Original Article

Principles and Techniques of Radiation Therapy for Esophageal and Gastroesophageal Junction Cancers

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Abstract
Radiation therapy serves an integral role in the primary and adjuvant treatment of esophagus cancer. Radiation techniques continue to improve, providing more accurate localization of the tumor while limiting dose to normal structures. This article reviews current practices and recommendations for radiation therapy technique for esophageal and gastroesophageal malignancies. (*JNCCN* 2008;6:870–878)

In 2008, an estimated 16,470 new cases of esophageal carcinoma will be diagnosed and 14,280 deaths will occur from the disease in the United States.[1] Potentially curative treatment options for medically fit patients with esophageal carcinoma without distant metastases include surgery alone, chemoradiation alone, or chemoradiation followed by surgery. Because radiation therapy serves an important definitive and adjuvant role in the treatment of esophagus carcinoma, radiation techniques to maximize tumor control and minimize morbidity are of importance. This article reviews pertinent issues in the design and delivery of radiation therapy.

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Field Design

Central to the design of the radiation therapy field is the accurate delineation of gross tumor volume (GTV). Areas at high risk for micrometastatic disease are included in the clinical target volume (CTV). Margin is added to the CTV to account for setup error, patient motion, organ/tumor motion, and other uncertainties; this volume is the *planning target volume* (PTV).[2]

Defining GTV

When defining gross primary tumor and nodal disease for radiation therapy planning, radiation oncologists cannot rely on a single imaging study, but rather must incorporate information from all available studies.

CT Scan: For esophagus carcinoma, CT simulation with oral contrast is generally recommended. Intravenous contrast should also be considered if clinically indicated or if prior intravenous contrasted CT scan of chest/abdomen has not been previously obtained for staging. To minimize effects of gastric filling, nothing-by-mouth status should be maintained for at least 3 hours before simulation should be considered. A custom immobilization device is encouraged to maximize reproducibility of patient positioning.

Radiation oncologists define gross disease on the axial CT scan, which is used for 3-D treatment planning. Although gross disease must be defined on CT scan for purposes of treatment planning, information from other imaging studies can complement and supplement the

CT scan. To ensure coverage of gross disease, the gross disease identified on each imaging modality should be included in the GTV.

Barium Swallow: A study by Gao et al.[3] showed that endoscopy and barium swallow have better accuracy in determining pathologic length of middle and lower esophageal tumors compared with CT. Therefore, the use of oral contrast at simulation, which serves as a barium swallow study, is recommended. For gastroesophageal junction carcinomas, Gao et al.[3] showed that CT scan predicted pathologic length of tumor better than barium swallow.

Endoscopy: Although endoscopy has good accuracy in determining length and location of disease, the location of tumor based on endoscopy cannot easily be translated to location on the CT scan. Nonetheless, radiation oncologists can ensure that the tumor length on CT approximates that reported on endoscopy, and can use landmarks reported on endoscopy or endoscopic ultrasound (EUS; e.g., location of carina or gastroesophageal junction) to confirm that gross disease outlined on CT is consistent with that reported on endoscopy. EUS provides additional information about depth of invasion (T stage) and nodal spread (N stage).

PET-CT: PET-CT scan is more accurate than CT alone in detecting distant metastases,[4] and treatment management in esophageal cancer is altered in 3% to 20% of patients based on information provided by PET scan that is not readily identified with CT and EUS.[5] Although PET-CT is an accepted staging study, its role in radiation therapy planning continues to evolve. GTV on PET-CT is variably defined. Standard uptake values (SUVs) of 2.0 to 2.5 have been suggested as appropriate cutoff values to distinguish benign from malignant disease in the esophagus.[6–8] Using an SUV cutoff of 2.5, Konski et al.[9] reported that mean GTV length as determined by PET-CT correlated closely with that determined by endoscopy. Leong et al.[10] reported that CT-defined GTV missed PET-avid disease in 11 of 16 patients (69%), and in 5 patients (31%) the difference in GTV would have resulted in a geographic miss. PET-CT has been shown to reduce interuse variability in GTV length and volume compared with CT alone.[11]

Defining CTV

The esophagus contains a rich network of submucosal lymphatics, through which microscopic dissemination can occur. Therefore, ample cranial and caudal margins are recommended. In general, the field (to block edge) should include tissue 5 cm cranial and caudal to the GTV and 1.5 to 2 cm in the radial direction from the GTV. However, creation of a CTV (to encompass potential micrometastatic disease) and PTV (to account for variability in patient setup and patient and organ motion) should be encouraged.

Gao et al.[3] prospectively collected and analyzed surgical specimens in 66 patients with esophageal cancer undergoing surgery in the absence of neoadjuvant treatment. The authors concluded that a 3-cm margin to CTV is adequate to cover proximal or distal microscopic disease in 94% of squamous cell carcinomas. A 3-cm proximal margin is sufficient to cover microscopic disease in 100% of patients with gastroesophageal junction carcinoma. However, a distal margin of 5 cm was necessary to cover microscopic disease in 94% of gastroesophageal junction carcinomas. Based on this study, proximal and distal margins of 3 cm to create CTV are reasonable, although a 5-cm margin for gastroesophageal junction carcinomas should be considered. The radial margin on GTV to create CTV is not clearly defined; Radiation Therapy Oncology Group (RTOG) 0113 used a 1-cm margin radially.[12]

The CTV incorporates high-risk lymph node basins. In the aforementioned prospective evaluation of surgical specimens, Gao et al.[3] also reported that in 34 esophageal squamous cell carcinomas of the middle and lower esophagus, 14% of T1 and 41% of T2 to T4 lesions had nodal metastases. The most common site of nodal disease was left gastric (15%), followed by subcarinal (12%), paracardiac (9%), paraesophageal (9%), and paratracheal (6%). In 32 patients with gastroesophageal junction adenocarcinoma, 0% of patients with T1 lesions and 50% with T2 to T4 lesions had lymph node metastases. The most common sites were paraesophageal (47%), left gastric (44%), and paracardiac (41%). One patient (3%) had perisplenic nodal metastases and one (3%) had postmediastinal nodal metastases.

In general, periesophageal lymph nodes should be included in all patients. Inclusion of supraclavicular lymph nodes for proximal esophagus cancers and celiac lymph nodes for distal esophageal cancer has been variable in prospective trials, as described in Table 1. Risk for lymph node involvement is associated with T stage, and prophylactic coverage of celiac lymph nodes for T3/4 distal esophageal/gastroesophageal junction carcinoma should be considered. In upper thoracic carcinoma, the risk for cervical lymph nodes

Table 1 Radiation Field Size in Selected Prospective Trials

Trial	Dose (GyFx)	Margin on GTV Esophagus*	Prophylactic Nodal Coverage
RTOG 85-01[43]	50.4/28	5 cm C-C 2 cm radial	GE junction covered in all patients SCF if middle or upper 1/3 esophagus
Intergroup 0123[44]	50.4/28	5 cm C-C 2 cm radial	SCF if cervical esophagus Locoregional nodes included
RTOG 0113†	50.4/28	CTV: GTV + 4 cm C-C GTV + 1 cm radial PTV: CTV + 1-2 cm	SCF if above carina Celiac if distal esophagus Local-regional nodes included in CTV
RTOG 0246†	50.4/28	3 cm C-C 2 cm radial	SCF if above carina Celiac lymph nodes not included Periesophageal nodes included
EORTC[41]	37/10, split course	5 cm C-C 2 cm radial	SCF if above carina Celiac lymph nodes not included Periesophageal nodes included
University of Michigan[45]	45/25	5 cm C-C 2 cm radial	Uninvolved lymph nodes not included
Walsh et al.[46]	40/15	5 cm C-C 2 cm radial	Uninvolved lymph nodes not included
CALGB 9781†	50.4/28	5 cm C-C 2 cm radial	SCF if proximal esophagus Celiac lymph nodes if distal esophagus

Abbreviations: C-C, cranial-caudal; CALGB, Cancer and Leukemia Group B; CTV, clinical target volume; EORTC, Eastern Organization for Research and Treatment of Cancer; fx, fractions; GE, gastroesophageal; GTV, gross tumor volume; PTV, planning target volume; RTOG, Radiation Therapy Oncology Group; SCF, supraclavicular field.
*Margin is to block edge, unless otherwise specified.
†Not published in manuscript form. Description of radiation field available at www.rtog.or or www.CALGB.org.

is increased with advanced T stage and known mediastinal nodal disease; prophylactic radiation to the supraclavicular region should be strongly considered.[13] Inclusion or exclusion of adjacent nodal basins depends partly on radiation field size and dose to critical structures.

Although PET has promising usefulness in defining GTV, its added efficacy compared with EUS and CT in defining CTV is less clear. PET is often unable to detect nodal metastases smaller than 1 cm,[4] and therefore lacks sensitivity in detection of regional lymph node metastases.[9,14–17] PET has higher sensitivity and specificity compared with CT alone but has lower sensitivity compared with EUS.[14,18,19] Therefore, adding PET-CT to EUS and CT has not been proven to significantly alter CTV.[19]

Defining PTV

An additional margin must be added to CTV to account for uncertainty in daily setup caused by patient positioning and internal motion. Motion can arise because of respiration, peristalsis, and cardiac action, although respiration has the greatest effects on esophagus motion.[20] The distal esophagus is more mobile compared with the proximal esophagus.[21,22] Mean superior–inferior esophageal motion ranges from 4 to 10 mm in the literature, with recommended margins on CTV ranging from 13 to 18 mm,[22,23] and in the radial direction from 4 to 8 mm. Studies evaluating esophagus motion are summarized in Table 2. A 4D CT scan, which captures CT data at multiple phases of the respiratory cycle, can yield more information on esophagus motion in individual patients.[24]

Respiratory gating can be used to account for respiratory movement. In most respiratory gating systems, the position of the tumor at various phases of the respiratory cycle is correlated to an external fiducial marker placed on the patient's chest. During treatment, the radiation beam is only turned on during a particular phase of the respiratory cycle, and thus margin on the gross tumor can be reduced to account for respiratory motion. Although promising, respiratory gating must be used cautiously. A breathing pattern during a 4D CT scan obtained at simulation will not necessarily be identical to that during treatment, and

Table 2 Esophagus Motion

Author	Method	N	Location in Esophagus	Ant:Post (mm) Mean	Ant:Post (mm) SD	Lateral (mm) Mean	Lateral (mm) SD	Sup:Inf (mm) Mean	Sup:Inf (mm) SD
Chen et al.[23]	Daily MVCT	10	Any	2.6	2.1	4.2	4.7	3.7	5.5
Yaremko et al.[22]	4D CT	31	Any	2.9	0.5	1.2	0.2	10.0	0.9
			Thoracic	2.3	0.10	1.3	0.06	7.1	0.21
			Abdominal	3.2	0.20	1.3	0.11	9.6	0.34
Hashimoto et al.[20]	Fiducial marker	14	Any	4.0	2.6	3.5	1.8	8.3	3.8
Sasidharan et al.[47]	CT on rails	6	GEJ junction	0.6/0.5 Ant:Post	1.1/0.9 Ant:Post	0.6/0.5 L/R	1.4/1.0 L/R	NR	NR
			3.0 cm above GEJ	0.7/0.1 Ant:Post	1.1/0.2 Ant:Post	0.7/0.5 L/R	1.3/0.9 L/R	NR	NR
			4.5 cm above GEJ	0.3/0.2 Ant:Post	0.7/0.5 Ant:Post	0.3/0.4 L/R	0.7/0.9 L/R	NR	NR
Dieleman et al.[21]	4D CT	29	Upper	5*		5*			
			Middle	6*		7*			
			Lower	8*		9*			

Abbreviations: 4D, 4-dimensional; Ant:Post, anterior posterior; GEJ, gastroesophageal junction; L/R, left/right; MVCT, megavoltage CT; N, number of patients; NR, not reported; SD, standard deviation; Sup:Inf, superior inferior.
*Reported margin needed to cover 95% of all esophageal mobility, not mean.

the location of the target with relation to the external fiducial markers do not necessarily remain constant. Therefore, gating is associated with a potential danger of missing the target. Data on respiratory gating in esophageal carcinoma are limited.

In addition or as an alternative to gating, dampening techniques can be used to minimize respiratory motion. Examples of dampening include abdominal compression, breath hold, or active breath control. The latter technique uses a device the blocks airflow at a predetermined lung volume, thus providing temporary arrest of respiratory motion. As with respiratory gating, dampening techniques can potentially reduce the necessary margin around the target volume, and further study of their use in esophageal cancer is warranted.

Radiation Planning

3-D Conformal

Compared with radiographs or fluoroscopy, CT scan–based radiation therapy offers the advantage of improved visualization of anatomic structures and 3D reconstruction of target and critical structures. Using the 3D data, noncoplanar radiation therapy beams can be designed to conform to the beam's eye view of the target shape, improving the conformity of the treatment. The 3D data can also be used to generate dose–volume histograms (DVHs), allowing the percent volume of a structure receiving a certain radiation dose to be estimated. The CT dataset also provides information on tissue density, allowing the use of heterogeneity corrections, such that differences in radiation absorption based on tissue density can be accounted for in radiation therapy planning. RTOG trials for esophageal cancer have not generally used heterogeneity corrections, and therefore their impact on outcome is unknown.

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) also uses 3D data, but unlike conventional 3D radiation therapy, IMRT modifies dose intensity within each radiation portal. Treatment-planning computer software calculates the optimal dose intensity map in each beam to minimize dose to normal structures and deliver full dose to the target, with sharp decline of dose immediately adjacent to the target volume. Moderate to high doses to critical organs adjacent to the target volume can be reduced. However, lower doses of radiation are often delivered to a larger volume. The lungs, which are perhaps the primary critical organ of concern in thoracic esophageal cancer, seem to be sensitive to low-dose radiation delivered to a large volume.[25] Furthermore, movement of both target and

critical structures during radiation treatment can significantly alter the calculated dose distribution and result in unanticipated over- or underdosing of both target and avoidance structures. Therefore, using IMRT in thoracic and abdominal malignancies, which are subject to motion caused by functions such as respiration and bowel filling, remains challenging.

Retrospective planning studies comparing 3D conformal with IMRT treatment plans for esophagus cancer generally have shown IMRT to be associated with superior dose conformity and homogeneity in the target volume and reduction in V20 and V30 to the lung (percent volume of the lung receiving 20 and 30 Gy, respectively).[26–28] Data on V10 conflict, with one study showing increase in V10 with IMRT and another showing a decrease in V10.[26,27] A study by Mayo et al.[29] showed that V5, which has been shown to predict postoperative lung toxicity in esophageal cancer, was higher using IMRT compared with 3D conformal radiation. The risk to normal tissues from radiation therapy for esophageal cancer is discussed more fully in the following section.

Few clinical data exist on IMRT in esophageal cancer. Wang et al.[30] reported on 6 patients with cervical and upper thoracic esophagus cancer treated with IMRT using 5 to 9 fields. Although clinical response rate was high, skin and esophageal toxicity was significant and the recurrence rate was 50%. The authors concluded that innovative approaches are necessary. Clinical data supporting the use of IMRT in esophageal cancer currently are not sufficient to warrant its routine use. If used, respiratory gating or other measures to limit motion caused by breathing should be considered.

Normal Tissue Tolerance

Pulmonary Toxicity

Lung damage from radiation can present as pneumonitis 2 to 6 months after radiation treatment, and can range in severity from asymptomatic radiographic findings to clinical symptoms, including cough, dyspnea, and respiratory distress or, rarely, death. Fibrosis of the lung can develop months to years after radiation. Risk for radiation pneumonitis depends on total dose, volume of lung irradiated, and dose per fraction.

Most dose–volume parameters associated with pneumonitis have been reported in patients with lung cancer. However, these patients are more likely to have smoking history or underlying lung disease, and the dose–volume predictors of radiation pneumonitis may not be directly applicable to patients with esophageal cancer. As with lung cancer, pulmonary function testing should be considered before radiation in patients with a smoking history or known lung disease.

Wang et al.[25] from M. D. Anderson studied pulmonary complications, including pneumonia or acute respiratory distress syndrome, occurring within 30 days of surgery in patients treated with neoadjuvant chemoradiation for esophageal cancer. These acute complications are distinct from radiation pneumonitis, which is generally considered a subacute or late complication. On multivariate analysis, the only significant DVH predictor of pulmonary complications was the total volume of lung receiving a dose of 5 Gy (V5) or less, emphasizing that the volume of lung receiving low radiation dose is important.

Because concurrent chemotherapy is typically delivered in the treatment of esophageal carcinoma, lung tolerance doses identified in studies using concurrent chemotherapy are most appropriate. Table 3 describes DVH parameters in selected studies for esophagus and lung cancer with or without chemotherapy. The best predictors of radiation pneumonitis continue to be defined and it is unlikely that any single parameter is sufficient. V20 of less than 25% to 30%, mean lung dose of less than 15 to 20 Gy, relative V5 of less than 42%, and absolute V5 less than 3000 cm^3 have all been suggested as appropriate goals in radiation treatment planning.[25,31–33]

Heart Toxicity

Mechanisms of radiation-induced heart toxicity are complex and poorly understood. Damage to muscle, vasculature, valves, and nerves probably all contribute to some degree. Potential radiation-related cardiac toxicities include pericardial effusion, pericarditis, coronary artery disease, cardiomyopathy, valvular dysfunction, conduction abnormalities, and autonomic dysfunction.

Data from patients with Hodgkin's disease undergoing radiation suggest that mediastinal radiation doses of more than 40 Gy increase the risk for death from cardiac causes and pericarditis.[34,35] However, more detailed information on radiation tolerance of substructures within the heart and dose–volume data remain limited. Until more detailed information is available, it seems prudent to minimize the volume of heart receiving more than 40 Gy. As information matures and more detailed DVH data emerge on late

Table 3 Radiation Lung or Heart Toxicity Risk by Dose Volume Histogram Parameters

Author	N	% Concurrent Chemotherapy	Disease Site	Predictors of Toxicity	Toxicity End Point	Parameter	Occurrence
Lung							
Wang et al.[33]	223	100	Lung	V5	Pneumonitis ≥ grade 3*†	V5 ≤ 42%	3%
						V5 > 42%	38%
Tsujino et al.[32]	71	100	Lung	V20	Pneumonitis ≥ grade 2†	V20 ≤ 20% V20 21%–25% V20 26%–30% V20 ≥ 31%	9% 18% 51% 85%
Kim et al.[31]	76	58	Lung	MLD	Pneumonitis ≥ grade 3‡	< 10 Gy 10–15 Gy ≥ 15 Gy	0% 10% 45%
Graham et al.[48]	99	45	Lung	V20	Pneumonitis ≥ grade 2‡	V20 < 22% V20 22%–31% V20 32%–40% V20 ≥ 40%	0% 7% 13% 36%
Hernando et al.[49]	201	6	Lung	V30	Pneumonitis ≥ grade 1†	V30 ≤ 18% V30 > 18%	6% 24%
				MLD		MLD < 10 Gy MLD 11–20 Gy MLD 21–30 Gy MLD > 30 Gy	10% 16% 27% 44%
Kong et al.[50]	109	0	Lung	V20	Pneumonitis ≥ grade 2§	V20 < 20%	2%
						V20 20%–27%	15%
						V20 ≥ 27%	48%
						MLD < 14 Gy	4%
						MLD ≥ 14 Gy	33%
Wang et al.[25]	110	100	Esophagus	VS5	Postoperative complications (within 30 days)	V5 > 3000 cm^2	< 5%
Heart							
Wei et al.[51]	101	100	Esophagus	V30	Pericardial effusion	V30 < 46% V30 > 46%	13% 73%
Martel et al.[52]	57	100	Esophagus	Fraction size	Pericardial effusion	< 3.5 Gy ≥ 3.5 Gy	0% 26%
				Bioaverage dose > 27 Gy		Not stated	Not stated
				Biomaximum dose > 47 Gy		Not stated	Not stated
Marks[53]	114	2	Left breast	< 5% of left ventricle in radiation field	New cardiac perfusion deficit at 1 year	≤ 5% > 5%	19% 53%
Hancock et al.[35]	635	0	Hodgkin's	Total dose mediastinum 40–45 Gy	Death from cardiac cause		1% RR 29.6
Cosset et al.[34]	199	0	Hodgkin's	Total dose mediastinum ≥ 41 Gy	Pericarditis		RR 3.25
				Fraction size > 3 Gy			RR 2.0

Table 3 Continued

Author	N	% Concurrent Chemotherapy	Disease Site	Predictors of Toxicity	Toxicity End Point	Parameter	Occurrence
Tripp et al.[54]	20	100	Esophagus	Trend (P = .12) for higher left ventricle V20	Decline in ejection fraction	Not stated	Not stated

Abbreviations: MLD, mean lung dose; RR, relative risk; V5/20/30, percent volume receiving 5/20/30 Gy; VS5, absolute volume receiving 5 Gy.
*National Cancer Institute Common Toxicity Criteria (CTCAE) version 3.0.
†National Cancer Institute CTCAE version 2.0.
‡Radiation Therapy Oncology Group toxicity criteria.
§Based on Southwestern Oncology Group toxicity criteria.

toxicity in patients undergoing 3D conformal radiation therapy, more specific recommendations regarding dose to substructures of the heart will be forthcoming. Table 3 describes studies evaluating predictors of radiation-associated cardiac toxicity.

Radiation Dose

For thoracic and gastroesophageal junction carcinoma, conventional radiation dose remains 50 to 50.4 Gy in 1.8- to 2.0-Gy fractions, and generally does not differ if radiation is delivered in the definitive, adjuvant, or neoadjuvant settings. Intergroup trial 0123 randomized 236 patients with esophageal carcinoma to 50.4 or 64.8 Gy radiation therapy, both delivered with concurrent chemotherapy, and showed no difference in local control or survival between the groups.[36]

RTOG 92-07 was a phase I and II study of external beam radiation (50 Gy) plus esophageal brachytherapy boost (15 Gy high-dose rate or 20 Gy low-dose rate).[37] Esophageal fistula occurred in 12% of patients, and life-threatening toxicity occurred in 24%. The treatment-related death rate was 10%. Local control was not superior to historical controls. Therefore, dose escalation using brachytherapy boost is not supported by this trial. Table 4 summarizes local failure and survival rates related to radiation dose.

Although radiation dose escalation is not recommended in thoracic and gastroesophageal junction carcinoma, dose escalation greater than 50 Gy has been used in cervical squamous cell carcinoma with excellent local control rates (77%–88%).[38,39] A patterns-of-care study from Canada reported the most commonly used dose for cervical esophageals squamous cell carcinoma was 60 Gy.[40] Although the optimal dose in this setting is not clearly defined, dose escalation greater than 50 Gy is reasonable.

Dose-per-fraction is generally 1.8 to 2.0 Gy. The EORTC evaluated split-course radiation using a total dose of 37 Gy given in 10 fractions followed by surgery.

Table 4 Radiation Dose and Outcome in Prospective Trials of Esophageal Carcinoma

Trial	Number of Patients	Proportion of Patients With T3–4 Tumors (%)	Radiation Dose (Gy)	Local Failure Rate	Survival
RTOG 85-01[43]	61	8	50	45% (crude) 47% (2-y)	36% (2-y) 30% (3-y) 26% (5-y)
INT 0123[44]	109	43	50	55% (crude) 52% (2-y)	40% (2-y)
INT 0123[44]	109	48	64	50% (crude) 56% (2-y)	31% (2-y)
Stahl et al.[55]	86	100	> 65	51% (crude) 58% (2-y)	35% (2-y)
RTOG 9207[37]	49	0	65–70	63% (crude)	31% (2-y) 29% (3-y)

Abbreviation: RTOG, Radiation Therapy Oncology Group.
Local failure rate includes local recurrence and local persistence.

Postoperative mortality was 17%, compared with 5% in a surgery-alone arm (P = .012).[41] The large dose per fraction was postulated as an explanation for the higher-than-expected postoperative mortality rate in the chemoradiation arm. In a meta-analysis of surgery with or without neoadjuvant chemoradiation, Fiorica et al.[42] noted increased postoperative mortality with the use of neoadjuvant chemoradiation (P = .007). However, this difference did not reach statistical significance when trials using greater than 2 Gy per fraction were excluded. Radiation pneumonitis risk is increased with higher dose per fraction, and radiation fraction size greater than 3 Gy has been associated with higher risk for heart toxicity.[34] Taken together, these observations support the use of a fraction size of 2 Gy or less.

Esophageal cancer is currently a treatable but rarely curable disease, as exemplified by its continued ranking among the top 10 causes of cancer deaths in United States men.[1] With continuing advances in imaging, treatment planning, and treatment delivery, radiation therapy may afford greater success in outcomes when used as part of a multidisciplinary approach to managing patients with esophageal cancer.

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