



Influence of Neoadjuvant Radiation Dose on Patients Undergoing Esophagectomy and Survival in Locally Advanced Esophageal Cancer

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Abstract

Background Neoadjuvant chemoradiotherapy followed by resection is standard of care for patients with locally advanced esophageal cancer, however, a significant portion of these patients do not undergo surgical intervention. This study evaluates radiation dose and other factors associated with undergoing esophageal resection and their impact on outcomes including survival.

Methods Patients diagnosed with esophageal cancer between 2010 and 15 were queried from the National Cancer Database and stratified into low-dose radiation (41.4 Gy) (LDR) or high-dose radiation (50.0 or 50.4 Gy) (HDR) groups. Multivariable Logistic and Cox Regression analyses were performed to investigate the effect of multiple variables on the likelihood of undergoing esophagectomy and overall survival, respectively. Propensity score matching was performed to reduce bias between groups.

Results A total of 3633 patients met study criteria with 3005 (82.7%) undergoing esophagectomy. A greater proportion received HDR (3163 (87.1%)) than LDR (470 (12.9%)). The use of LDR increased from 4.7% ($n = 22$) in 2010 to 20.7% ($n = 154$) in 2015. Factors associated with undergoing esophagectomy included LDR, adenocarcinoma histology, and younger age. Radiation dosage did not impact overall survival, but undergoing esophagectomy was associated with improved survival. After propensity matching, a greater portion of the LDR group underwent esophagectomy (87.0 vs 81.1%, $p = 0.013$). There was no difference in R0 resection (93.2 vs 92.4%, $p = 0.678$) or complete pathologic response (19.3 vs 21.5%, $p = 0.442$) between LDR and HDR groups.

Conclusion The use of LDR is increasing but still underutilized. LDR is associated with increased rates of esophagectomy without negatively impacting overall survival, R0 resection, or complete pathologic response.

Keywords Radiation dosage · Esophagectomy · Esophageal cancer

Introduction

Esophageal cancer is the sixth most common cause of cancer death worldwide.¹ Its incidence is expected to rise in the USA from 17,000 in 2018 to 20,000 by 2030.^{2,3} Patients presenting

with very early stage disease may be treated with endoscopic therapy or surgery alone, and palliative chemotherapy is used for patients with distant metastases. However, most patients present with locally advanced disease. The standard treatment varies from center to center but generally includes neoadjuvant two-drug chemotherapy or chemoradiotherapy followed by esophageal resection.⁴ While systemic therapy is standardized, usually including a combination of a platinum agent with either a fluorouracil or paclitaxel,^{5,6} there is no consensus on an appropriate radiation regimen.

The most commonly used dose of radiation in the USA is 50.4 Gy.⁷ This dose in the neoadjuvant setting was developed from RTOG 8501 and the INT 0123 trials which showed better response and survival rates with chemoradiotherapy compared to radiotherapy alone and no benefit for dose escalation past 50.4 Gy, in the definitive setting.^{8,9} More recently, the CALGB 9781 trial randomized patients with locally advanced disease to surgery alone and cisplatin 5-fu

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chemotherapy with 50.4 Gy of radiation administered concurrently. The trial closed early due to poor accrual but did show a benefit for neoadjuvant therapy.⁵

Outside the USA, radiation doses in clinical trials vary. The CROSS trial, arguably the most influential recent study regarding esophageal cancer, randomized patients to surgery alone or neoadjuvant carboplatin/paclitaxel with 41.4 Gy of concurrently administered radiation.¹⁰ Complete pathologic response rate, local control, and overall survival compared favorably with previous trials with higher radiation doses. Additionally, toxicity from the treatment regimen was low, and 93% of patients were able to complete the treatment.

Despite the efficacy of the CROSS regimen, many radiation oncologists have been hesitant to use a lower dose of radiation in the neoadjuvant setting citing theoretical concerns of potentially lower complete response and R0 resection rates. Additionally, if 41.4 Gy is administered and the patients do not undergo esophagectomy, they are considered to have received an inadequate radiation for definitive therapy.^{11,12} Conversely, there are theoretical advantages of reduced dosage. Lower doses may lead to less pulmonary and cardiac toxicity preventing postoperative complications.¹³ Lower radiation toxicity may also increase the chance patients can complete their systemic therapy and tolerate esophagectomy.

Consequently, there is no clear consensus on the appropriate radiation dosage for patients with locally advanced esophageal cancer who are appropriate for esophagectomy. In fact, the National Comprehensive Cancer Networks recommendations range from 41.4 to 50.4 Gy.¹⁴ This study attempts to assess the impact of neoadjuvant radiation dosage in patients undergoing trimodality therapy for esophageal cancer. Specifically, we aimed to investigate the likelihood of undergoing resection and compare complete pathologic response rates, R0 resection rates, and short- and long-term survival in patients treated with both 41.4 and 50 or 50.4 Gy of radiation.

Methods

Data Source and Patient Population

The National Cancer Database (NCDB) was queried for patients diagnosed with esophageal cancer between 2010 and 2015 who were treated with both chemotherapy and radiation. Inclusion criteria included age greater than 18 years of age, squamous cell or adenocarcinoma histology, cancers located in the middle or lower esophagus, and clinical stage T₁N₁ or T₂₋₃N₀₋₁ without metastasis. Patients were excluded if esophageal resection was not part of the planned course or if they underwent a procedure that was limited to local tumor destruction. Patients were excluded if they received 45 Gy of

radiation to in an effort to enhance therapeutic differences between groups. Patients were stratified into groups depending on if they received low-dose radiation (LDR) (41.4 Gy) or high-dose radiation (HDR) (50.0 or 50.4 Gy) (Fig. 1).

The International Classification of Disease for Oncology codes used to identify adenocarcinoma were 8140–41, 8143–47, 8255, 8260, 8310, 8340, and 8480–81 and the codes for squamous cell carcinoma were 8052–53, 8070–76, 8078, and 8083–84. Patients were considered to have undergone esophagectomy whether they underwent total or partial resection (primary site of surgery codes: 30, 40, 50–55, 80). Facilities with the designation of academic, research, or National Cancer Institute designated comprehensive cancer centers were considered academic centers for this study. Patient race was stratified into Caucasian, black, or other. Insurance status was stratified into private, Medicare, Medicaid, and other which included uninsured patients. Overall survival is defined as the duration between diagnosis and last known follow-up. For patients that underwent esophagectomy, postoperative survival, which is not specifically reported in the database, was calculated as the difference between overall survival and time to surgery.

Statistical Analysis

All statistical analysis was performed using SPSS (version 25, IBM, Armonk, NY). Baseline characteristics between the two study groups were compared with Student *t* test and chi-square estimates and reported as mean ± standard deviation and number (percentage) for continuous and categorical variables, respectively.

Outcomes including proportion of patients undergoing esophageal resection, time to surgery, postoperative length of stay and mortality, R0 resection, and complete pathologic response were compared between the LDR and HDR groups. Multivariable logistic regression and Cox regression analyses were performed to investigate the effect of multiple variables on the likelihood of undergoing esophagectomy and overall survival, respectively. Differences between the study groups are shown in Table 1. Propensity score matching was performed to make the study groups more comparable and reduce selection bias. Propensity scores were generated with a logistic regression model. Propensity matching was then performed with a 1:1 ratio using a match tolerance of 0.05 (Table 2). Survival was compared using Kaplan–Meier analysis. The database does not provide survival information for patients diagnosed in the most recent year, the year 2015 in this study, and they were not included in the survival analyses.

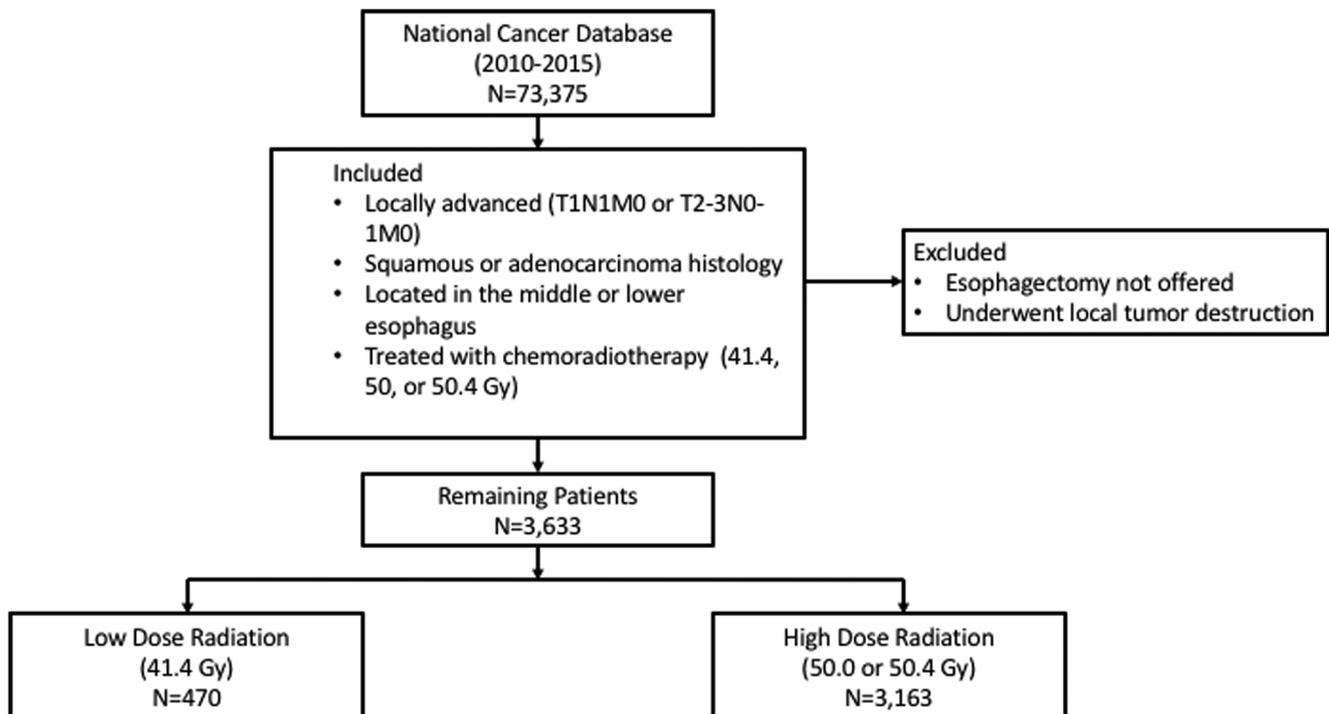


Fig. 1 Flow diagram for selection of patients and stratification into LDR and HDR groups

Results

A total of 3633 patients met study criteria with 3005 (82.7%) undergoing esophagectomy. A greater proportion of the study group received HDR (3163 (87.1%)) than LDR (470 (12.9%)). The annual proportion of patients receiving LDR increased from 4.7% ($n = 22$) in 2010 to 20.7% ($n = 154$) in 2015.

Prior to matching, the LDR group had a greater proportion of patients with squamous cell carcinoma (22.6 vs 18.5%, $p = 0.036$) (Table 1). Additionally, the proportion of ethnicities were dissimilar between the groups with the LDR having a lower proportion of Caucasian (89.8 vs 93.6%, $p = 0.003$) and higher proportion of other ethnicities (5.5 vs 2.3%, $p \leq 0.001$). Patients in the LDR group more frequently underwent esophagectomy (87.0 vs 82.1%, $p = 0.008$) and underwent surgery almost 2 weeks earlier (131.2 vs 143.3 days, $p < 0.001$). In patients undergoing esophagectomy, the LDR group had slightly more mean lymph nodes examined compared to the HDR group (15.37 vs 14.02, $p = 0.007$); however, there was no difference in the portion of patients with positive nodes (36.5 vs 36.7%, $p = 0.960$). There was no significant difference in postoperative length of stay, complete pathologic response, R0 resection, or mortality at 30 and 90 days. Additionally, when stratified by histology, patients with adenocarcinoma underwent esophagectomy more frequently with LDR than HDR (90.1 vs 84.1%, $p = 0.003$), but there was no significant difference in patients with squamous cell carcinoma (76.4 vs 73.3%, $p = 0.507$). In both the LDR and HDR groups, the rate of complete pathologic response was lower in

patients with adenocarcinoma (15.5 and 18.7%) than squamous cell carcinoma (34.6 and 28.7%).

Predictors of patients undergoing esophagectomy are shown in Fig. 2. The strongest positive predictors included being treated at an academic center, LDR, adenocarcinoma histology, and lower esophageal location. Additional significant factors included younger age, no comorbidities, Caucasian compared to other ethnicities, living further from the treatment center, and private insurance compared to Medicaid or uninsured. Results of the Cox regression analysis examining predictors of overall survival are shown in Fig. 3. Undergoing esophagectomy was the strongest predictor of improved survival. Younger age, treatment at an academic center, female gender, and lower clinical stage were also associated with better survival. Radiation dosage did not have a statistically significant impact on overall survival.

Propensity matching yielded groups with similar distributions of histology, cancer location, and ethnicity (Table 2). After propensity matching, the LDR group continued to have a greater proportion of patients undergoing esophagectomy (87.0 vs 81.1%, $p = 0.013$) with a shorter time to surgery (131.2 vs 143.4 days, $p < 0.001$). In patients who underwent esophagectomy, there was no difference in rates of R0 resection (93.2 vs 92.4%, $p = 0.678$) or complete pathologic response (19.3 vs 21.5%, $p = 0.442$) between LDR and HDR groups. Additionally, postoperative length of stay, unplanned 30-day readmissions, and mortality at 30 and 90 days were not significantly different. Kaplan–Meier survival analysis did not show a difference between the LDR and HDR groups in

Table 1 Baseline characteristics and postoperative outcomes of the unmatched groups

	Low-dose radiation	High-dose radiation	<i>p</i> value
Baseline characteristics			
Age	64.1 ± 9.5	63.9 ± 9.5	0.668
Male gender	389 (82.8%)	2631 (83.2%)	0.823
Ethnicity			
Black	22 (4.7%)	130 (4.1%)	< 0.001
Other	26 (5.5%)	74 (2.3%)	
Caucasian	422 (89.8%)	2959 (93.6%)	
Charlson comorbidity (any)	119 (25.3%)	855 (27%)	0.434
Insurance			
Medicaid	31 (6.6%)	182 (5.8%)	0.319
Medicare	197 (41.9%)	1468 (46.4%)	
None/other	26 (5.5%)	172 (5.4%)	
Private	216 (46%)	1341 (42.4%)	
Area > 21% w/o high school degree	63 (13.4%)	346 (10.9%)	0.115
Area median income < \$38,000	60 (12.8%)	413 (13.1%)	0.861
Academic program	249 (53%)	1580 (50%)	0.221
Distance from hospital (miles)	47.7 ± 131.6	46 ± 151.9	0.806
Lower esophageal Cancer	401 (85.3%)	2735 (86.5%)	0.499
Adenocarcinoma histology	364 (77.4%)	2578 (81.5%)	0.036
Clinical stage			
IIA	184 (39.1%)	1169 (37%)	0.654
IIB	80 (17%)	563 (17.8%)	
IIIA	206 (43.8%)	1431 (45.2%)	
Esophagectomy performed	409 (87%)	2596 (82.1%)	0.008
Postoperative outcomes			
Days to surgery	131.2 ± 35	143.3 ± 37.8	< 0.001
Complete pathologic response	79 (19.3%)	528 (20.3%)	0.632
R0 resection	381 (93.2%)	2397 (92.3%)	0.560
Number of lymph nodes examined	15.4 ± 9.5	14.0 ± 9.1	0.007
Any positive lymph node	141 (36.5%)	874 (36.7%)	0.960
Postoperative length of stay	11.9 ± 10.2	12.5 ± 11.3	0.391
Unplanned readmission < 30 days	27 (6.6%)	139 (5.4%)	0.305
30-day mortality	7 (2.6%)	73 (3.4%)	0.472
90-day mortality	14 (5.2%)	160 (7.5%)	0.165

overall survival (*p* = 0.091) (Fig. 4a) or when stratified by whether patients underwent esophagectomy (*p* = 0.173) or not (*p* = 0.833) (Fig. 4b). Additionally, postesophagectomy survival was similar between LDR and HDR groups (*p* = 0.126) (Fig. 4c).

Discussion

While the need for neoadjuvant therapy prior to esophagectomy for patients with locally advanced esophageal cancer is widely accepted, its specifics, including the proper dose of radiation, continue to be debated in multidisciplinary tumor boards around the country. Recently, two other groups have independently published studies of the National

Cancer Database comparing radiation dosages and their association with long-term survival.^{7,15} Buckstein et al. and Haque et al. stratified patients undergoing esophagectomy into groups of 40–41.4, 45, 50.4, and 54 Gy and 40–41.4 and 50–50.4 Gy, respectively, and found no difference in overall survival, similar to our results here. Also similar to here, there was no difference in the complete pathologic response and R0 resection rates and the annual usage of LDR increased over time. Previously, a greater portion of patients receiving LDR were treated at academic center. We did not find a significant difference between academic and non-academic centers suggesting greater adoption of LDR in the community.

Unique to this study is the finding that LDR is associated with an increased rate of undergoing esophagectomy,

Table 2 Baseline characteristics and postoperative outcomes of the propensity matched group

	Low-dose radiation	High-dose radiation	<i>p</i> value
Baseline characteristics			
Age	64.1 ± 9.5	63.3 ± 9.8	0.237
Male gender	389 (82.8%)	386 (82.1%)	0.797
Ethnicity			
Black	22 (4.7%)	17 (3.6%)	0.638
Other	26 (5.5%)	23 (4.9%)	
Caucasian	422 (89.8%)	430 (91.5%)	
Charlson comorbidity (any)	119 (25.3%)	138 (29.4%)	0.164
Insurance			
Medicaid	31 (6.6%)	35 (7.4%)	0.822
Medicare	197 (41.9%)	207 (44%)	
None/other	26 (5.5%)	24 (5.1%)	
Private	216 (46%)	204 (43.4%)	
Area > 21% w/o high school degree	63 (13.4%)	60 (12.8%)	0.772
Area median income < \$38,000	60 (12.8%)	50 (10.6%)	0.31
Academic program	249 (53%)	241 (51.3%)	0.601
Distance from hospital (miles)	47.7 ± 131.6	65.5 ± 274.6	0.205
Lower esophageal cancer	401 (85.3%)	398 (84.7%)	0.784
Adenocarcinoma histology	364 (77.4%)	374 (79.6%)	0.427
Clinical stage			
IIA	184 (39.1%)	190 (40.4%)	0.848
IIB	80 (17%)	74 (15.7%)	
IIIA	206 (43.8%)	206 (43.8%)	
Esophagectomy performed	409 (87%)	381 (81.1%)	0.013
Postoperative outcomes			
Days to surgery	131.2 ± 35	143.3 ± 38	< 0.001
Complete pathologic response	79 (19.3%)	82 (21.5%)	0.442
R0 resection	381 (93.2%)	352 (92.4%)	0.678
Number of lymph nodes examined	15.37 ± 9.54	13.8 ± 8.89	0.02
Any positive lymph node	141 (36.5%)	139 (40.3%)	0.296
Postoperative length of stay	11.9 ± 10.2	11.8 ± 10	0.928
Unplanned readmission < 30 days	27 (6.6%)	20 (5.2%)	0.422
30-day mortality	7 (2.6%)	5 (1.9%)	0.591
90-day mortality	14 (5.2%)	15 (5.7%)	0.792

as compared to HDR. One theory for this increase may be a decrease in radiation toxicity and better tolerance of LDR, allowing more patients to be considered surgical candidates at the completion of chemoradiotherapy. Alternatively, this effect may be explained purely by selection bias. Unfortunately, the data available in the NCDB does not allow for a more in-depth analysis of the causative factors. The increased rate of esophagectomy occurred without sacrificing the theoretical benefits of HDR including complete pathologic response and R0 resection rates. Additionally, in this study, esophagectomy was associated with improved survival. While not born out in this data, it is possible that LDR could increase survival by increasing esophagectomy rate. An increased rate of esophagectomy would coincide with overall

increase in R0 resection, which has been associated with improved survival.^{16,17} However, this correlation remains controversial. Retrospective single center studies have shown a survival advantage of trimodality therapy over definitive chemoradiotherapy,^{18,19} while the GOCSG and FFCO 9102 trials did not.^{20,21} Although the latter were limited to patients with squamous cell carcinoma.

Interestingly, in the subset of patients that failed to undergo esophagectomy, there was no difference in overall survival between the LDR and HDR groups. This finding may encourage radiation oncologist to reconsider the idea of prophylactic administration of HDR, in the event patients fail to undergo esophagectomy. Historically, an analysis of the NCDB comparing 50–50.4 Gy to doses greater than 50.4 Gy found no difference in survival.²² Moreover, escalation of radiation

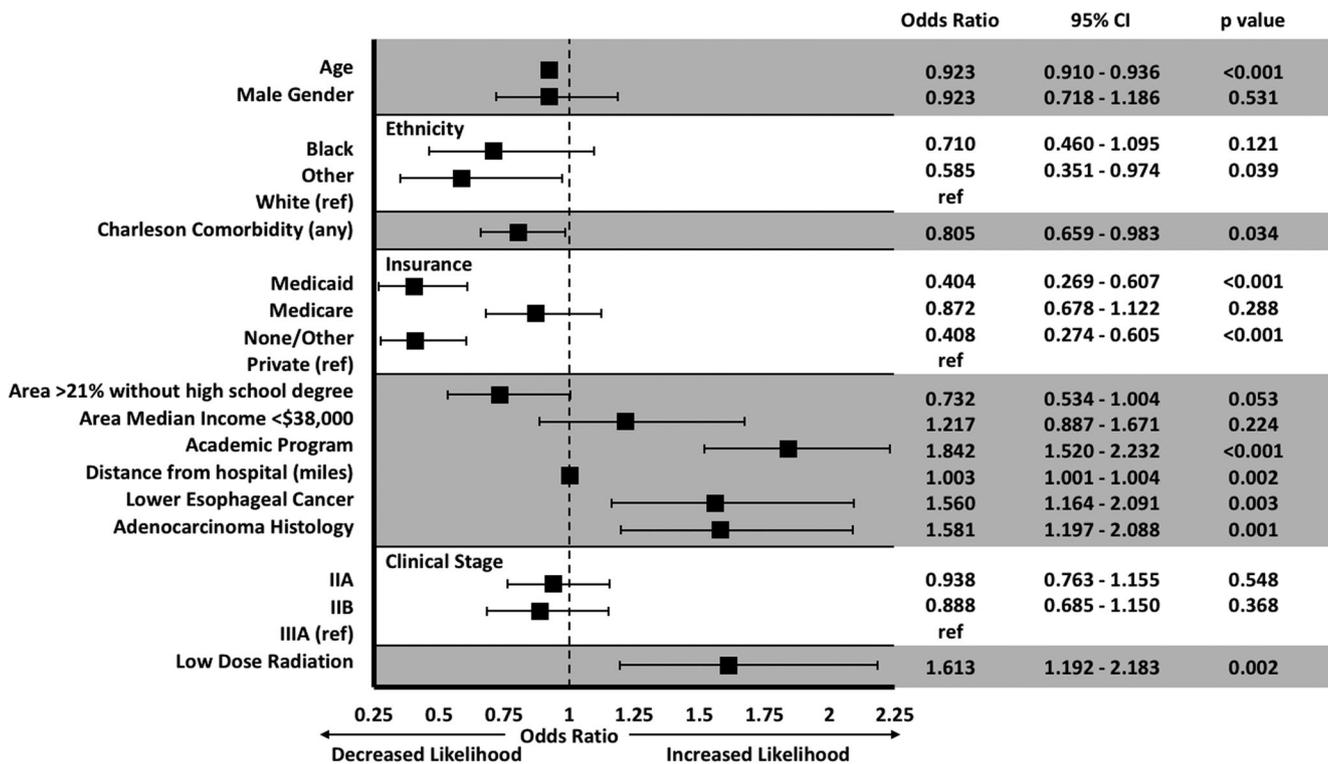


Fig. 2 Multivariable logistic regression model for factors associated with undergoing esophagectomy

dosages to 64.8 Gy did not provide a survival advantage compared to 50.4 Gy and resulted in significantly worse quality of

life in the Intergroup 0123 Trial.^{9,23} Higher radiation dosages have shown to correlate with increased postoperative

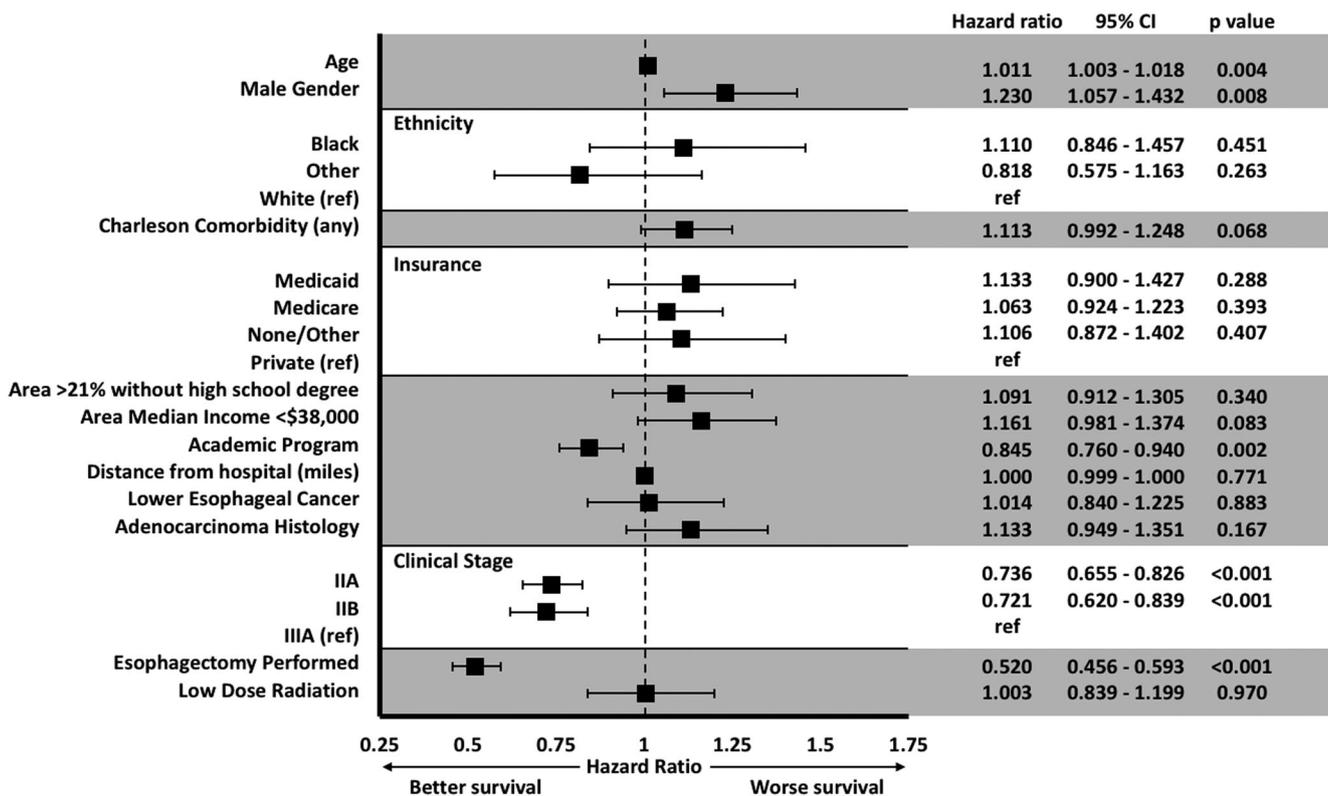


Fig. 3 Cox regression model for factors associated with overall survival

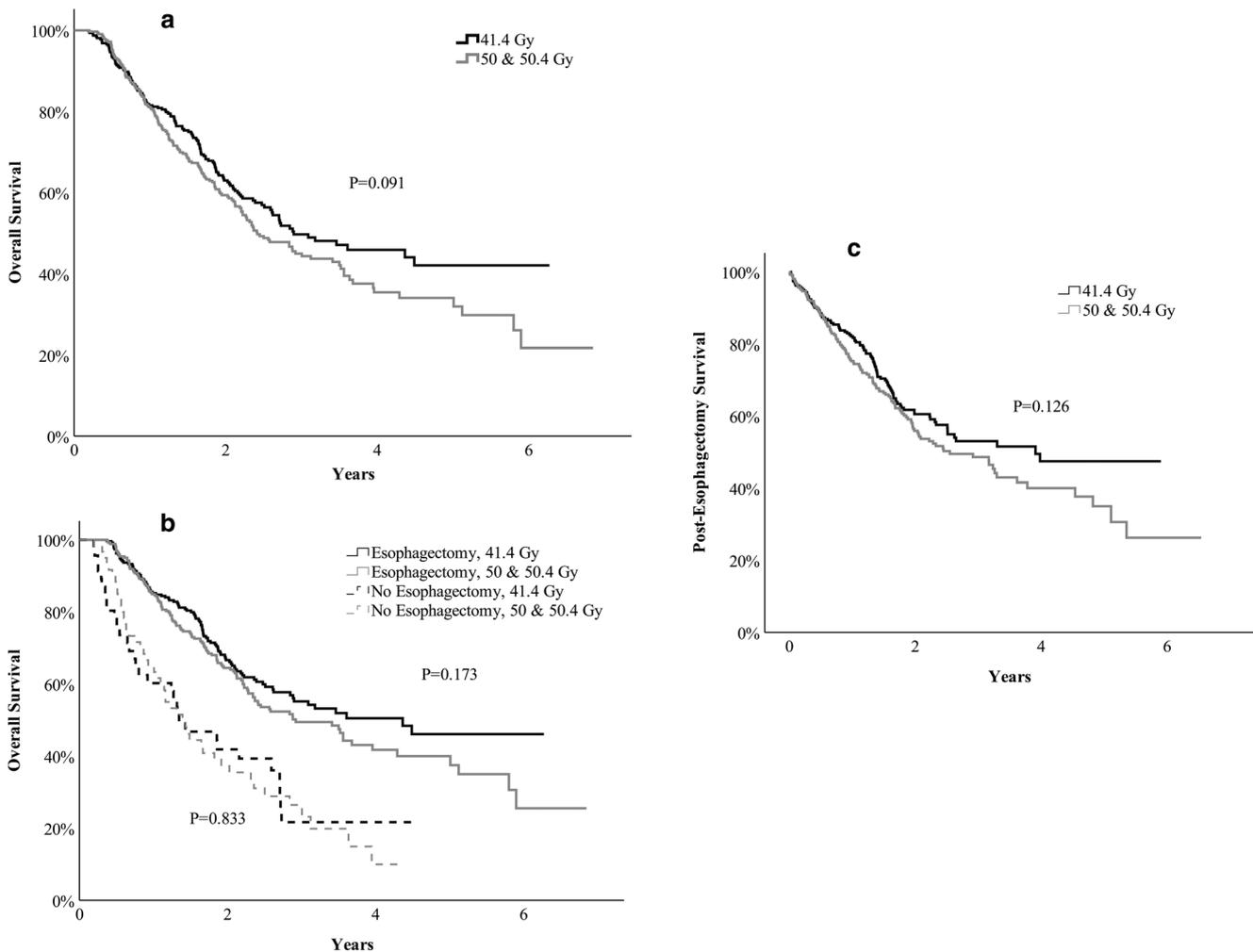


Fig. 4 Comparisons of **a** overall survival between low-dose radiation (41.4 Gy) and high-dose radiation (50 and 50.4 Gy) groups. **b** Overall survival for patients between low-dose radiation (41.4 Gy) and high-dose radiation (50 and 50.4 Gy) groups stratified by whether patients

underwent esophagectomy ($p = 0.173$) or not ($p = 0.833$). **c** Postoperative survival between patients receiving low-dose radiation (41.4 Gy) and high-dose radiation (50 and 50.4 Gy) groups

complication rates.^{13,24,25} It is possible that 50.4 Gy offers nothing but additional toxicity over 41.4 Gy.

This study has limitations inherent to the use of a national database including inability to validate the accuracy of data or to control for confounding factors. Analyses are limited to the data available, and we were unable to collect additional factors, for example information on local control or chemotherapy regimen. The authors feel the omission of local recurrence and or control rate is a particular weakness, as one would expect this outcome to be more directly affected by radiation compared to overall survival.

By performing an observational study, we are unable to identify causations and only can report associations. Selection bias is almost certainly present. It is certainly conceivable such as patients with larger tumors or who appeared sicker may have been more likely to receive HDR. These patients may have had worse survival and been less likely to undergo esophagectomy, biasing our results.

The NCDB identifies patients for who surgery was not part of the initial treatment plan, but only provides limited details for the remainder of patients that did not undergo esophagectomy. Thus, this study assumes these remaining patients would have been surgical candidates but may include patients who in actuality were not. Finally, we did not control for radiation types and patients receiving advanced types (e.g., intensity-modulated radiotherapy) may have had decreased toxicity rendering the findings here invalid. Unfortunately, most of these limitations cannot be addressed outside the context of a randomized clinical trial, and given the current level resources available, such a trial is unlikely to occur.

Conclusion

This study used the national cancer database to evaluate the impact on radiation dosage in patients with locally advanced

esophageal cancer. The usage of 41.4 Gy continues to rise but is still used in the minority of patients. It is associated with similar overall survival, complete pathologic response rate, and R0 resection rate as higher dose regimens. These findings may reassure radiation oncologist that patients' overall survival will not be impacted by the use of LDR but their likelihood of undergoing esophagectomy may be increased.

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Author Contributions Per the guidelines of the International Committee of Medical Journal Editors (ICMJE), all persons listed as authors meet all of the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work.
- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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