Palliative Radiotherapy Versus Esophageal Stent Placement in the Management of Patients With Metastatic Esophageal Cancer

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ABSTRACT

Background: Patients with advanced esophageal cancer often experience pain and dysphagia, yet the optimal palliative management remains unclear. This retrospective study evaluated outcomes and adverse effects of palliative radiotherapy (RT) compared with esophageal stenting among a cohort of U.S. veterans with metastatic esophageal cancer. **Patients and Methods:** We identified 1,957 veterans in the United States with metastatic esophageal cancer who received palliative RT to the esophagus or esophageal stenting, and assessed the risks of severe adverse effects, including esophageal fistula formation, perforation, obstruction, hemorrhage, and esophagitis. We determined palliative efficacy by evaluating pain and dysphagia scores before and after intervention. Multivariable analyses were used to control for potential confounding factors. **Results:** In our cohort, 1,593 patients underwent RT and 364 underwent esophageal stenting. The cumulative incidence of any severe adverse effect at 6 months was higher among patients who received stents compared with those who received RT (21.7% vs 12.4%; $P < .0010$). In multivariable analysis, patients who received stents had an increased risk of any severe adverse effect, including fistula, perforation, and hemorrhage (all $P < .0500$). Multivariable analysis also showed that, compared with stenting, RT was associated with more rapid and durable pain relief ($P < .0010$) with no difference in relief of dysphagia over time when accounting for pretreatment dysphagia scores ($P = .1029$). **Conclusions:** Compared with esophageal stenting, RT was associated with a decreased risk of adverse effects, greater pain relief, and equivalent relief of moderate to severe dysphagia over time. Unmeasured patient- or tumor-related factors could have influenced the choice of intervention, thereby impacting our study outcomes. To our knowledge, this is the largest study to date analyzing the comparative risks and benefits of palliative RT and esophageal stenting among patients with metastatic esophageal cancer.

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Background

Most patients with esophageal cancer are found to have locally advanced or metastatic disease at the time of initial diagnosis.^{1–4} Such advanced disease is associated with significant symptom burden and corresponding decrease in quality of life.⁵ Dysphagia and pain, secondary to either odynophagia or local tumor extension, are the most frequently reported symptoms among patients with advanced, incurable esophageal cancer.⁴ Optimal treatment of these patients would ideally provide rapid and durable relief of dysphagia and pain while minimizing the risk of toxicity.

Multiple palliative treatment modalities are available for patients with metastatic esophageal cancer, though palliative radiotherapy (RT) to the esophagus and esophageal stenting are the most frequently used interventions.⁶ Data comparing the complication rates and palliative efficacy of these modalities are limited, however, and largely based on single-center studies with small sample sizes.^{6–8} The purpose of this analysis was to assess the efficacy and complications of palliative external-beam RT compared with esophageal stent placement among a large, multi-institutional cohort of veterans diagnosed with metastatic esophageal cancer.

Methods

Data Source

We conducted this study using the Veterans Affairs (VA) Informatics and Computing Infrastructure database. This database contains access patient-level electronic medical record data for all veterans within the VA healthcare system, including detailed patient, demographic, cancer, treatment, and long-term outcome information.⁹ The VA Institutional Review Board approved this study.

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Study Subjects

We initially identified 7,190 patients with stage IV esophageal cancer diagnosed between 2000 and 2015 from the VA Central Cancer Registry. Using ICD-9 and ICD-10 diagnosis and procedure codes, we identified 2,115 patients treated using palliative external-beam RT to the esophagus and/or esophageal stenting. The 158 patients who received both interventions were excluded because there were too few for meaningful analysis. Therefore, the final study cohort consisted of 1,957 patients. Figure 1 shows the selection process.

Study Covariates

Baseline patient, demographic, and cancer data were extracted from the VA Central Cancer Registry. Patient ZIP codes were used to estimate median household income level and population density (urban vs rural). ICD diagnosis codes in the year before initiation of cancer treatment were used to define the NCI-adapted Charlson comorbidity index, which excludes cancer-related comorbidities.^{10–13}

Study Endpoints

Adverse effects occurring after RT or esophageal stenting were identified using ICD diagnosis codes; specifically, esophageal fistula formation, perforation, obstruction, hemorrhage, and esophagitis. We assessed efficacy of radiation or endoluminal stenting by measuring long-term pain and dysphagia scores, and extracted longitudinal pain scores for each patient (Likert scale 0–10) before and for up to 1 year after RT or stenting. All patients with at least one preintervention and one postintervention

pain score were included in this subgroup analysis, with the most recent preintervention pain score serving as the patient's baseline pain level. Dysphagia scores were determined through manual review of clinical notes. We focused our review on the following keywords identifiable in clinical notes: "dysphagia," "swallow(ing)," "liquid," "solid," "stuck," "food," or "diet." Dysphagia scores were assigned using a well-established 5-point dysphagia scoring system, with 0 representing no dysphagia and 4 representing complete inability to swallow.^{14–20}

Statistical Analysis

We assessed differences in baseline covariates between the RT and stent groups using χ^2 and Wilcoxon rank-sum tests. We assessed the unadjusted cumulative incidence of adverse effects after RT or stenting. We measured the impact of RT or stenting on adverse effects using multivariable Fine-Gray competing risk regression, treating death as a competing risk, and censoring at last follow-up. A linear mixed effects model was used to analyze change in pain scores over time, with time serving as a continuous variable. This model was also used to analyze dysphagia scores over time. Analyses of adverse effect endpoints were conducted using the entire study cohort. Analyses of pain scores were conducted in subjects with pain scores before and up to 1 year after the intervention ($n=766$), which included a higher proportion of patients treated with RT than with stenting (41% vs 31%; $P<.0010$). Analysis of dysphagia scores was conducted in subjects with both preintervention and postintervention dysphagia scores ($n=527$), which included a similar proportion of patients treated using RT compared with endoluminal stenting (28% vs 24%; $P=.1500$). To account for differences in preintervention dysphagia scores, we conducted a subgroup analysis of patients with a preintervention dysphagia score ≥ 2 ($n=454$). Analyses were performed using SAS version 9.4 software (SAS Institute Inc). All tests were 2-sided, and P values $<.0500$ were considered significant.

Results

Study Cohort

Of the 1,957 patients in this study, 1,593 (81.4%) underwent palliative RT to the esophagus and 364 (18.6%) underwent esophageal stent placement. Table 1 contains baseline patient characteristics stratified by intervention. The 2 groups differed in terms of race, tumor histology, tumor location in the esophagus, age, and Charlson comorbidity index.

Adverse Effects

The unadjusted cumulative incidence of fistula, perforation, hemorrhage, obstruction, or esophagitis at 6 months after intervention was significantly higher for

Figure 1. Patient selection.

Table 1. Baseline Patient Characteristics

Characteristic	Radiotherapy n (%)	Stent n (%)	P Value
Total, n	1,593	364	
Age, y, median (IQR)	64 (58–71)	64 (59–72)	.0250*
Sex			.9900
Male	1,580 (99)	361 (99)	
Female	13 (1)	3 (1)	
Race			.0060*
White	1,251 (79)	308 (85)	
Black	309 (19)	46 (13)	
Other	33 (2)	10 (3)	
Married	679 (43)	140 (39)	.1600
Employment status			.1000
Unemployed	1,424 (89)	314 (86)	
Employed	169 (11)	50 (14)	
History of alcohol use	748 (47)	153 (42)	.1000
History of tobacco use	1,338 (84)	303 (83)	.7800
Tumor location in esophagus			.0022*
Cervical or upper third	119 (7.5)	11 (3.0)	
Middle third	255 (16.0)	44 (12.1)	
Lower third or GEJ	923 (57.9)	237 (65.1)	
Unknown	296 (18.6)	72 (19.8)	
Histology			<.0010*
Adenocarcinoma	871 (55)	243 (67)	
Squamous cell carcinoma	578 (36)	84 (23)	
Other	144 (9.0)	37 (10)	
Median household income			.1100
More than median	782 (49.1)	196 (53.8)	
Less than median	811 (50.9)	168 (46.2)	
Charlson comorbidity index			.0020*
0	964 (60.5)	187 (51.4)	
1	261 (16.4)	67 (18.4)	
2	184 (11.6)	65 (17.9)	
≥3	184 (11.6)	45 (12.4)	
Population density			.4900
Metropolitan	1,179 (74.0)	278 (76.4)	
Nonmetropolitan	320 (20.1)	320 (20.1)	
Rural	94 (5.9)	16 (4.4)	

Abbreviations: GEJ, gastroesophageal junction; IQR, interquartile range.

*Meets statistical significance of $P < .0500$.

individuals who underwent stent placement than for those who underwent RT (21.7% vs 12.4%; $P < .0010$) (Figure 2A). The median time to any adverse effect was 43 days (1.41 months) for patients who received esophageal stenting and 114 days (3.75 months) for patients who received palliative RT ($P < .0010$). When considering

individual adverse effects, we found that patients receiving stents had a higher incidence of perforation and hemorrhage and a trend toward an increased incidence of fistulas (Figure 2B). These findings persisted in multivariable analysis, with patients who received stents having a 51% increased risk of any adverse effect

Figure 2. (A) Cumulative incidence of any adverse effect, and (B) 6-month cumulative incidence of individual adverse effects after esophageal stent placement or radiotherapy.

compared with those treated with RT (subdistribution hazard ratio [SDHR], 1.51; 95% CI, 1.17–1.95; $P=.0014$). Similarly, regarding individual adverse effects in multivariable analysis, patients who underwent stent placement had an increased risk of fistula formation (SDHR, 3.56; 95% CI, 1.49–8.48; $P=.0042$), perforation (SDHR, 16.89; 95% CI, 3.95–72.25; $P<.0010$), and hemorrhage (SDHR, 1.51; 95% CI, 1.01–2.26; $P=.0456$). In multivariable analysis, we observed no difference in the rate of obstruction (SDHR, 1.06; 95% CI, 0.64–1.75; $P=.8155$) or esophagitis (SDHR, 1.21; 95% CI, 0.81–1.81; $P=.3505$) between the 2 groups (supplemental eTable 1, available with this article at JNCCN.org).

Palliative Efficacy

No statistically significant differences in unadjusted pre-intervention pain levels were found between the stent and RT groups ($P=.3627$). Compared with esophageal stent placement, palliative RT was associated with more rapid and persistent pain relief over time ($P<.0010$) (Figure 3). In multivariable analysis, the increased pain relief persisted for the RT group compared with the endoluminal stent group ($P<.0010$) (supplemental eTable 2). The pre-intervention mean dysphagia score was higher (worse) in the esophageal stent group than in the RT group ($P<.0010$), although at 90 to 120 days, there was no difference in dysphagia ($P=.1000$) (Figure 4). At 90 to 120 days after intervention, 75.8% of patients who received stents had a net improvement (reduction) in dysphagia compared with 58.8% of those treated with RT ($P=.0109$). In multivariable analysis of the 527 patients for whom we had preintervention and postintervention dysphagia scores, stenting showed a larger, more rapid improvement in dysphagia than RT over time ($P=.0190$) (supplemental

eTable 2). In analysis of the 454 patients with a pre-intervention dysphagia score ≥ 2 , however, improvement in dysphagia over time was not significantly different between the groups ($P=.1029$) (supplemental eTable 2).

Discussion

Approximately 70% of patients with advanced esophageal cancer experience malignant dysphagia, which directly contributes to impaired health-related quality of life.^{21,22} Pain due to odynophagia or local effects of the tumor is also common and similarly associated with diminished quality of life.⁵ In the setting of metastatic disease, the focus of medical management is palliation of symptoms, with endoluminal stenting

Figure 3. Pain scores over time. This plot shows a spline with 95% confidence bands (shaded regions) for patient self-reported pain scores. Time (x axis) represents days from esophageal stent placement or radiotherapy. Pain scores before time 0 reflect the last pain score within 6 months before stent placement or radiotherapy.

Figure 4. Average dysphagia score over time.

and external-beam RT the most commonly pursued treatment modalities.^{23–25} Understanding the comparative effectiveness of these 2 interventions will help define the potential benefits and risks of treatment among patients with local symptoms due to esophageal cancer.

The key finding of this study relates to the risk of adverse effects associated with the 2 interventions in this patient population. Specifically, esophageal stenting was associated with an increased risk of fistula formation, perforation, and hemorrhage compared with RT. This finding complements existing retrospective studies that have shown a 2% to 8% incidence of esophageal perforation and a 3% incidence of fistula formation among patients treated using esophageal stenting.^{26–29} Regarding obstruction, the <5% rate after stent placement in our study was much lower than the 30% to 40% rates previously described in the literature.^{26,28,29} In addition, our study only considered severe complications, although when considering all complications, the rate of stent-associated adverse effects in the literature ranges from 46% to 65%.^{24,30–33} Our study did not assess stent migration or revisions, although the literature shows that stent migration can occur in up to 20% and reintervention procedures occur in 25% to 50% of patients with stents.^{24,32–38} We lack large randomized trials comparing stent placement with RT, although the results of a small study involving 32 patients with advanced esophageal cancer randomized to external-beam palliative RT or stent placement have been summarized in an abstract by Turrisi et al.³⁹ Despite its small sample size, the Turrisi et al³⁹ study found that RT was more commonly associated with stricture and esophagitis, whereas stent placement was more commonly associated with bleeding and tumor ingrowth.

Other important observations of our study relate to the impact of these palliative modalities on symptom relief. Our study found modestly greater pain relief with palliative RT than with stenting. This difference in pain control likely reflects the antitumor effect of palliative RT, which stands in contrast to the physical effects associated with stent placement. We found that, overall, the stent group had more severe preintervention dysphagia than the RT group,

a difference also noted in the existing literature.²³ Because the onset of relief of dysphagia after RT is typically measured in weeks, stenting is often favored for patients with nearly complete esophageal obstruction or a very limited life expectancy, when rapid onset of relief is a priority.^{23,24} Importantly, however, the literature also shows a durable response with RT in up to 90% of patients.^{27,36,40–42} Our study complements these findings with a similar long-term reduction in dysphagia associated with RT, although it also shows persistent relief of dysphagia with stenting at 90 to 120 days. Notably, among patients with a preintervention dysphagia score ≥ 2 , improvement of this symptom over time was not significantly different between the 2 treatment groups.

Our study has limitations. As with most nonrandomized observational research, the potential of unmeasured patient-, disease-, institution-, and physician-associated confounding factors that may contribute to the observed outcomes must be considered. Because of the complexity of treatment in this patient cohort, we did not include other treatment-related factors, such as chemotherapy or pain medications received before, concurrent with, or after the 2 interventions we assessed. Given the typical multimodal approach to symptom control in patients with advanced esophageal cancer, one must consider that these ancillary treatments could influence dysphagia or pain. Additionally, in research involving electronic health records, the possibility exists of misclassification (or underreporting) of study endpoints, including pain, dysphagia, or adverse effects. Finally, although we can assess correlation between treatment modality (stent placement or RT) and our study endpoints, we lack the ability to establish causality. Pain, dysphagia, or adverse effects in this study could all arise (or improve) due to factors unrelated to esophageal stenting or RT. Despite these limitations, our study provides practical evidence for practitioners and patients to consider when choosing between palliative RT and esophageal stenting.

Conclusions

Our results support prior evidence that in patients with metastatic esophageal cancer, palliative RT is associated with significantly lower risk of toxicity, improved pain control, and equivalent relief of moderate to severe dysphagia compared with esophageal stenting. Prospective trials are needed to fully understand the comparative effectiveness of palliative RT and stent placement in metastatic esophageal cancer.

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eTable 1: Multivariable Fine-Gray Model Results

eTable 2: Multivariable Linear Mixed-Effects Model Results

eTable 1. Multivariable Fine-Gray Model Results

Parameter	P Value	SDHR
Fistula		
Intervention (stent vs radiation)	.0042	3.56 (1.49–8.48)
Race (nonwhite vs white)	.8656	1.08 (0.45–2.57)
Age at diagnosis	.0203	0.96 (0.93–0.99)
Alcohol history	.2055	0.61 (0.28–1.31)
Tobacco history	.0678	2.33 (0.94–5.77)
Histology (adenocarcinoma vs SCC)	<.0010	0.09 (0.02–0.34)
Histology (other vs SCC)	.2282	0.39 (0.09–1.80)
Perforation		
Intervention (stent vs radiation)	<.0010	16.89 (3.95–72.25)
Race (nonwhite vs white)	.8695	1.14 (0.24–5.32)
Age at diagnosis	.1410	0.96 (0.92–1.01)
Alcohol history	.9123	0.93 (0.24–3.61)
Tobacco history	.7418	1.33 (0.24–7.33)
Histology (adenocarcinoma vs SCC)	.2896	0.46 (0.11–1.93)
Histology (other vs SCC)	<.0010	0.00 (0.00–0.00)
Hemorrhage		
Intervention (stent vs radiation)	.0456	1.51 (1.01–2.26)
Race (nonwhite vs white)	.3643	0.79 (0.48–1.31)
Age at diagnosis	.0023	0.97 (0.96–0.99)
Alcohol history	.9919	1.00 (0.69–1.47)
Tobacco history	.7618	1.08 (0.66–1.76)
Histology (adenocarcinoma vs SCC)	.0405	1.57 (1.02–2.42)
Histology (other vs SCC)	.3995	1.34 (0.68–2.64)
Obstruction		
Intervention (stent vs radiation)	.8155	1.06 (0.64–1.75)
Race (nonwhite vs white)	.5800	0.86 (0.50–1.47)
Age at diagnosis	.6066	1.00 (0.98–1.01)
Alcohol history	.3702	0.83 (0.55–1.25)
Tobacco history	.3889	1.26 (0.75–2.13)
Histology (adenocarcinoma vs SCC)	.0042	2.00 (1.25–3.22)
Histology (other vs SCC)	.9764	0.99 (0.40–2.44)
Esophagitis		
Intervention (stent vs radiation)	.3505	1.21 (0.81–1.81)
Race (nonwhite vs white)	.9813	1.01 (0.66–1.54)
Age at diagnosis	.0019	0.97 (0.96–0.99)
Alcohol history	.9869	1.00 (0.74–1.37)
Tobacco history	.8080	1.06 (0.69–1.62)
Histology (adenocarcinoma vs SCC)	.3205	1.22 (0.83–1.79)
Histology (other vs SCC)	.9629	0.99 (0.53–1.84)

(continued)

eTable 1. Multivariable Fine-Gray Model Results (cont.)

Parameter	P Value	SDHR
Any toxicity		
Intervention (stent vs radiation)	.0014	1.51 (1.17–1.95)
Race (nonwhite vs white)	.4902	0.91 (0.69–1.20)
Age at diagnosis	<.0010	0.98 (0.97–0.99)
Alcohol history	.4262	0.92 (0.74–1.13)
Tobacco history	.7101	1.06 (0.79–1.41)
Histology (adenocarcinoma vs SCC)	.0731	1.25 (0.98–1.61)
Histology (other vs SCC)	.8154	0.95 (0.63–1.43)

Abbreviations: SCC, squamous cell carcinoma; SDHR, subdistribution hazard ratio.

eTable 2. Multivariable Linear Mixed-Effects Model Results

Parameter/Effect	Estimate	P Value
Dysphagia		
Intercept	2.7668	<.0010
Time, d	−0.0074	<.0010
Charlson comorbidity index score (0 vs ≥3)	−0.0523	.6917
Charlson comorbidity index score (1 vs ≥3)	0.1550	.3245
Charlson comorbidity index score (2 vs ≥3)	−0.1324	.4229
Income (more than median vs less than median)	−0.0441	.5934
Population density (metropolitan vs rural)	0.1699	.3004
Population density (nonmetropolitan vs rural)	0.0530	.7733
Intervention (radiation vs stent)	−0.2768	.0231
Tumor location in esophagus (unknown vs middle third)	−0.2159	.1352
Tumor location in esophagus (cervical or upper third vs middle third)	−0.0307	.8754
Tumor location in esophagus (lower third or GEJ vs middle third)	−0.3938	.0014
Interaction between time and intervention (radiation vs stent)	0.0031	.0190
Baseline dysphagia score ≥2		
Intercept	2.9486	<.0010
Time, d	−0.0077	<.0010
Charlson comorbidity index score (0 vs ≥3)	−0.2100	.1048
Charlson comorbidity index score (1 vs ≥3)	−0.0003	.9983
Charlson comorbidity index score (2 vs ≥3)	−0.2692	.0929
Income (above median vs below median)	−0.0255	.7459
Population density (metropolitan vs rural)	0.0408	.7980
Population density (nonmetropolitan vs rural)	−0.0151	.9332
Intervention (radiation vs stent)	−0.0456	.6887
Tumor location in esophagus (unknown vs middle third)	−0.0950	.4860
Tumor location in esophagus (cervical or upper third vs middle third)	−0.0148	.9353
Tumor location in esophagus (lower third or GEJ vs middle third)	−0.2923	.0104
Interaction between time and intervention (radiation vs stent)	0.0021	.1029

(continued)

eTable 2. Multivariable Linear Mixed-Effects Model Results (cont.)

Parameter/Effect	Estimate	P Value
Pain		
Intercept	2.6758	<.0010
Time, d	0.0084	<.0010
Charlson comorbidity index score (0 vs ≥3)	−0.1790	.6230
Charlson comorbidity index score (1 vs ≥3)	0.2284	.5822
Charlson comorbidity index score (2 vs ≥3)	−0.6761	.1161
Income (above median vs below median)	−0.3664	.0915
Population density (metropolitan vs rural)	0.1475	.7343
Population density (nonmetropolitan vs rural)	0.2524	.6024
Intervention (radiation vs stent)	−0.3321	.3627
Tumor location in esophagus (unknown vs middle third)	−0.4439	.2512
Tumor location in esophagus (cervical or upper third vs middle third)	−0.0986	.8461
Tumor location in esophagus (lower third or GEJ vs middle third)	0.0556	.8627
Interaction between time and intervention (radiation vs stent)	−0.0040	<.0010

Abbreviation: GEJ, gastroesophageal junction.