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Original Article

Adjuvant Radiotherapy Use by US Radiation Oncologists After Radical Cystectomy for Muscle-invasive Bladder Cancer

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Abstract

Aims: Historic trials suggested significant toxicity with adjuvant radiotherapy (ART) after radical cystectomy for muscle-invasive bladder cancer (MIBC). However, recent trials have found improved locoregional control and the 2016 National Comprehensive Cancer Network (NCCN) guidelines recommend ART consideration for select patients at high risk of local recurrence. ART practice patterns among US radiation oncologists are unknown and we carried out a survey to explore current trends.

Materials and methods: We conducted a survey of US radiation oncologists regarding the management of patients with cT2-3N0M0 transitional cell MIBC. Responses were reported using descriptive statistics. Chi-square and univariate logistic regression of clinical and demographic covariates were conducted, followed by multivariable logistic regression analysis to identify factors predicting for ART use.

Results: In total, 277 radiation oncologists completed our survey. Nearly half (46%) have used ART for MIBC at least once in the past. In ART users, indications for ART include gross residual disease (93%), positive margins (92%), pathological nodal involvement (64%), pT3 or T4 disease (46%), lymphovascular invasion (16%) and high-grade disease (13%). On univariate logistic regression, ART use was associated with the number of years in practice ($P = 0.04$), pre-cystectomy radiation oncology consultation ($P = 0.004$), primarily treating MIBC patients fit for cystectomy ($P = 0.01$) and intensity-modulated radiotherapy use ($P = 0.01$). On multivariable logistic regression analysis, routine pre-cystectomy radiation oncology consultation (odds ratio 1.91, 95% confidence interval 1.04–3.51; $P = 0.04$) and intensity-modulated radiotherapy use (odds ratio 2.77, 95% confidence interval 1.48–5.22; $P = 0.002$) remained associated with ART use.

Conclusions: ART use is controversial in bladder cancer, yet unexpectedly has commonly been used among US radiation oncologists treating patients with MIBC after radical cystectomy. NRG-GU001 was a randomised trial in the US randomizing patients with high-risk pathological findings for observation or ART after cystectomy. However, due to poor accrual it recently closed and thus it will be up to other international trials to clarify the role of ART and identify patients benefiting from this adjuvant therapy.

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Key words: Adjuvant radiotherapy; bladder cancer; muscle-invasive bladder cancer; radiation oncology; radical cystectomy

Introduction

Radical cystectomy is the most commonly used curative treatment in patients with muscle-invasive bladder cancer (MIBC) [1]. Modern series suggest encouraging outcomes with this approach in most patients, but in patients with pT3/4 disease, locoregional recurrence with or without

distant metastases can occur in up to nearly 50% of patients [2,3], particularly those with high-risk features, such as positive margins or limited nodal dissection [4].

Adjuvant radiotherapy (ART) is routinely used in other pelvic malignancies to reduce the risk of locoregional recurrence and improve survival in some patients, and is supported by randomised data in these disease entities [5–8]. ART for bladder cancer was explored in an Egyptian randomised trial of observation versus two ART regimens using two-dimensional radiotherapy techniques; an improvement in 5 year local control from 50% to ~90% and improved disease-free survival were found [9]. However, oncologists have not historically embraced ART, primarily

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due to concern for gastrointestinal toxicity, with rates as high 37% in one study [10].

Yet, with the development of advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), as well as recognition of the high incidence of locoregional recurrence and consequent morbidity of pelvic recurrence, there has been a renewed interest in ART use for patients with MIBC. A second Egyptian randomised trial, this time using modern three-dimensional radiotherapy techniques, was recently presented and showed an improved locoregional control with the addition of ART, with grade ≥ 3 gastrointestinal toxicity of 7–8% [11]. There are multiple international randomized trials testing the benefit of ART versus observation after radical cystectomy in patients with high-risk pathologic features after cystectomy.

There are no data exploring radiation oncologists' practice patterns regarding the use of ART in MIBC in routine practice. We carried out a survey to describe US radiation oncologists' actual radiotherapy and chemotherapy practices in the management of MIBC, and here we report the findings regarding ART utilisation.

Materials and Methods

Survey Design

In October 2015, we designed an electronic survey regarding the radiotherapy and chemotherapy practices of US radiation oncologists for cT2-T3 N0 transitional cell carcinoma bladder cancer patients using Google Forms (Google, Mountain View, CA, USA; [Supplementary Table S1](#)). We included 24 questions regarding respondent demographics, volume and type of MIBC patients seen in consultation, whether pre-cystectomy radiation oncology consultation is routinely carried out, preferred radiotherapy target volume and dose/fractionation, chemotherapy practices, IMRT utilisation and ART utilisation. The results of our bladder-preservation therapy analysis will be reported in a separate manuscript. The survey was e-mailed to 4057 US radiation oncologists on 26 October 2015, with one reminder e-mailed a week later.

Statistical Analysis

A statistical analysis was conducted using SAS release 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics for each item were carried out. Univariate analyses (UVA) were conducted using chi-square and logistic regression analyses to compare respondent and practice characteristics with treatment details. During the analysis, the state of practice was grouped into US Census regions. Based on the UVA results, a multivariable logistic regression analysis (MVA) was then carried out to identify respondent and practice characteristics associated with ART use, and included covariates that had a P value < 0.1 on UVA. During MVA, the most commonly treated bladder cancer patients were dichotomised into either patients who were unfit for cystectomy or patients who were fit for cystectomy (patients

who were fit for surgery but were unwilling to undergo cystectomy and patients who were candidates for cystectomy and bladder-preserving therapy and were considering both options). IMRT use was dichotomised into almost never ($< 10\%$) versus in select cases, frequently or almost always (10% to $> 90\%$). An alpha < 0.05 was considered statistically significant.

Results

Respondents

One hundred and eighty-one e-mails were undeliverable. There were seven responses stating that they would not take the survey because the respondent was either retired or did not treat MIBC. Seven respondents were not practicing radiation oncologists, and one respondent practiced outside of the USA. In total, there were 277 evaluable responses.

Table 1 describes the respondent demographic and clinical practice characteristics. Nearly half (46%) of the respondents reported that they have used ART in MIBC patients at least once in the past. Over half (56%) of the respondents have been in practice > 10 years. Only 28% routinely see MIBC patients before cystectomy to discuss radiotherapy options. Most respondents most commonly see patients who are unfit for cystectomy (74%). Most (75%) use IMRT in select cases or more often (10 to $> 90\%$ of patients).

Univariate Analysis for Adjuvant Radiotherapy Use

Table 2 depicts the UVA results for ART utilisation. The number of years in practice was associated with ART use, with those who were 0–2 years in practice or > 10 years in practice more likely to use ART ($P = 0.04$). Routine pre-cystectomy radiation oncology consultation ($P = 0.004$) and most commonly treating patients fit for cystectomy ($P = 0.01$) were also associated with ART use, whereas 'Almost never ($< 10\%$ of patients)' IMRT use was inversely related to ART use ($P = 0.01$).

Multivariable Analysis for Adjuvant Radiotherapy Use

Table 3 depicts the MVA results for ART utilisation. Routine pre-cystectomy radiation oncology consultation (odds ratio 1.91, 95% confidence interval 1.04–3.51; $P = 0.04$) and IMRT use (odds ratio 2.78, 95% confidence interval 1.48–5.22; $P = 0.002$) were associated with increased odds of ART use. The number of years in practice ($P = 0.05$) and most commonly treating patients fit for cystectomy ($P = 0.07$) were no longer significantly associated with ART use, but did continue to exhibit a trend towards increased ART use.

Indications for Adjuvant Radiotherapy Use

Within the subgroup of ART users, the most common indications for ART (**Figure 1**) were gross residual disease

Table 1
Respondent demographic and clinical characteristics (*n* = 277)

Respondent characteristic	<i>n</i> (%)
Number of years in practice	
0–2	18 (6%)
3–5	30 (11%)
6–10	45 (16%)
>10	156 (56%)
In residency	28 (10%)
Primary practice setting	
VA 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%)
Number of patients with non-metastatic bladder cancer treated over the past year	
0	19 (7%)
1–3	160 (58%)
4–6	64 (23%)
>6	34 (12%)
Routinely see patients before cystectomy to discuss radiotherapy options	
No	200 (72%)
Yes	77 (28%)
Non-metastatic 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%)
Intensity-modulated radiotherapy use	
Almost never (<10%)	64 (23%)
In select cases (10–50%)	73 (26%)
Frequently (51–90%)	67 (24%)
Almost always (>90% of patients)	73 (26%)
Adjuvant radiotherapy use	
Yes	127 (46%)
No	150 (54%)

(93%) or positive margins (92%), followed by pathological nodal involvement (64%), pT3/4 disease (46%) and lymphovascular space invasion (16%), and high-grade disease (13%).

Discussion

Radical cystectomy is the most common definitive therapy delivered to patients with MIBC [1]. For patients with aggressive features at the time of surgery, such as pT3/4 disease or positive surgical margins, the risk of locoregional recurrence may be as high as nearly 50% [2,3]. Furthermore, these patients have an extremely poor prognosis after recurrence, with a median survival of about 6 months [12]. Combining concerns for morbidity/mortality related to pelvic recurrences with the principles of other pelvic

malignancies, ART to the pelvis is an attractive approach to try to prevent disease recurrence. Yet, studies conducted in the two-dimensional radiotherapy era, with relatively rudimentary radiotherapy techniques, raised concern for toxicity with this approach, despite also showing disease control benefits, and have tempered enthusiasm for this approach [9].

More recent studies, the evolution of sophisticated radiotherapy techniques that limit the dose to normal tissues and better quantification and stratification of the risk of pelvic recurrence have brought renewed interest in ART and NRG Oncology leadership deemed it important to investigate the clinical importance of ART in a randomised phase II trial, NRG-GU001, which was developed for patients in North America, including trials at Tata Memorial Hospital in India, the University of Ghent in Belgium, GETUG-AFU in France, and the Cairo NCI. Given the usually

Table 2
Univariate analysis for adjuvant radiotherapy use

Practice characteristic	Adjuvant radiotherapy		P value*
	No	Yes	
Number of years in practice			0.04
0–2	8 (44%)	10 (56%)	
3–5	21 (70%)	9 (30%)	
6–10	28 (62%)	17 (38%)	
>10	74 (47%)	82 (53%)	
In residency	19 (68%)	9 (32%)	
Primary practice setting			0.94 [†]
VA Hospital	3 (50%)	3 (50%)	
Academic Hospital	56 (55%)	45 (45%)	
Community hospital or private practice	91 (54%)	79 (46%)	
US Census Region			0.42
Midwest	54 (60%)	36 (40%)	
Northeast	25 (46%)	29 (54%)	
South	44 (55%)	36 (45%)	
West	27 (51%)	26 (49%)	
Consultation clinic setting			0.20
Single specialty clinic as a referral from a physician from another specialty	126 (56%)	99 (44%)	
Multidisciplinary clinic with physicians representing multiple specialties	24 (46%)	28 (54%)	
Number of patients with non-metastatic bladder cancer treated over the past year			0.36
0	12 (63%)	7 (37%)	
1–3	90 (56%)	70 (44%)	
4–6	34 (53%)	30 (47%)	
>6	14 (41%)	20 (59%)	
Routinely see patients before cystectomy to discuss radiotherapy options			0.004
No	119 (60%)	81 (40%)	
Yes	31 (40%)	46 (60%)	
Non-metastatic bladder cancer patients most commonly treated			0.01
Patients who are unfit for cystectomy	121 (59%)	85 (41%)	
Patients who are fit for cystectomy	29 (41%)	42 (59%)	
Intensity-modulated radiotherapy use			0.01
Almost never (<10% of patients)	46 (72%)	18 (28%)	
In select cases (10–50%)	33 (45%)	40 (55%)	
Frequently (51–90%)	36 (54%)	31 (46%)	
Almost always (>90%)	35 (48%)	38 (52%)	

* Chi-square test.

† Fisher's exact test.

Table 3
Multivariable analysis predicting for adjuvant radiotherapy use

Covariate	Odds ratio (95% confidence interval)	P value*
Number of years in practice		0.05
0–2	Reference	
3–5	0.38 (0.11–1.37)	0.14
6–10	0.53 (0.16–1.70)	0.28
>10	0.88 (0.31–2.49)	0.82
In residency	0.30 (0.08–1.08)	0.07
Routinely see patients before cystectomy to discuss radiotherapy options		
No	Reference	
Yes	1.91 (1.04–3.51)	0.04
Non-metastatic bladder cancer patients most commonly treated		
Unfit for cystectomy	Reference	
Fit for cystectomy	1.77 (0.95–3.29)	0.07
Intensity-modulated radiotherapy use		
Almost never (<10% of patients)	Reference	
In select cases, frequently, or almost always (10% to >90%)	2.78 (1.48–5.22)	0.002

* Logistic regression.

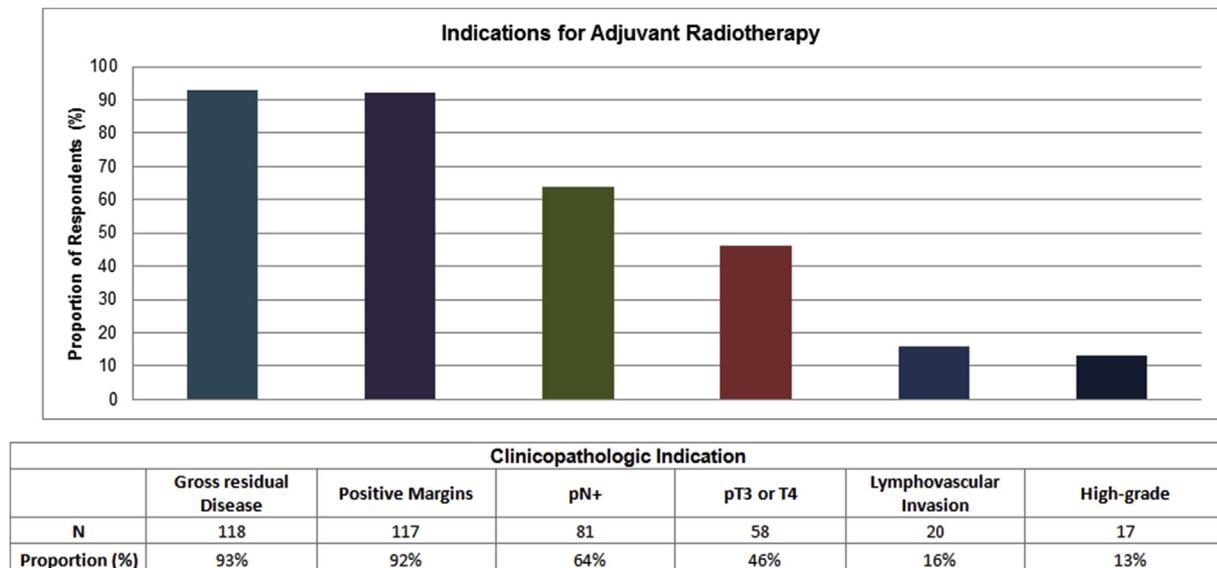


Fig 1. Indications for adjuvant radiotherapy in those who used it ($n = 127$).

conservative nature of radiation oncology practice patterns in the USA, with solid clinical evidence required for incorporation of treatment modality in any disease site and where toxicity concerns must be weighed against proven clinical benefits, we were surprised by our observation that nearly half of responding radiation oncologists in the USA recommend ART, with various indications cited by respondents for pursuing this approach.

The incremental benefit and potential toxicities of ART are not fully elucidated. The best data exploring ART come from the Egyptian National Cancer Institute. The first trial randomised 236 patients with bladder cancer to either observation, ART using 1.25 Gy three times daily to a total dose of 37.5 Gy or ART using 2 Gy per fraction daily to 50 Gy [9]. Eligibility included what would be today's pT2b-T4, any N-stage, patients. The use of adjuvant or neoadjuvant chemotherapy was not specified in the trial, but is unlikely given that adding chemotherapy is a more modern approach. Of note, about 75% were N0, two-thirds had pT3/4 disease and two-thirds had squamous cell carcinoma, whereas only about 20% had transitional cell carcinoma. Patients receiving either of the ART regimens had improved 5 year local control (87% and 93% versus 50%, $P < 0.0001$) and improved 5 year disease-free survival (49% and 44% versus 25%, $P < 0.0001$). Interestingly, the distant metastasis rate was 27% in the conventional fractionation ART group, whereas it was $< 10\%$ in the other groups. Acute toxicity was modest, but late small bowel toxicity occurred in 36% of the conventional fractionation ART group, with more intestinal fistulas and increased uropathy and deterioration of renal function in this group. An analysis of 78 patients who received a regimen of split preoperative and postoperative radiotherapy using two-dimensional radiotherapy corroborated the potential for gastrointestinal toxicity, with 37% of patients who received ART developing bowel obstructions. Thus, despite improvements in local control and disease-free survival, ART was not taken up by general practice

due to concern for undue toxicity as a result of bowel falling into the pelvis post-cystectomy.

However, the results of a second Egyptian randomised trial, using three-dimensional radiotherapy techniques and a higher proportion of transitional cell patients, were recently presented [11], but not yet published. This study enrolled 198 patients ≤ 70 years of age and treated with radical cystectomy with negative surgical margins who had high-risk factors (\geq pT3b disease, high-grade or involved lymph nodes) and randomised them to either ART, adjuvant sequential chemotherapy and radiotherapy or adjuvant chemotherapy alone. In this study 53% had urothelial carcinoma and 41% had squamous cell carcinoma, suggesting a population potentially more similar to the population of bladder cancer patients treated in the US today. The two radiotherapy groups had improved 3 year local recurrence-free survival in the ART arms (87% and 96% versus 69%, $P < 0.01$). Three year disease-free survival was numerically higher in the ART arms (63% and 68% versus 56%), but this was not statistically significant ($P = 0.25$) and there was no difference in distant metastasis-free survival or overall survival. Toxicity was improved compared with the previous trial, with grade ≥ 3 gastrointestinal toxicity of 7 and 8% in the ART arms, but one could argue that this is still relatively high compared with ART in other diseases. A subsequent presentation focusing on the comparison between the sequential chemoradiotherapy ($n = 75$) and the chemotherapy ($n = 45$) arms revealed dramatically improved 2 year local recurrence-free survival (96% versus 69%, $P < 0.01$), a trend towards improved 2 year disease-free survival (68% versus 56%, $P = 0.07$) and a numerically but not significantly improved 2 year overall survival (71% versus 60%, $P = 0.11$) [13]. The late grade ≥ 3 gastrointestinal toxicity rate was 7% versus 2% for the chemoradiotherapy and chemotherapy alone groups, respectively.

To test the benefit of ART in the North American population, NRG-GU001 randomized patients with pT3/4 N0-2

urothelial carcinoma after radical cystectomy to either observation or ART (with neoadjuvant or adjuvant chemotherapy per physician discretion). This study recently closed to accrual and thus it will be up to the other international trials to answer the question of whether ART in bladder cancer improves outcomes with acceptable toxicity. However, accrual to this study has been slow. Interestingly, despite active trials evaluating the benefit, the most recent NCCN bladder cancer guideline has endorsed consideration for ART in some patients with high-risk disease [14].

It is in this setting that we carried out our survey of US radiation oncologists to further evaluate the patterns of ART use in MIBC patients. Our finding that nearly half of radiation oncologists have used ART in the past suggests that a large proportion of radiation oncologists have used this approach clinically. One could argue, however, that the fact that a co-operative group trial is actively randomising patients to ART gives credence to this approach and establishes a clear equipoise in this field. This also questions whether ART should be used in routine clinical practice outside of a clinical trial setting. It is important to offer eligible patients an opportunity to be treated on the NRG-GU001 trial whenever possible, rather than offering patients treatment off a clinical trial.

We found that respondents who use IMRT in bladder cancer are independently more likely to offer ART to patients than those who do not. IMRT is commonly used in other pelvic malignancies in the ART setting, and thus clinicians are probably applying these same principles to patients with MIBC. In the setting of bladder-preservation therapy, IMRT has been associated with lower normal organ doses and potentially reduced toxicity. The ability of IMRT to spare bowel and the urinary diversion may be even more important in the postoperative setting, and may help to further reduce the 7–8% grade ≥ 3 gastrointestinal toxicity seen in the recent Egyptian trial conducted using three-dimensional radiotherapy. IMRT is the modality chosen in NRG-GU001, and the results of this study will shed light on to any differential toxicity with ART using IMRT.

Our exploration of the indications for ART revealed interesting findings. Based on the above studies, there are no subgroups that differentially benefit from ART more than others. However, a three-tiered risk stratification for local failure developed in a University of Pennsylvania cohort and validated in a cohort of patients treated on SWOG 8710 may be helpful for identifying the patients who would probably benefit from ART. Patients were stratified into low risk ($\leq pT2$), intermediate risk ($\geq pT3$ with ≥ 10 benign or malignant lymph nodes identified and negative surgical margins) and high risk ($\geq pT3$ with < 10 benign or malignant lymph nodes identified or positive surgical margins). The 5 year risk of local failure was 8%, 20% and 41%, for each of the groups, respectively. The rationale for ART in those with positive surgical margins and $pT3/4$ disease is supported by this. Furthermore, a study validating this risk stratification schema found that lymphovascular invasion aids in identifying a group at higher risk of locoregional recurrence [15]. High-grade disease was also used as an

indication in our respondents. There was no interaction between grade and benefit to ART in the older Egyptian trial, thus suggesting that this may not be as effective a selection tool. Many respondents reported using nodal involvement as an indication for ART. Interestingly, there was no disease-free survival benefit for node-positive patients in the original Egyptian randomised trial, although the locoregional control was still improved in this group. Subgroup analysis of the lymph node-positive subgroup in the more recent Egyptian randomised trial is not available. A single institution retrospective patterns of failure study found that patients with nodal involvement had significantly higher locoregional recurrences [16]. Potentially, modern chemotherapy approaches may magnify the impact of pelvic disease control and make ART even more beneficial.

Limitations to this study include the relatively low response rate. This was probably, at least partially, due to self-selection of participants, as there is frequently specialisation within departments with physicians focusing on specific disease sites, and thus those who do not treat bladder cancer may have been less likely to respond. The relative rarity of cases probably also contributed to the response rate. Additionally, we cannot make conclusions regarding the optimal ART field to use, although multiple recent studies have described the patterns of nodal involvement and recurrence after radical cystectomy, and most studies have used a standard 'whole pelvis' field encompassing up to L5/S1 [9,16,17]. A contouring atlas was created specifically for NRG-GU001 to aid in target delineation [18]. We also cannot comment on the optimal dose/fractionation to use, although NRG-GU001 used 50.4 Gy and the most recent Egyptian trial used 45 Gy twice daily. Additionally, given the inherent limitations of the survey study design, we cannot make conclusions regarding the actual rates of utilisation of ART, which are probably low given the emerging nature of the data supporting its use in the modern era. Also, we did not ask about the frequency with which respondents used ART, and cannot identify whether respondents had only used it in the past or currently use it as well.

Conclusions

ART is an unexpectedly commonly utilised treatment modality for patients with MIBC after radical cystectomy. With modern radiotherapy techniques there is renewed interest in this approach for high-risk patients, with the available data suggesting a locoregional control benefit. There are multiple international randomized studies investigating the benefit of ART, and these studies will hopefully elucidate its role in bladder cancer patients.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.clon.2017.02.005>.

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