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Research Letter

Patterns of Dose Escalation Among Patients With Esophageal Cancer Undergoing Definitive Radiation Therapy: 2006-2016

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Abstract

Purpose: Although single-institution series suggest potential benefit to dose escalation in definitive radiation therapy for esophageal cancer, randomized trials including intergroup-0123 and the recently presented A Randomized Trial of Dose Escalation in definitive Chemoradiotherapy for patients with Oesophageal cancer (ARTDECO) trial showed no improvement in outcomes with higher radiation therapy dose. As such, there may be significant variation in radiation dose for definitive treatment of esophageal cancer.

Methods and Materials: The National Cancer Database was used to identify patients who received a diagnosis of nonmetastatic T2+ esophageal cancer between 2006 and 2016 who did not receive definitive surgery and were treated with chemotherapy and radiation therapy doses between 41.4 and 74 Gy. Multivariable logistic regression defined adjusted odds ratios (AORs) of receipt of >50.4 Gy, including year of diagnosis (2006-2013 vs 2014-2016) * histology (squamous cell carcinoma [SCC] vs adenocarcinoma) and year of diagnosis (2006-2013 vs 2014-2016) * disease site (cervical esophagus vs noncervical esophagus) interaction terms, to assess whether the effect of diagnosis year on dose varied by histology and disease site, respectively.

Results: Among 14,517 patients, the most common dose was 50.4 Gy, used for 6955 (47.9%) patients. Dose escalation above 50.4 Gy was observed in 4440 (30.6%) patients and declined by year, from 42.2% in 2006 to 23.5% in 2016. Patients with SCC versus adenocarcinoma had higher odds of dose escalation (39.3% vs 23.8%; AOR 1.46; $P < .001$), as did those with cervical esophageal primaries versus other primary sites (54.9% vs 27.4%; AOR 2.51; $P < .001$). The effect of later diagnosis year was greater for adenocarcinoma than for SCC (pint $= 0.001$, AOR 0.54, $P < .001$ vs AOR 0.71, $P < .001$) and significant for noncervical esophagus but not cervical esophagus (pint <0.001, AOR 0.56, $P < .001$ vs AOR 0.95, $P = .616$).

Conclusions: Dose escalation in definitive chemoradiotherapy for esophageal cancer declined over time, particularly for adenocarcinoma histology and noncervical primary site. Given the recent results of ARTDECO, our findings can serve as a benchmark from which to measure future shifts in practice patterns.

Introduction

Although trimodality therapy for locally advanced esophageal cancer using neoadjuvant chemoradiation is recommended by the National Cancer Center Network guidelines[1] based upon the Chemoradiotherapy for

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Oesophageal Cancer followed by Surgery Study (CROSS) trial,[2] esophagectomy remains a potentially highly morbid surgery,[3] and many patients and tumors are medically or surgically inoperable, respectively.

Definitive chemoradiation is a potentially curative option[4]; however, the prescribed radiation dose has been controversial. An increase in early patient deaths was observed in the dose-escalation arm of intergroup-0123 (50.4 vs 64.8 Gy),[5] although interpretation is not straightforward because the majority of deaths in the dose-escalation arm occurred before patients received 50.4 Gy. In contrast, a single-arm phase 1/2 study using more modern intensity modulated radiation therapy (IMRT) techniques demonstrated high local control and no grade 4 or 5 toxicities with a simultaneous integrated boost to 63 Gy.[6] More recently, however, the results of the phase 3 randomized A Randomized Trial of Dose Escalation in definitive Chemoradiotherapy for patients with Oesophageal cancer (ARTDECO) trial, comparing 50.4 to 61.6 Gy using an integrated boost, showed no benefit with dose escalation, even when stratified by histology.[7]

Given these results, it would not be surprising to observe significant variation in prescribed radiation doses for definitive treatment of esophageal cancer. As such, we assessed national practice patterns of dose escalation in patients with locally advanced, unresectable esophageal cancer.

Methods and Materials

The National Cancer Database (NCDB) was used to identify patients with at least T2, nonmetastatic (ie, cT2-4 N0-3 M0) esophageal adenocarcinoma or squamous cell carcinoma (SCC) diagnosed between 2006 and 2016 who did not undergo definitive surgery and were treated with chemotherapy and a radiation therapy dose between 41.4 Gy and 74 Gy in 37 or fewer fractions (CONSORT diagram, Fig 1). A dose of 41.4 Gy was chosen as a lower limit based on the CROSS trial[2] and 74 Gy as the upper limit based on previously published literature on dose escalation for cervical esophageal tumors.[8] Primary tumor locations were categorized based on recorded PRIMARY_SITE codes in the NCDB as cervical (C150 "cervical esophagus" and C153 "upper third of esophagus"), thoracic (C151 "thoracic esophagus" and C154 "middle third of esophagus"), abdominal (C152 "abdominal esophagus" and C155 "lower third of esophagus"), overlapping (C158 "overlapping lesion of esophagus"), or unknown (C159 "esophagus, NOS"). Year of diagnosis was stratified into early (2006-2013) versus late (2014-2016). This cutoff was chosen because we wished to assess any changes in dose levels in the era of IMRT, a modality that potentially permits safer dose escalation through more conformal planning. The use of IMRT for esophageal cancer was reported in dosimetric studies[9,10] published in 2012 and 2013, followed by institutional[11,12] and multi-institutional prospective[6,13] studies published in 2014 and later.

Multivariable logistic regression defined adjusted odds ratios (AORs) and associated 95% confidence intervals (CIs) for receipt of lower (<50.4 Gy) versus dose-escalated (>50.4 Gy) radiation dose with year of diagnosis as the primary independent variable of interest. In addition to histology, other clinical and sociodemographic variables included are shown in Table 1. Additionally, 2 interaction terms were evaluated in separate models—a year of diagnosis (2006-2013 vs 2014-2016) * histology (SCC vs adenocarcinoma) interaction term and a year of

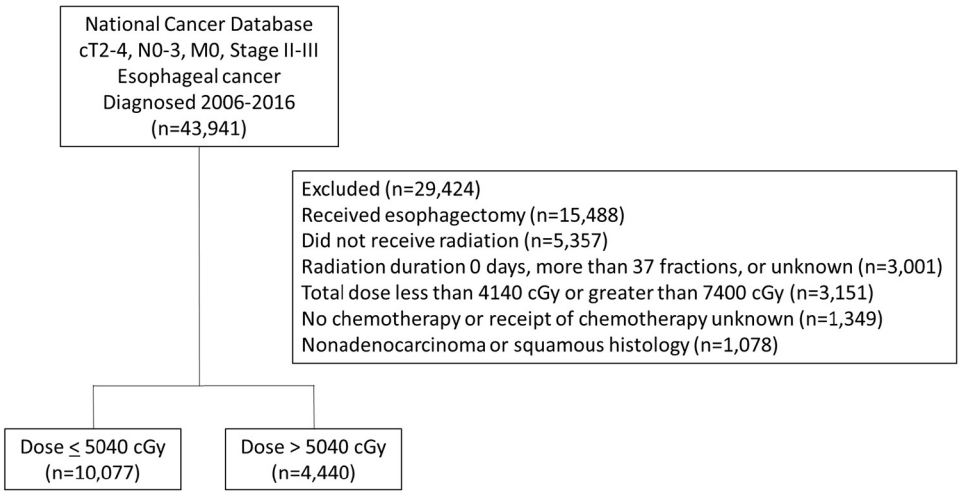

Figure 1 Patient selection diagram (CONSORT).

Table 1 Patient characteristics and multivariate analysis

Characteristics	41.4-50.4 Gy N = 10,077		>50.4 Gy N = 4440		AOR	*P* value	95% CI
	n	(%)	n	(%)			
Age (y)							
18-44	170	(1.7)	69	(1.6)			
45-64	3736	(37.1)	1559	(35.1)	1.16	.443	0.79-1.72
>65	6171	(61.2)	2812	(63.3)	1.35	.125	0.92-1.99
Sex							
M	7719	(76.6)	3257	(73.4)			
F	2358	(23.4)	1183	(26.6)	0.94	.175	0.86-1.03
Race							
White	8582	(86.2)	3680	(84.0)			
Black	1085	(10.9)	587	(13.4)	0.95	.431	0.84-1.08
Asian	226	(2.3)	98	(2.2)	0.78	.053	0.60-1.00
Other	59	(0.6)	17	(0.4)	0.56	.051	0.32-1.00
Insurance status							
Insured	9778	(97.0)	4305	(97.0)			
Uninsured	299	(3.0)	135	(3.0)	0.95	.638	0.76-1.19
Income quartile							
1	1940	(19.5)	933	(21.3)			
2	2250	(22.7)	1023	(23.4)	0.99	.854	0.88-1.11
3	2457	(24.7)	1017	(23.2)	0.90	.076	0.80-1.01
4	3285	(33.0)	1407	(32.1)	0.93	.226	0.84-1.04
Facility type							
Community	6434	(64.2)	3134	(71.0)			
Academic	3585	(35.8)	1278	(29.0)	0.70	<.001	0.64-0.75
Charlson-Deyo score							
0	7291	(72.4)	3225	(72.6)			
1	1960	(19.5)	849	(19.1)	1.02	.649	0.93-1.12
2	577	(5.7)	255	(5.7)	1.08	.366	0.92-1.27
3	249	(2.5)	111	(2.5)	1.22	.101	0.96-1.55
Analytical stage group							
II	3975	(39.5)	1850	(41.7)			
III	6102	(60.6)	2590	(58.3)	0.97	.479	0.90-1.05
Histology							
Adenocarcinoma	6229	(61.8)	1948	(43.9)			
SCC	3848	(38.2)	2492	(56.1)	1.46	<.001	1.31-1.63
Location							
Cervical	754	(7.5)	919	(20.7)			
Thoracic	2078	(20.6)	1058	(23.8)	0.42	<.001	0.37-0.48
Abdominal	6146	(61.0)	1955	(44.0)	0.34	<.001	0.30-0.39
Overlapping/unknown	501	(5.0)	185	(4.2)	0.35	<.001	0.29-0.43
Not recorded	598	(5.9)	323	(7.3)	0.51	<.001	0.43-0.61
Year							
2006-2013	6220	(61.7)	3193	(71.9)			
2014-2016	3857	(38.3)	1247	(28.1)	0.54	<.001	0.48-0.61
Histology * year					1.32	.001	1.12-1.55

Abbreviation: SCC = squamous cell carcinoma.

diagnosis (2006-2013 vs 2014-2016) * disease site (cervical vs noncervical esophagus) interaction term—to assess whether the effect of diagnosis year on radiation dose varied by histology and disease site, respectively. Furthermore, the multivariable logistic regression models were repeated, stratified by both histology and disease site (Table 2).

Survival by dose level, defined as time from diagnosis to death or censoring, was analyzed using the Kaplan-Meier method and was stratified by histology. Statistical testing was 2-sided, with $\alpha = 0.05$. Data were analyzed with Stata/SE 15.1 (StataCorp). The study was deemed exempt by our institutional review board.

Table 2 Percentage of patients treated with dose escalation by histology, site, and early (2006-2013) versus late (2014-2016) year of diagnosis

		Cervical, n	(%)	Thoracic, n	(%)	Abdominal, n	(%)
Adenocarcinoma	2006-2013						
	41.4-50.4 Gy	44	(63.8)	276	(69.7)	3069	(73.5)
	>50.4 Gy	25	(36.2)	120	(30.3)	1109	(26.5)
	2014-2016						
	41.4-50.4 Gy	30	(65.2)	147	(79.9)	2041	(82.9)
	>50.4 Gy	16	(34.8)	37	(20.1)	422	(17.1)
	P value*	.678		.011		<.001	
SCC	2006-2013						
	41.4-50.4 Gy	448	(43.5)	1043	(61.9)	656	(66.8)
	>50.4 Gy	583	(56.5)	641	(38.1)	326	(33.2)
	2014-2016						
	41.4-50.4 Gy	232	(44.0)	612	(70.2)	380	(79.5)
	>50.4 Gy	295	(56.0)	260	(29.8)	98	(20.5)
	P value*	.737		<.001		<.001	

Abbreviation: SCC = squamous cell carcinoma.

* *P* values are reported from separate multivariable logistic regression models for each combination of tumor site and histology. In addition to treatment era (2006-2013 vs 2014-2016) with *P* values shown, other variables included in the model were age, sex, race, insurance status, income quartile, Charlson-Deyo score, facility type, and analytical stage.

Results

Among 14,517 evaluable patients with T2+ non-metastatic esophageal cancer, 10,976 (75.6%) were male, 8177 (56.3%) had adenocarcinoma histology, and 8101 (55.8%) had tumors in the distal esophagus. Table 1 displays the clinical characteristics of the cohort.

The most common dose was 50.4 Gy, used for 6955 (47.9%) patients, and dose escalation above 50.4 Gy was observed in 4440 (30.6%). Later year of diagnosis was associated with lower odds of dose escalation beyond 50.4 Gy (33.9% for 2006-2013 vs 24.4% for 2014-2016; AOR 0.52; $P < .001$). The effect was seen for both SCC and adenocarcinoma histologies and appeared to be driven by a greater proportion of patients receiving 50 to 50.4 Gy after 2013 (Fig 2). However, there was a statistically significant year of diagnosis * histology interaction (pint = 0.001) such that the effect of later diagnosis year was greater for adenocarcinoma (AOR 0.54; $P <.001$) than for SCC (AOR 0.71; $P <.001$; Fig 3A).

Among the entire cohort, nonclinical factors associated with lower odds of dose escalation included treatment at an academic cancer center versus community cancer center (26.3% vs 32.8%; AOR 0.70; $P < .001$; Fig 3B). Clinical factors associated with radiation dose included histology, with SCC histology having higher odds of receiving dose escalation compared with adenocarcinoma (39.3% vs 23.8%; AOR 1.46; $P < .001$) and 16.4% of patients with SCC receiving more than 59.4 Gy. There was no association between dose escalation and overall survival for either histology (Fig 4).

Tumors in the cervical esophagus were more likely to be treated with dose-escalated radiation therapy, compared with other primary locations (54.9% vs 27.4%; AOR 2.51; $P < .001$). Within site and histology categories (Table 2), the proportion of patients who were treated with dose escalation did not decrease over time (2006-2013 vs 2014-2016) for those with cervical esophageal cancers of either squamous ($P = .737$) or adenocarcinoma histology ($P = .678$). However, a decrease in dose escalation was observed in thoracic esophageal adenocarcinomas (30.3% vs 20.1%; AOR 0.57; $P = .011$), thoracic esophageal SCC (38.1% vs 29.8%; AOR 0.67; $P = .011$), abdominal esophageal adenocarcinoma (26.5% vs 17.1%; AOR 0.55; $P < .001$), and abdominal esophageal SCC (33.2% vs 20.5%; AOR 0.51; $P < .001$). Furthermore, there was a statistically significant year of diagnosis * disease site interaction (pint <0.001) such that the effect of later diagnosis year was significant for noncervical esophagus (AOR 0.56; $P < .001$) but not cervical esophagus (AOR 0.95; $P = .616$).

Discussion

In this population-based study on patterns of definitive radiation therapy dose, use of dose escalation decreased over time. This trend was most notable in patients with noncervical esophageal cancers and adenocarcinoma histology. In contrast, 34.4% of patients with SCC, including 59.5% with SCC in the cervical esophagus, were treated with dose-escalated radiation therapy in 2016. Treatment

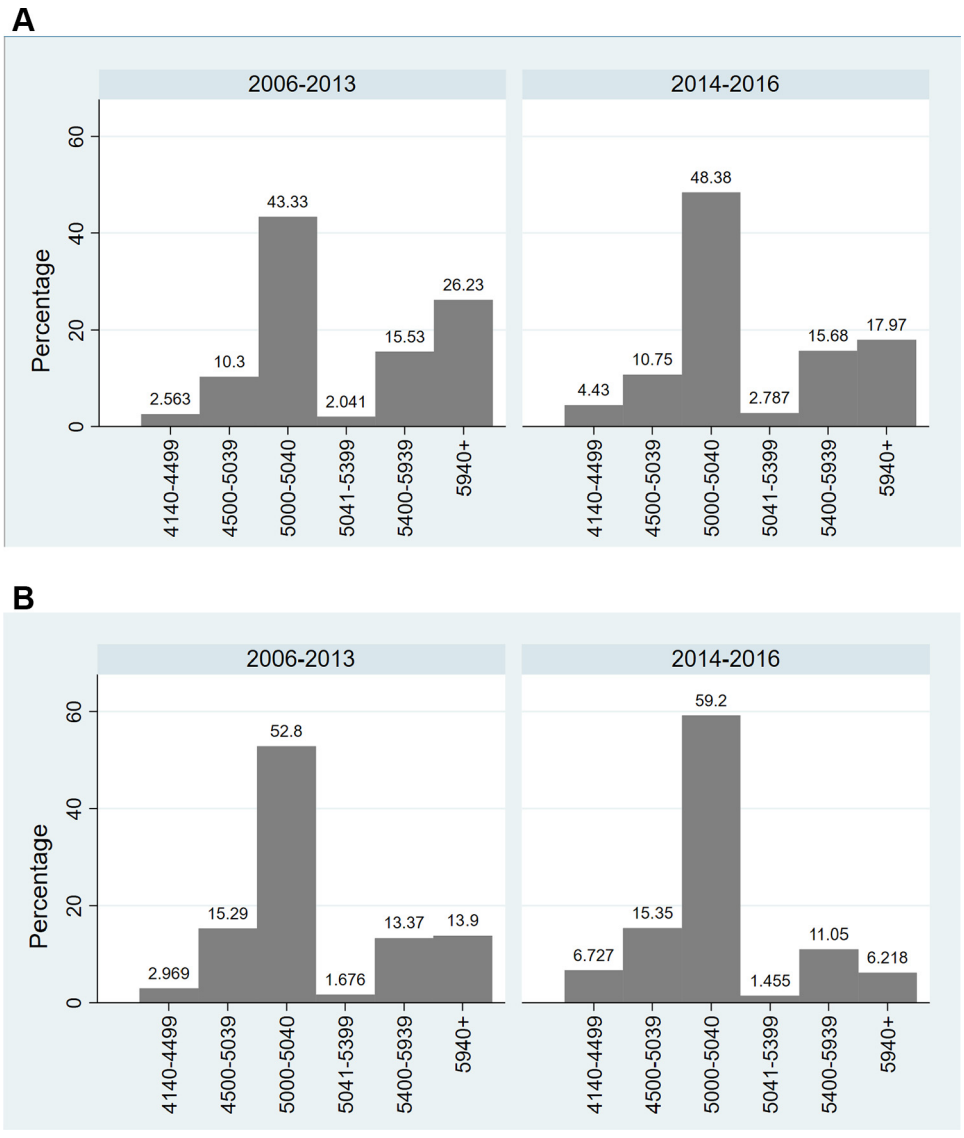

Figure 2 Histogram displaying proportion of patients receiving specific ranges of radiation therapy doses, stratified by year (before 2014 vs after 2014) and histology. (A) Squamous cell carcinoma and (B) adenocarcinoma.

at a community cancer center was associated with higher odds of dose escalation.

The decline in dose escalation appears to be due to increasing use of dose ranges between 50.0 and 50.4 Gy. Whether this dose range is radiobiologically optimal for definitive treatment of esophageal cancer is unclear, especially in view of the molecular heterogeneity of esophageal cancers.[14] Notably, dose de-escalation is occurring in the era of increased use of highly conformal radiation therapy techniques that would technically allow for treatment to higher doses while respecting normal tissue constraints.[9,10] This finding may reflect the durable effect of the intergroup-0123 trial results,[5] and we hypothesize that dissemination of the ARTDECO trial results[7] will result in a further decrease in utilization of dose escalation. The transition to bundled care payments for radiation therapy could further drive this trend by eliminating financial incentives for prolonged courses of radiation therapy. At the same time, multiple ongoing studies continue to explore the potential benefit of dose escalation for esophageal cancer in select patients,[6] and a subset of radiation oncologists continue to believe that certain

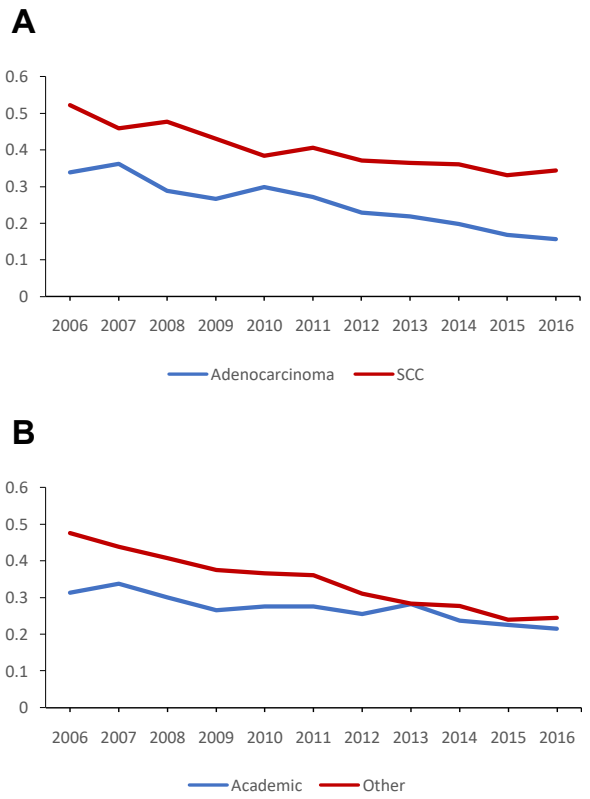

Figure 3 Proportion of total patients treated with dose escalation (>50.4 Gy) by year of diagnosis, stratified by (A) histology and (B) treating facility type. *Abbreviation*: SCC = squamous cell carcinoma.

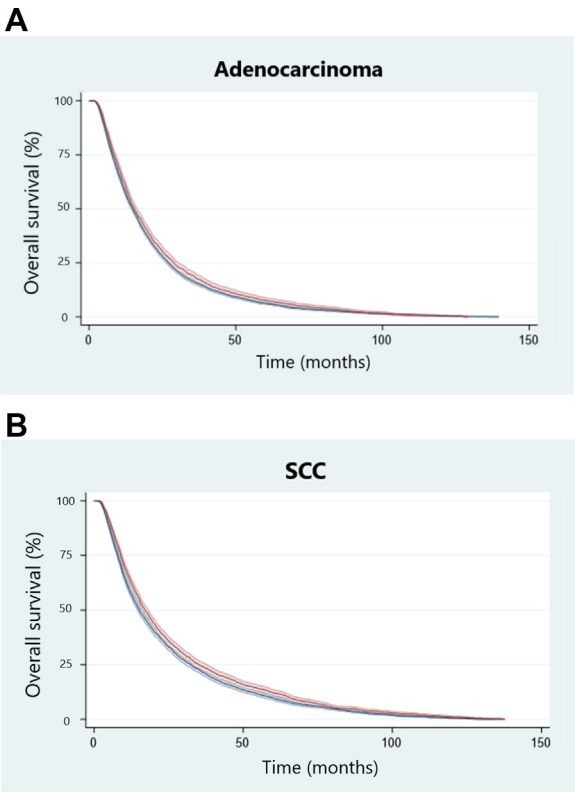

Figure 4 Overall survival in patients treated with (red) or without (blue) dose escalation above 50.4 Gy for (A) esophageal adenocarcinomas and (B) esophageal squamous cell carcinomas (SCC). (A color version of this figure is available at https://doi.org/10.1016/j.adro.2020.09.020.)

patients not undergoing surgery could benefit from higher radiation dose, potentially in combination with novel systemic agents.

Limitations of our study include lack of detail on the specifics of radiation therapy and on the nuances behind surgical decision-making and treatment-related toxicity. Our survival analyses are consistent with previously reported data showing a lack of benefit with dose escalation, such as in the ARTDECO trial[7] and earlier NCDB analyses,[8,15] but are limited due to the selection bias inherent to retrospective database design.

Conclusions

Use of dose-escalated radiation therapy for esophageal cancer appears to be declining, but it remains a more common practice for SCC histology and cervical primary site. Because the optimal radiation dose for esophageal cancer remains an active area of investigation and may continue to change pending publication of prospective studies, our study findings can serve as a benchmark from which to measure future shifts in practice patterns for this population.

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