irradiation. More data regarding the optimal targets are necessary to allow for standardization within our community and trials moving forward.

A key concerning finding in our study is that carboplatin is frequently preferred in non-cisplatin candidates. Carboplatin was found to be less effective than cisplatin in a randomized trial in the metastatic setting, and retrospective and single-institution data suggest worse complete response rates in BPT patients treated with carboplatin compared with single-agent cisplatin or gemcitabine (7-9). Thus the data argue that carboplatin should be avoided as concurrent therapy for MIBC. ROs should advocate for and educate colleagues about better radiosensitizing agents.

Limitations to our study include the low response rate. In addition, some physicians may have radiation therapy and chemotherapy practices that fall outside of the options available among the survey items, although we attempted to make our items inclusive of most accepted or frequently encountered practices. Moreover, given the anonymous nature of this survey, we were unable to identify any meaningful differences between respondents to the survey and nonrespondents. We also did not ask about neoadjuvant chemotherapy use in our survey and thus cannot make conclusions regarding this practice.

Conclusions

We performed a survey of US ROs regarding their practice patterns for patients with MIBC and found significant heterogeneity in various aspects of BPT treatment delivery. Our results identify important areas where research and education are greatly needed, identify targets for standardization, and will aid in pragmatic future trial design by describing the most common practice patterns.

References

1. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012;366:1477-1488.
2. Mak RH, Hunt D, Shipley WU, et al. 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* 2014;32:3801-3809.
3. Arcangeli G, Arcangeli S, Strigari L. A systematic review and meta-analysis of clinical trials of bladder-sparing trimodality treatment for muscle-invasive bladder cancer (MIBC). *Crit Rev Oncol Hematol* 2015;94:105-115.
4. Quilty P, Duncan W, Kerr G. Results of a randomised study to evaluate influence of dose on morbidity in radiotherapy for bladder cancer. *Clin Radiol* 1985;36:615-618.
5. Whillis D, Howard G, Kerr G, et al. Radical radiotherapy with salvage surgery for invasive bladder cancer: Results following a reduction in radiation dose. *J R Coll Surg Edinb* 1992;37:42-45.
6. Tunio MA, Hashmi A, Qayyum A, et al. Whole-pelvis or bladder-only chemoradiation for lymph node-negative invasive bladder cancer: Single-institution experience. *Int J Radiat Oncol Biol Phys* 2012;82:e457-e462.

7. Petrioli R, Frediani B, Manganelli A, et al. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients: A randomized phase II study. *Cancer* 1996;77:344-351.
8. Sauer R, Birkenhake S, Kuhn R, et al. Efficacy of radiochemotherapy with platin derivatives compared to radiotherapy alone in organ-sparing treatment of bladder cancer. *Int J Radiat Oncol Biol Phys* 1998;40:121-127.
9. Choudhury A, Swindell R, Logue JP, et al. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. *J Clin Oncol* 2011;29:733-738.