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Underutilization of the CROSS Regimen Among US Radiation Oncologists: A National Survey of Practice Patterns

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Abstract. *Aim: To examine patterns of clinical practice in locally advanced esophageal cancer among US radiation oncologists after publication of the CROSS trial. Materials and Methods: US radiation oncologists were surveyed on 13 questions pertaining to the management of esophageal cancer. Respondents' demographics and their clinical rationale were analyzed for statistical association with their treatment recommendations. Results: Few respondents (15%) offered the CROSS regimen to patients considered suitable surgical candidates, while a near-equivalent number (16%) prescribed between 41.4 and 50.4 Gy contingent upon radiation planning parameters. Among respondents who prescribed 50.4 Gy, 50% and 17% reported concurrent administration of carboplatin/paclitaxel and cisplatin/5-FU, respectively. Higher radiation doses, over 50.4 Gy, were utilized by 15% and 38% of respondents for borderline surgical candidates and candidates unfit for surgery, respectively. The majority of respondents believed that higher complete pathological response and R0 resection would be achieved, as well as higher toxicity conferred using 50.4 Gy instead of 41.4 Gy. A clinical trial comparing 41.4 Gy to 50.4 Gy with concurrent carboplatin/paclitaxel was supported by 76% of respondents. Conclusion: Despite results from the CROSS trial, the majority of responding US radiation oncologists do not offer 41.4 Gy with concurrent chemotherapy for surgically-fit patients with locally advanced esophageal cancer, believing that a higher dose will translate to improved response.*

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Esophageal cancer predominantly manifests as a locally aggressive malignancy, ranking it globally as the sixth leading cause of cancer-related deaths (1). In 2018, there will be an estimated 17,290 individuals diagnosed with esophageal cancer with estimated deaths of 15,850 patients (2). Its clinical behavior has correspondingly shifted therapeutic management from a single modality to more aggressive tri-modality therapy (TMT) in the form of pre-operative chemoradiation (3-6).

CALGB 9781 was one of the initial prospective evaluations of preoperative chemoradiation, which randomized esophageal cancer patients to concurrent 50.4 Gy, cisplatin, and 5-fluorouracil followed by surgery *versus* surgery alone. With significant improvement in median overall survival (OS) to 4.5 years with TMT compared to 1.8 years in the surgery-alone arm, the current standard radiation dose was extrapolated from this study (4). However, this trial closed early due to poor accrual and reported on only 56, out of 500 planned patients, who were treated in the pre-intensity modulated radiation therapy (IMRT) era. The CROSS trial is the most recent randomized trial elucidating the role of preoperative (TMT), and it reported on a larger number of operable patients (n=368) randomized to surgery alone *versus* 41.4 Gy, carboplatin, and paclitaxel, followed by surgery. TMT with radiation dose at 41.4 Gy conferred a median OS of 49.4 months *versus* 24.0 months among surgery-alone patients. Furthermore, a R0 resection was achieved in 92% with TMT compared to 29% in the surgery alone patients (5).

As the CROSS trial did not specifically address dose de-escalation compared to the North American standard radiation dose, the adoption of the CROSS regimen has been

met with uncertainty (7). In this light, we implemented a survey to ascertain the management of esophageal cancer among US radiation oncologists after the publication of the CROSS regimen.

Materials and Methods

Study population. Institutional Review Board approval was obtained for formulation and dissemination of an electronic email-based survey. A national database of radiation oncology personnel including attending and resident physicians was used to invite participation; respondents were assured anonymity. No honorarium for survey completion was offered. In the pre-determined interval of data acquisition and final analysis, we received 296 evaluable responses.

Survey design. The survey was comprised of thirteen questions. The initial five questions addressed respondent demographics. Questions 6-8 asked respondents to choose their preferred treatment option for patients considered good, borderline, or unresectable surgical candidates. The remaining questions addressed physicians' beliefs in regard to radiation dose, 50.4 Gy *vs*. 41.4 Gy, its effect on toxicity, pathologic complete response, R0 resection and the physician's willingness to enroll to a trial comparing 41.4 Gy *vs*. 50.4 Gy with concurrent carboplatin/paclitaxel. Data were securely collected and stored using the institutional Research Electronic Data Capture (REDCAP) (8).

Statistical analysis. Descriptive statistics were applied to report basic respondent characteristics. Univariate and multivariate nominal logistic regression analysis was performed to examine final treatment recommendations based on physician-respondent characteristics and clinico-pathologic rationale. Application of statistical tests was performed with senior departmental biostatisticians. All *p*-values were two-sided. In an attempt to reduce false positive results, an alpha level of 0.01 declared statistical significance. JMP Version 12 (Cary, NC) was used for statistical analysis.

Results

Physician demographics. Physician demographics included year since completing residency, practicing setting, practice region, and approximation of definitive esophageal cases seen over the last year are summarized in Table I. Over half (56%) of the respondents were over 10 years from completion of residency, while the majority of the remainder were either new graduates or less than 10 years from completion of residency. Sixty-one percent treated greater than five definitive cases of esophageal cancer within the previous calendar year. The response rates between academic and private practice centers were similar.

Management recommendations. Radiation oncologist recommendations based on surgeon-evaluated operative candidacy are summarized in Table II. The most common pre-operative or definitive regimen administrated across all patients is carboplatin/paclitaxel in combination with 50.4 Gy. Chemoradiation to 50.4 Gy with concurrent cisplatin/5-FU is used by 17%, 19% and 23% of respondents for good, borderline and poor surgical candidates, respectively. Few (15%) respondents recommend the CROSS regimen for good surgical candidates. For resectable candidates, dosimetric planning parameters influenced 16% of respondents on their use of either 41.4 or 50.4 Gy. Dose escalation beyond 50.4 Gy with concurrent chemotherapy is prescribed by 15% and 38% of physicians for borderline surgical candidates and poor surgical candidates, respectively.

Table I. *Characteristics of 296 US radiation oncologists who responded to the survey.*

Respondent characteristics	n	%
Years since residency completion		
Still a resident	16	(5)
0-2	35	(12)
3-5	39	(13)
6-10	41	(14)
Over 10	165	(56)
Number of patients treated with definitive intent in the past year		
None	14	(5)
Less than 5	102	(34)
6-10	107	(36)
Over 10	73	(25)
Practice setting		
Academic center	132	(45)
Private practice	164	(55)
Practice region		
Midwest	73	(25)
Northeast	57	(19)
South	99	(33)
West	67	(23)

Factors influencing recommendations. Eighty-five percent (n=251) of respondents held the opinion that 50.4 Gy yields a higher pathologic complete response rate than 41.4 Gy. On multivariate analysis, these subset of respondents were more likely to prescribe doses higher than 41. 4 Gy for good surgical candidates, and private practice physicians were more likely than academic radiation oncologists to hold this opinion. There was a trend toward significance among physicians in closer temporal proximity, namely less than 10 years, to their training to hold the opposite view (Table III).

Sixty-six percent (n=195) of respondents believe 50.4 Gy increases the likelihood of R0 resection compared to 41.4 Gy. The significant influences on this opinion were similar to those observed regarding higher dose and pathologic response. The additional distinct significant parameter was that physicians with less than 10 years of post-residency experience were less likely to believe doses higher than 41.4 Gy would lead to higher likelihood of R0 resection (Table IV).

Table II. *Recommended treatments by US radiation oncologists based on patient's surgical candidacy.*

Recommended treatment	Surgical candidacy					
	Good		Borderline		Poor	
41.4 Gy with concurrent Carbo/Taxol	44	(15)	9	(3)	0	(0)
50.4 Gy with concurrent Carbo/Taxol	140	(47)	155	(53)	101	(34)
50.4 Gy with concurrent Cis/5-FU	51	(17)	56	(19)	67	(23)
Between 41.4 and 50.4 Gy depending On DVH with either chemotherapy	46	(16)	17	(6)	4	(1)
Greater Than 50.4 Gy with either chemotherapy	4	(1)	44	(15)	112	(38)
Other	10	(3)	14	(5)	11	(4)

Table III. *Correlation between physician's belief that 50.4 Gy of radiation therapy yields a higher pathological complete response compared to 41.4 Gy and respondent's characteristics.*

	Physician (n)	OR (95% CI)	*p*-Value
Dose utilized for good surgical candidate			
41.4 Gy	28	1 [Reference]	-
>41.4 Gy	214	4.53 (2.15-9.41)	<0.001
Dose utilized for borderline candidate			
<50.4 Gy	22	1.02 (0.36-3.65)	0.973
50.4 Gy	178	1 [Reference]	-
>50.4 Gy	38	1.17 (0.49-3.28)	0.734
Dose utilize for poor surgical candidate			
≤50.4 Gy	141	1[Reference]	-
>50.4 Gy	101	2.01 (1.00-4.38)	0.052
Years since residency completion			
10 or less	103	0.36 (0.18-0.70)	0.002
Over 10	148	1 [Reference]	-
Number of patients treated with definitive intent in the past year			
10 or less	188	0.87 (0.41-1.88)	0.735
Over 10	63	1 [Reference]	-
Practice setting			
Academic center	99	1 [Reference]	-
Private practice	152	3.66 (1.86-7.57)	<0.001
Practice region			
Midwest	64	1.12 (0.41-3.06)	0.819
Northeast	48	0.84 (0.31-2.32)	0.737
South	81	0.80 (0.32-1.91)	0.617
West	57	1 [Reference]	-

Table IV. *Correlation between physician's belief that 50.4 Gy of radiation therapy increases resectability and the likelihood of R0 resection compared to 41.4 Gy and respondent's characteristics.*

	Physician (n)	OR (95% CI)	*p*-Value
Dose utilized for good surgical candidate			
41.4 Gy	11	1 [Reference]	-
>41.4 Gy	178	8.48 (4.16-18.51)	<0.0001
Dose utilized for borderline candidate			
<50.4 Gy	19	1.66 (0.69-4.40)	0.263
50.4 Gy	131	1 [Reference]	-
>50.4 Gy	33	1.83 (0.90-3.98)	0.096
Dose utilize for poor surgical candidate			
≤50.4 Gy	107	1 [Reference]	-
>50.4 Gy	83	1.87 (1.12-3.18)	0.017
Years since residency completion			
10 or less	74	0.44 (0.27-0.72)	0.001
Over 10	121	1 [Reference]	-
Number of patients treated with definitive intent in the past year			
10 or less	144	0.79 (0.45-1.41)	0.434
Over 10	51	1[Reference]	-
Practice setting			
Academic center	74	1 [Reference]	-
Private practice	121	2.08 (1.27-3.41)	0.003
Practice region			
Midwest	49	1.25 (0.61-2.51)	0.537
Northeast	42	1.71 (0.80-3.75)	0.174
South	63	1.13 (0.59-2.16)	0.713
West	41	1 [Reference]	-

Fifty-four percent (n=158) of respondents believe that 50.4 Gy causes more toxicity than 41. 4 Gy. Multivariate analysis determined that physicians early in their career (<10 years practicing) were significantly more likely to believe 50.4 Gy causes more toxicity than 41.4 Gy (p=0.01) (Table V).

Interest in a prospective comparison of 50.4 vs. 41.4 Gy in esophageal tri-modality therapy. Seventy-six percent (n=223) of respondents were willing to enroll patients in a neoadjuvant chemoradiotherapy clinical trial comparing 41.4 Gy to 50.4 Gy with concurrent carboplatin/paclitaxel in

Table V. *Correlation between physician's belief that 50.4 Gy of radiation therapy would cause more toxicity compared to 41.4 Gy and respondent's characteristics.*

	Physician (n)	OR (95% CI)	*p*-Value
Dose utilized for good surgical candidate			
41.4 Gy	28	1 [Reference]	-
>41.4 Gy	125	0.62 (0.31-1.18)	0.147
Dose utilized for borderline candidate			
<50.4 Gy	18	1.95 (0.84-4.94)	0.124
50.4 Gy	113	1 [Reference]	-
>50.4 Gy	19	0.66 (0.34-1.26)	0.210
Dose utilize for poor surgical candidate			
≤50.4 Gy	92	1 [Reference]	-
>50.4 Gy	61	1.04 (0.65-1.68)	0.872
Years since residency completion			
10 or less	84	2.10 (1.32-3.37)	0.002
Over 10	78	1 [Reference]	-
Number of patients treated with definitive intent in the past year			
10 or less	122	1.25 (0.74-2.13)	0.402
Over 10	36	1[Reference]	-
Practice setting			
Academic center	78	1 [Reference]	-
Private practice	80	0.63 (0.39-1.00)	0.049
Practice region			
Midwest	36	0.67 (0.34-1.32)	0.248
Northeast	35	1.10 (0.53-2.28)	0.794
South	48	0.68 (0.36-1.27)	0.227
West	39	1 [Reference]	-

Table VI. *Correlation between physician's willingness to enroll a patient with operable esophageal cancer on a randomized trial of 41.4 vs. 50.4 Gy of radiation therapy with concurrent chemotherapy and respondent's characteristics.*

	Physician (n)	OR (95% CI)	*p*-Value
Years since residency completion			
10 or less	111	2.41 (1.35-4.26)	0.002
Over 10	112	1 [Reference]	-
Number of patients treated with definitive intent in the past year			
10 or less	171	1.35 (0.75-2.46)	0.003
Over 10	52	1 [Reference]	-
Practice setting			
Academic center	94	1 [Reference]	-
Private practice	129	1.37 (0.81-2.34)	0.245
Practice region			
Midwest	63	1.54 (0.63-3.90)	0.342
Northeast	42	0.69 (0.29-1.60)	0.383
South	64	0.48 (0.22-0.98)	0.043
West	53	1 [Reference]	-

locally advanced esophageal cancer (Table VI). Physicians early in their career were more willing to enroll to a trial addressing this question ($p<0.001$). There was no significant correlation between common radiation doses used in physician practice and willingness to enroll in a clinical trial comparing 41.4 Gy, including those that commonly treated to doses >50.4 Gy (Table VI).

Discussion

Tri-modality therapy is the standard of care for patients with resectable locally advanced esophageal cancer (4-6, 9-15). In the United States, 50.4 Gy with concurrent cisplatin/5-FU was adopted nearly two decades ago as the standard treatment.

The more contemporary investigation of TMT in the CROSS trial implemented a lower dose of radiation of 41.4 Gy with concurrent carboplatin/paclitaxel chemotherapy. Despite the lower radiation dose, this TMT regimen maintained superior efficacy over surgery, appears to be similar in efficacy, and better tolerated than cisplatin/5-FU and 50.4 Gy (5, 15). Nevertheless, a substantially low number (15%) of US radiation oncologists implement the CROSS regimen in good surgical candidates who are receiving neoadjuvant chemoradiotherapy. However, physicians have changed the concurrent chemotherapy to carboplatin/paclitaxel while maintaining the higher radiation dose of 50.4 Gy with thoughts that the higher radiation dose increases the likelihood of R0 resection and pathological complete response; while possibly leading to higher toxicity (16). These data also support enrolling on a clinical trial comparing 41.4 Gy *versus* 50.4 Gy in neoadjuvant chemoradiotherapy.

This study revealed insights into why US providers may continue to use higher doses of radiotherapy while changing the chemotherapy backbone to the better tolerated CROSS regimen. The respondents to the survey were evenly distributed in age, location, practice location and time from training. Data are challenging to extrapolate to all practicing radiation oncologists in the US, but can serve as an indicator of current practice patterns.

US practicing radiation oncologist continue to practice and believe that higher radiation dose correlates to a high likelihood of tumor response; however, there are insufficient data to support this conclusion, especially in the era following RTOG 0617, which failed to show a benefit of radiation dose escalation in non-small cell lung cancer. While the data from this survey supports enrollment in a clinical trial comparing 50.4 Gy to 41.4 Gy with concurrent

carboplatin/paclitaxel; this is a costly endeavor that would require a considerable number of patients to accurately assess a difference between the two radiotherapy doses. This is a question that may be answered in the future with hospital or population-based databases.

Conclusion

This study reports the current practice patterns among US radiation oncologists for patients with locally advanced esophageal cancer: poor adoption of the CROSS regimen for resectable patients due to beliefs of improved pathological complete response rate and R0 resection with a higher radiation dose.

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