Samuel Bak. BK1509 *Questionable*. Oil on canvas, 18″ × 24″.

Neoadjuvant chemoradiotherapy followed by surgical resection is the current standard of care for localized cancer of the esophagus.

Radiation Therapy and Esophageal Cancer

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Background: Squamous cell carcinoma and adenocarcinoma account for more than 90% of all esophageal cancer cases. Although the incidence of squamous cell carcinoma has declined, the incidence of adenocarcinoma has risen due to increases in obesity and gastroesophageal reflux disease.

Methods: The authors examine the role of radiation therapy alone (external beam and brachytherapy) for the management of esophageal cancer or combined with other modalities. The impact on staging and appropriate stratification of patients referred for curative vs palliative intent with modalities is reviewed. The authors also explore the role of emerging radiation technologies.

Results: Current data show that neoadjuvant chemoradiotherapy followed by surgical resection is the accepted standard of care, with 3-year overall survival rates ranging from 30% to 60%. The benefit of adjuvant radiation therapy is limited to patients with node-positive cancer. The survival benefit of surgical resection after chemoradiotherapy remains controversial. External beam radiation therapy alone results in few long-term survivors and is considered palliative at best. Radiation dose-escalation has failed to improve local control or survival. Brachytherapy can provide better long-term palliation of dysphagia than metal stent placement. Although three-dimensional conformal treatment planning is the accepted standard, the roles of IMRT and proton therapy are evolving and potentially reduce adverse events due to better sparing of normal tissue.

Conclusions: Future directions will evaluate the benefit of induction chemotherapy followed by chemoradiotherapy, the role of surgery in locally advanced disease, and the identification of responders prior to treatment based on microarray analysis.

Introduction

In 2012, an estimated 17,460 cases of esophageal cancer were diagnosed in the United States and approximately 15,070 people died of the disease.[1] Worldwide, an estimated 482,000 new esophageal cancer cases were diagnosed and approximately 407,000 deaths occurred in 2008.[2] Squamous cell carcinoma (SqCC) and adenocarcinoma (AC) account for more than 90% of all esophageal cancer cases. Although the incidence of SqCC has declined due to long-term reductions in smoking and alcohol consumption, the incidence of esophageal AC has risen as a result of increases in obesity and gastroesophageal reflux disease.[1]

The management of locoregional or locally advanced esophageal or gastroesophageal junction cancer has shifted from surgery or radiation single modality approaches to trimodality with the addition of chemotherapy. A Radiation Therapy Oncology Group study (RTOG 8501) demonstrated a survival benefit with the addition of platinum-based chemotherapy to radiation compared with radiation alone for patients with nonsurgical esophageal cancer.[3,4] Several meta-analyses have also confirmed the survival benefit of trimodality therapy over surgery alone.[5-10]

It has been suggested that histology and tumor location within the esophagus should dictate the course of therapy. This has led to significant changes in the TNM staging system for esophageal cancer,[11] including the change that cancers within the first 5 cm of the proximal stomach involving the esophagus are now classified as esophageal cancers. In addition, separate staging is performed for AC and SqCC and involves tumor grade and location.[11] However, data to support different treatment regimens based on histology or location are limited. The treatment pathway at our institute is to treat locally advanced and resectable SqCC and AC for the upper, middle, and lower esophagus with neoadjuvant chemoradiotherapy followed by surgical resection. Cervical esophageal cancers are treated definitively with radiation doses, field design, and chemotherapy regimens similar to head and neck cancers.

In this review, we report on the literature examining the role of radiation therapy in the management of esophageal cancer. We review data on radiation alone, chemoradiation, trimodality therapy, and brachytherapy (BT). Finally, we examine emerging radiation technologies such as intensity-modulated radiotherapy (IMRT), image-guided radiation therapy, proton therapy, endoscopic ultrasonography (EUS)-guided fiducial placement, and positron emission tomography (PET) fusion.

Radiation Alone
Definitive Radiation
Radiation therapy alone results in poor local control and poor survival. Local recurrence rates range from 52% to 77% with standard fractionation.[4,12] Five-year overall survival (OS) rates range from 0% to 21%.[4,13-18] In the largest review, which comprised 49 series and included 8,500 patients with esophageal cancer treated with radiation therapy alone, 1-, 2-, and 5-year OS rates were 18%, 8%, and 6%, respectively.[19] The control arm of RTOG 8501, in which patients were treated with 64 Gy without chemotherapy, resulted in a 5-year OS rate of 0%.[3,4]

Preoperative Radiation
Several attempts have been made to improve local control and survival by combining radiation and surgery. Many randomized trials were conducted with various hypofractionated radiation regimens to lower total doses and shorter intervals from end of radiation to surgery compared with modern treatment regimens. The 5-year OS rates ranged from 9% to 30% for surgery alone and 9% to 45% for radiation and surgery.[20-25] Dose regimens included 20 Gy in 10 fractions,[20] 33 Gy in 10 fractions,[21] 39 to 45 Gy in 8 to 12 fractions,[23] and 35 Gy in 20 fractions.[24] The time to surgery also varied, ranging from 8 days or less[21,23] to 2 to 4 weeks.[24] A meta-analysis of randomized trials was conducted to assess the benefit of neoadjuvant radiation compared with surgery alone.[26] Five randomized trials with a combined 1,147 patients were identified for analysis. There was a trend for increased survival with preoperative radiation. With a median follow-up of 9 years, the hazard ratio (HR) was 0.89 (95% confidence interval [CI], 0.78–1.01) in patients with mostly SqCC, suggesting a 11% reduction in mortality with an absolute survival benefit of 3% at 2 years and 4% at 5 years ($P = .062$).

Postoperative Radiation
Adjuvant radiation after resection was attempted to improve local control and survival. An early retrospective analysis showed that adjuvant radiation improved survival in patients with node-negative[27] and node-positive cancer[28]; however, two randomized controlled trials (RCTs) failed to show any survival benefit despite improvements in locoregional control, which was associated with high rates (37%) of gastric complications.[29,30] Radiation regimens included 45 to 55 Gy delivered in 5 to 6 weeks[30] and 52.5 Gy in 15 fractions[29] using two-dimensional (2D) techniques.

In conclusion, radiation alone should be considered only for palliative treatment and should not be considered for curative intent.

Chemoradiotherapy
Chemotherapy delivered concurrently with radiation has been shown in multiple malignancies to improve local control and survival. The addition of chemotherapy serves two purposes, including radiosensitization and control of micrometastatic disease. Several randomized trials have demonstrated local control and survival benefit from chemoradiotherapy in patients with SqCC of the esophagus (Table 1).[3,4,31,32] However, two randomized trials, including a large Eastern Cooperative Oncology Group (ECOG) study, failed to show a survival benefit between radiation alone and radiation in combination with bleomycin[33] or radiation alone and radiation with 5-fluorouracil (5-FU), bleomycin, and mitomycin C (MMC).[34] The ECOG EST 1282 trial was based on earlier data that showed a synergistic effect of MMC and 5-FU with radiation for the treatment of SqCC of the anus.[31] In

this trial, 119 patients with SqCC of the esophagus were randomized to receive radiation alone (40 Gy) or radiation with MMC/5-FU. Patients not fit for surgery received an additional 20 Gy. There was a statistically significant difference in survival. Median and 5-year survival rates with and without chemoradiation were 14.8 months and 9% compared with 9.2 months and 7%, respectively. Although surgery was not part of randomization, there was a trend for increased survival in patients who underwent resection (P = .07). A survival advantage was reported in an European Organisation for Research and Treatment of Cancer (EORTC) randomized trial of chemoradiation vs radiation alone for esophageal cancer.[32] Patients were randomized to 20 Gy in 5 fractions or the same radiation with cisplatin. Median survival rates for chemoradiation vs radiation alone were 10.5 and 7.8 months, respectively. A randomized trial from the Radiation Therapy Oncology Group (RTOG 8501) demonstrated a significant survival benefit with the addition of concurrent and adjuvant cisplatin and 5-FU to radiation for patients with esophageal cancer.[4] Patients were randomly assigned to radiation alone (64 Gy) or chemoradiation (50 Gy) with cisplatin and 5-FU concurrently; an additional 2 cycles were adjuvantly given to the study participants. More than 80% of patients had SqCC. At the first interim analysis, a survival benefit was detected after the first 121 patients were enrolled and the trial was prematurely stopped; however, an additional 69 patients were enrolled only in the chemoradiation arm. In an updated analysis, the researchers reported that the 5-year survival rate for all patients receiving chemoradiation was 26%, and it was 0% for patients receiving radiation only.[3] The 5-year survival rates for randomized and nonrandomized patients who received chemoradiation were 26% and 14%, respectively. The 8-year survival rate for patients randomized to chemoradiation was 22%, and

no deaths that occurred after 5 years were due to esophageal cancer. A meta-analysis of 19 randomized trials of nonsurgical patients with 11 concurrent and 8 sequential chemoradiotherapy studies concluded that concurrent chemoradiation provided significant reduction in mortality (HR = 0.73; 95% CI, 0.64–0.84; P < .05).[35] There was an absolute 2-year survival benefit of 4%, and the absolute reduction of local recurrence rate was 12%. The results from sequential chemoradiotherapy studies showed no significant benefit in survival or local control but significant toxicities.

Despite improved local, regional, and distant control and increased survival, roughly 50% of patients treated with chemoradiation will have persistent local disease or recurrence (Table 1).[3,4,31,32] In an attempt to improve local control and survival, a radiation dose-escalation phase II trial was conducted in 45 patients with a radiation dose of 64.8 Gy in 7 weeks concurrent with cisplatin and 5-FU.[36,37] Median and 5-year survival rates were 20 months and 20%, respectively, and the local failure rate was 40%. Six patients died of treatment-related complications. Although the intensive neoadjuvant regimen was not considered superior to the experimental arm of RTOG 8501, a phase III trial was conducted that compared standard dose standard-dose (50.4 Gy in 5.5 weeks) chemoradiation to high-dose (64.8 Gy in 7 weeks) chemoradiation.[38] No difference was seen in survival or local control. Eleven deaths occurred in the high-dose arm and 7 deaths in the 50.4-Gy arm.

These two randomized trials established the standard of care for definitive treatment of esophageal cancer as 50.4 Gy concurrent with cisplatin/5-FU. Although the entire esophagus was treated to 30 Gy followed by a 20-Gy boost to gross tumor volume with a 5-cm craniocaudal margin to block edge, the INT 0123 study established treating gross tumor volume with a 5-cm craniocaudal margin to 50.4 Gy as the new standard treatment field.[38]

Table 1. — Trials of Chemoradiation vs Radiation Alone in Esophageal Cancer

Study	No. of Patients	Radiation Dose	Chemotherapy	Median Survival (mos)	5-yr Overall Survival (%)	Persistent and Local Recurrence (%)
ECOG EST 1282[31]	59	40–60 Gy/6–7 wks	5-FU/mitomycin C	14.8	9	–
	60		None	9.2	7	
RTOG 8501[3,4]	61	50 Gy/5 wks	Cisplatin/5-FU	14.1	26	46
	60	64 Gy/6.4 wks	None	9.3	0	68
	69[a]	50 Gy/5 wks	Cisplatin/5-FU	–	14	58
EORTC GTCCG[32]	110	20 Gy/1 wk	Cisplatin	10.5	8	59
	111		None	7.8	10	69.7

[a] Nonrandomized patients.
5-FU = 5-fluorouracil.

Adjuvant Chemoradiotherapy

In patients with node-positive AC of the gastroesophageal junction, adjuvant chemoradiotherapy is the standard of care based on results from the INT 0116 study.[39] In this seminal trial, 556 patients with resected AC of the stomach or gastroesophageal junction were randomly assigned to surgery plus postoperative chemoradiotherapy (45 Gy with 5-FU) or surgery alone. Median and 3-year survival rates in the chemoradiotherapy group were 36 months and 50% compared with 27 months and 41% in the surgery alone group (*P* = .005). A Chinese study of stages II and III SqCC of the esophagus was conducted in which patients were randomized into three groups: preoperative chemoradiation (n = 80), postoperative chemoradiation (n = 78), and surgery alone (n = 80).[40] The radiation dose was 40 Gy in 4 weeks concurrent with cisplatin and paclitaxel. OS was significantly better in patients treated with postoperative and preoperative chemoradiation than in those treated with surgery alone. For patients receiving postoperative chemoradiation, median, 5-, and 10-year OS rates were 48 months, 42.3%, and

Table 2. — Selected Trials of Neoadjuvant Chemoradiation vs Surgery Alone in Esophageal Cancer

Study	No. of Patients	Radiation Dose	Chemotherapy	Pathological Complete Response (%)	Median Survival	3-yr Overall Survival (%)	P
Nygaard[24] [a] [b]	50	None	None	–	–	9	.009*
	58	None	Cisplatin/bleomycin			3	
	56	35 Gy/4 wks	None			21	
	53	35 Gy/4 wks	Cisplatin/bleomycin			17	
Le Prise[42] [a] [b]	41	20 Gy/2 wks	Cisplatin/5-FU	–	10 mos	19	NS
	45	None	None		10 mos	14	
Apinop[43] [a] [b]	35	40 Gy/4 wks	Cisplatin/5-FU	20	10 mos	–	NS
	34	None	None		10 mos		
Bosset[44] [a] [b]	143	18.5 Gy/1 wk[c]	Cisplatin	26	18.6 mos	32	NS
	139	None	None		18.6 mos		
Walsh[45] [b]	58	40 Gy/3 wks	Cisplatin/5-FU	25	16 mos	32	.01
	55	None	None		11 mos	6	
Urba[46] [d]	50	45 Gy (1.5 Gy twice daily)	Cisplatin/5-FU/vinblastine	28	17 mos	30	.15
	50	None	None		18 mos	16	
Lee[47] [b]	51	45.6 Gy (1.2 Gy twice daily)	Cisplatin/5-FU	43	28 mos	–	.69
	50	None	None		27 mos		
Burmeister[48] [e]	128	35 Gy/3 wks	Cisplatin/5-FU	12.5	22 mos	–	.57
	128	None	None		19 mos		
Tepper[49] [d]	30	50.4 Gy/5.5 wks	Cisplatin/5-FU	40	4.5 yrs	39 (5-yr)	.002
	26	None	None		1.8 yrs	16 (5-yr)	
Lv[40] [b]	80	40 Gy/4 wks	Cisplatin/paclitaxel	–	53 mos	44 (5-yr)	.04
	80	None			36 mos	34 (5-yr)	
Mariette[50] [f]	97	45 Gy/5 wks	Cisplatin/5-FU	–	32 mos	48.6	.68
	98	None	None		45 mos	55.2	
van Hagen[51] [d]	175	41.4 Gy/4.5 wks	Carboplatin/paclitaxel	29	49 mos	47 (5-yr)	.003
	188	None	None		24 mos	34 (5-yr)	

* Radiation vs no radiation.
[a] Sequential chemotherapy and radiation.
[b] 100% of patients had squamous cell carcinoma.
[c] Given twice split course.
[d] 75% of patients had adenocarcinoma.
[e] 62% of patients had adenocarcinoma.
[f] 71% of patients had squamous cell carcinoma.
5-FU = 5 fluorouracil, NS = not significant.

24.4% compared with 36 months, 33.8%, and 12.5% in the surgery-only group. No difference was seen in survival between patients receiving preoperative or postoperative chemoradiation. However, a randomized trial of 45 patients with resected esophageal SqCC that compared adjuvant chemotherapy with chemoradiotherapy failed to show a survival benefit.[41] In addition, no survival benefit was reported in patients with node-positive cancer. However, caution must be taken when making conclusions about these results because the study was underpowered.

Neoadjuvant Chemoradiation
Randomized Trials
Several randomized trials have been conducted to determine the benefit of neoadjuvant chemoradiotherapy (Table 2).[24,40,42-51] Four trials were conducted with preoperative sequential chemotherapy and radiation[24,42-44] and eight trials were performed with chemoradiotherapy.[40,45-51] The sequential trials were restricted to SqCC and all but three of the concurrent trials were mostly AC. None of the four trials of sequential therapy showed a survival benefit.[24,42-44] However, the combined radiation arms in the second Scandinavian trial showed a survival benefit compared with the nonradiation arms.[24] In addition, chemotherapy was not associated with a survival benefit. Although preoperative therapy in the EORTC trial was associated with longer disease-free survival (DFS), longer interval of local control, and lower rates of cancer-related deaths, postoperative deaths were higher and were attributed to the hypofractionated radiation regimen used.[44] Of the eight randomized trials of neoadjuvant chemoradiation,[40,45-51] four showed a survival benefit.[40,45,49,51] In the Irish study, 113 patients were randomized to 40 Gy in 3 weeks concurrent with cisplatin and 5-FU followed by surgery vs surgery alone.[45] The trial resulted in a significant survival benefit with median and 3-year survival rates of 16 months and 32% for the chemoradiation group and 11 months and 6% for the surgery-only group, respectively (P = .01). However, survival in the surgery-only arm was lower compared to the other randomized trials (Table 2). Tepper et al[49] intended to randomize 475 patients to neoadjuvant chemoradiotherapy with 50.4 Gy over 5.5 weeks concurrent with cisplatin and 5-FU and surgery or surgery alone in a Cancer and Leukemia Group B study; however, the trial was closed due to poor accrual, with only 56 patients enrolled. Median and 5-year survival rates were 4.5 years and 39% for patients receiving chemoradiation and 1.8 years and 16% for patients receiving only surgery, respectively (P = .002). Although a study

by Urba et al[46] showed that 3-year survival almost doubled in patients receiving chemoradiation, the study was also underpowered to detect a significant difference. Rather, the study was powered to detect an increase in median OS from 1 year to 2.2 years. In the CROSS trial,[51] 363 patients were randomized to neoadjuvant chemoradiation with 41.4 Gy radiation in 4.5 weeks concurrent with carboplatin and paclitaxel followed by surgery or surgery alone. Median and 3-year survival rates were 49 months and 59% for the chemoradiation group and 26 months and 48% for the surgery-only group, respectively (P = .011). A 3-arm study that took place in China, in which patients with SqCC were randomized to preoperative chemoradiation, postoperative chemoradiation, or surgery alone, showed a survival benefit for both preoperative and postoperative chemoradiation.[40] A recent French trial (FFCD9901)[50] determined the effect of preoperative chemoradiation in stages I and II esophageal cancers (71% were SqCC). No difference in survival was seen, and postoperative 30-day mortality rates trended higher in patients receiving chemoradiation (7.3% vs 1.1%; P = .054).

Meta-Analyses
Several meta-analyses have been published to examine survival after chemoradiotherapy and surgery compared with surgery alone for esophageal cancer (Table 3).[5-10,52] All but one analysis[52] showed a significant reduction in mortality when chemoradiotherapy was added to surgery.[5-9] Urschel et al[7] looked at nine RCTs that included 1,116 patients and concluded that 3-year survival was improved with chemoradio-

Table 3. — Meta-Analyses of Preoperative Chemoradiation vs Surgery in Esophageal Cancer

Study	No. of Studies	No. of Patients	RR/OR/HR (95% CI)	P
Urschel[7]	9	1,116	0.66 (0.47–0.92) (3-yr)	.016
Fiorica[8]	6	764	0.53 (0.31–0.92) (3-yr)	.03
Greer[52]	6	738	0.86 (0.74–1.01)	.07
Gebski[5]	10	1,209	0.81 (0.70–0.93) (2-yr)	.002
Jin[6]	11	1,308	1.46 (1.07–1.99) (5-yr)	.02
Kranzfelder[10]	9	1,099 (100% SqCC)	0.81 (0.70–0.95)	.008
Sjoquist[9]	12	1,854	0.78 (0.70–0.88)	< .0001

CI = confidence interval, HR = hazard ratio, OR = odds ratio, RR = relative risk, SqCC – squamous cell carcinoma.

therapy (odds ratio [OR] = 0.66; 95% CI, 0.47–0.92; P = .016). There was a trend toward increased operative mortality (OR = 1.63; 95% CI, 0.99, 2.68; P = .053), and survival was most pronounced with concurrent chemoradiotherapy (OR = 0.45; 95% CI, 0.26–0.79; P = .005) compared with sequential therapy (OR = 0.82; 95% CI, 0.54–1.25; P = .36). Fiorica et al[8] reviewed six RCTs comprising 764 patients and concluded that chemoradiotherapy plus surgery compared with surgery alone significantly reduced the 3-year mortality rate (OR = 0.53; 95% CI, 0.31–0.92; P = .03). The risk for postoperative mortality was higher in the group receiving chemoradiotherapy plus surgery (OR = 2.10; 95% CI, 1.18–3.73; P = .01). A meta-analysis of 10 RCTs including 1,209 patients determined that there was a 19% reduction in mortality with patients receiving chemoradiotherapy (HR = 0.81; 95% CI, 0.70–0.93; P = .002), which corresponded to a 13% absolute difference in survival at 2 years regardless of histology.[5] Jin et al[6] concluded from 11 RCTs including 1,308 patients that 5-year survival was lower in patients assigned to surgery alone (OR = 1.46; 95% CI, 1.07–1.99; P = .02), and the benefit of radiation was restricted to patients with AC. In addition, postoperative mortality was increased with chemoradiotherapy (OR = 1.68; 95% CI, 1.03–2.73; P = .04). Kranzfelder et al[10] found similar results for patients with SqCC who were treated with neoadjuvant chemoradiation (HR = 0.81; 95% CI, 0.7–0.95; P = .008). Interestingly, it was also concluded that definitive chemoradiation did not demonstrate any survival benefit over other curative strategies. More recently, the largest meta-analysis conducted looked at 12 RCTs with a total of 1,854 patients comparing chemoradiation and surgery vs surgery, revealing that the HR for all-cause mortality for patients receiving neoadjuvant chemoradiotherapy was 0.78 (95% CI, 0.70–0.88; P < .0001), and this benefit was regardless of histology.[9]

Barrett's Esophagus After Chemoradiotherapy
Tumor response to chemoradiation is well described; however, little is known about the effect on Barrett's esophagus, which is a precursor to AC. Barthel et al[53] analyzed 43 patients with stage I to IVA esophageal AC associated with Barrett's esophagus who were treated with either neoadjuvant or definitive chemoradiation therapy and underwent either esophagectomy or surveillance. Barrett's esophagus persisted after chemoradiation therapy in 40 (93%) of the 43 cases studied. A total of 27 patients were treated with neoadjuvant chemoradiation therapy and esophagectomy, and persistent Barrett's esophagus was detected in all surgical specimens (100%). Pathological complete tumor response was seen in 16 (59%) of the 27 cases, and 14 (88%) of the 16 patients who received definitive chemoradiation therapy had persistent Barrett's esophagus determined by surveillance endoscopy. Persistent Barrett's esophagus after chemoradiation can undergo malignant transformation; therefore, it requires either surgical resection or ablative techniques like cryotherapy.[53,54]

Preoperative Chemotherapy vs Chemoradiotherapy
In the MAGIC trial,[55] perioperative chemotherapy was associated with a significant survival benefit in gastric and gastroesophageal ACs. Data continued to emerge that suggested that neoadjuvant chemoradiation was associated with higher survival than chemotherapy alone. The German POET study[56] was a randomized trial of preoperative chemotherapy compared with preoperative chemotherapy followed by chemoradiation in patients with gastroesophageal AC. Unfortunately, the trial was stopped due to poor accrual after only 125 of the intended 354 patients were enrolled in the study. Induction chemotherapy included cisplatin, leucovorin, and 5-FU, and the radiation dose was 30 Gy in 3 weeks concurrent with cisplatin and etoposide. With a median follow-up of 46 months, there was a trend for increased survival with radiation. The 3-year survival rate for the patients receiving radiation was 47% vs 27% for patients treated with preoperative chemotherapy alone (P = .07). Although this result was not significant, preoperative chemoradiation after chemotherapy was accepted as the new standard. A randomized phase II trial comparing 75 patients receiving preoperative chemotherapy or preoperative chemotherapy followed by chemoradiotherapy[57] failed to show a survival benefit; however, there was a significant difference in pathological response and R0 resections favoring radiation. A recent meta-analysis suggested a trend toward increased survival for patients receiving preoperative chemoradiation compared with preoperative chemotherapy (HR = 0.88; 95% CI, 0.76–1.01; P = .07).[9]

Role of Surgery
The role of surgery in the management of locally advanced esophageal cancer is controversial. A patterns-of-care study involving 400 patients undergoing esophagectomy from 65 different institutions showed that radiation therapy as part of primary treatment was associated with higher survival.[58] A study from the Los Angeles County Cancer Surveillance Program[59] involving 2,233 patients showed that chemoradiation and surgery were associated with a survival benefit compared with chemoradiation alone. The median survival was 25.2 months for trimodality therapy vs 12.3 months for chemoradiation alone (HR = 0.66; 95% CI, 0.56–0.77; P < .001) for both AC and SqCC. In the ECOG EST 1282 trial, patients with SqCC of the esophagus were randomized to receive radiation

alone (40 Gy) or radiation with MMC/5-FU.[31] Although surgery was not part of randomization, there was a trend for increased survival in patients who underwent resection (P = .07). PET has been increasingly used to determine response to neoadjuvant therapy in esophageal cancer. Although it was shown that a negative PET scan after therapy was a poor predictor of pathological complete response,[60] Monjazeb et al[61] showed that in patients with a negative PET scan after therapy, no difference was reported in survival associated with surgical resection.

Three randomized trials have addressed the role of surgery. In a German trial, 172 patients with locally advanced SqCC of the esophagus were randomly allocated to either induction chemotherapy (cisplatin, etoposide, 5-FU, leucovorin) followed by chemoradiotherapy (40 Gy in 4 weeks with cisplatin and etoposide) followed by surgery (arm A) or the same induction chemotherapy followed by chemoradiotherapy and then a radiation boost of 15 Gy (1.5 Gy twice daily) for obstructing tumors or 20 Gy externally delivered followed by BT boost (4 Gy × 2 to 5 mm) (arm B).[62] The study had a median follow-up time of 6 years and found that OS was equivalent among the groups. Median and 3-year OS rates for arm A compared with arm B were 16.5 months and 31.3% and 14.9 months and 24.4%, respectively. Progression-free survival, local control, and treatment-related mortality were significantly higher in the surgery arm. In a French trial, FFCD 9102,[63] 444 patients received 2 cycles of cisplatin and 5-FU and either conventionally fractionated radiation (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concurrently. Patients were randomly assigned to surgery (arm A) or continuation of chemoradiation (arm B). There was no difference in survival between the two arms. Median and 2-year OS rates were 17.7 months and 34% for arm A compared with 19.3 months and 40% for arm B. Local control and treatment-related mortality were significantly higher in arm A. A prospective randomized trial comparing the efficacy and survival outcome by chemoradiation with esophagectomy as a curative treatment was conducted on 80 patients with SqCC of the mid and lower thoracic esophagus.[64] Those receiving chemoradiation were given cisplatin and 5-FU and 50 to 60 Gy radiation concurrently. With a median follow-up time of 17 months, there was no difference in OS or DFS. Patients who underwent surgery had cancer that tended to recur in the mediastinum, while patients receiving chemoradiation had recurrence in the cervical and abdominal lymphatics. Finally, a meta-analysis of three randomized trials of 512 patients reported by Kranzfelder et al[10] comparing definitive chemoradiotherapy vs neoadjuvant therapy followed by surgery and surgery alone showed lower risk of mortality with definitive treatment (HR = 7.60,

95% CI,1.76–32.88, P = .007) but no differences in OS among treatment groups.

Brachytherapy

Esophageal BT is a form of intraluminal BT and consists of the placement of an endoesophageal catheter down the esophagus usually in the form of a nasogastric tube, although the tube can alternatively be orally placed. Subsequently, a radioactive source is moved down the tube to deliver a high dose of radiation to the luminal component of the tumor. Typically, the treatments are short in duration, lasting less than 5 minutes. Because BT precisely delivers the radiation dose to the tumor in an internal fashion, it can better spare normal surrounding tissues such as the lungs, heart, and liver compared with external beam radiation therapy (EBRT). BT has been used primarily in two settings, either as palliation for locally advanced obstructing or bleeding tumors or as a boost to EBRT for the definitive management of nonsurgical candidates.

Esophageal cancer, which presents with advanced disease, has a poor prognosis. For this reason treatment is commonly palliative. Various methods of palliation have been employed to improve patient quality of life and maintain normal or near normal swallowing function until death occurs due to progression of systemic disease. Palliative options include surgical bypass, cryotherapy, laser, chemotherapy, stenting, and EBRT. A combination of these modalities in advanced cases has marginally improved results at the cost of increased toxicity. The advent of intraluminal BT in the late 1980s allowed the noninvasive delivery of a high dose of radiation to the intraluminal tumor delivered over a short period time. To this end, there have been several investigations evaluating the palliative ability of BT. Several series are looking at single-fraction palliative BT; however, this approach has been shown to be inferior to multifraction BT. Table 4 lists important esophageal BT studies.[4,38,65-68] One multifraction prospective study performed in South Africa[69] involved 172 patients with advanced esophageal cancer. In this dose-escalation trial, patients were randomized to receive either 12 Gy in 2 fractions (arm A), 16 Gy in 2 fractions (arm B), or 18 Gy in 3 fractions (arm C). Treatment was delivered weekly and prescribed at 1 cm from the source axis. Patients were subsequently followed monthly and assessed for dysphagia relief and complications. At 12 months, the OS rate for the entire group was 19.4%; 21 patients died prior to completion of treatment. Patients who underwent treatment with a higher dose had a better OS rate (arm A: 9.8%; arm B: 22.5%; arm C: 35.3%, not significant [NS]). At 12 months, the dysphagia-free survival rate was 28.9% (arm A: 10.8%; arm B: 25.4%; arm C: 39.0%, NS). Forty-three

Table 4. — Selected Studies of Esophageal Brachytherapy

Study	No. of Patients	EBRT Dose	Brachytherapy Dose/Fractions	Chemotherapy	Grade ≥ 3 Toxicity (%)	Local Control (%)	Overall Survival (%)
Calais[65]	53	60 Gy	10 Gy/2	Cisplatin/5-FU/mitomycin C	23/7	74	27 (3-yr)
RTOG 9207[66]	50	50 Gy	15 Gy/3	Cisplatin/5-FU	58/26	77	48 (1-yr)
Vuong[67]	53	50 Gy	20 Gy/5	Cisplatin/5-FU	NA	75	28 (5-yr)
JASTRO[68]	103	60 Gy / 70 Gy	10 Gy/5 / None	None	11.6 / 5.9	NA	20 (5-yr)
RTOG 8501[4]	121	50 Gy / 64 Gy	None	Cisplatin/5-FU None	23[a] / 29[a]	62 / 47	27 (5-yr) / 0
INT 0123[38]	236	50.4 Gy / 64.8 Gy	None	Cisplatin/5-FU	37[a] / 46[a]	45 / 50	40 (2-yr) / 31

[a] Late reactions (randomized patients only).
5-FU = 5-fluorouracil, EBRT = external beam radiation therapy, NA = not available.

patients had developed fibrotic strictures requiring dilatation and 27 patients had persistent intraluminal disease. On multivariate analysis, BT dose was found to have a significant effect on OS ($P = .002$) and local control ($P = .0005$). Based on these initial data, a second randomized trial was performed this time by the International Atomic Energy Agency looking at BT for palliation for advanced thoracic esophageal cancers.[70] In this multi-institutional trial, 232 patients were randomized to receive 18 Gy in 3 fractions (n = 112) on alternative days or 16 Gy in 2 fractions (n = 120) on alternate days. Exclusion criteria included cervical esophagus location, tumor smaller than 1 cm from the gastroesophageal junction, tracheoesophageal fistula, Karnofsky performance status (KPS) lower than 50, altered mental status, or extension to great vessels. They found a dysphagia-free survival for the entire group of 7.1 months (arm A: 7.8; arm B: 6.3, NS) and an OS rate of 7.9 months (arm A: 9.1; arm B: 6.9, NS). The researchers concluded that there were no significant differences between the two fractionation schemes, including incidence of strictures and fistulas.

BT has been investigated for its use as a boost to EBRT with or without chemotherapy in both patients with early- and late-stage disease who are undergoing definitive management. The premise of using BT in addition to EBRT is that further dose escalation beyond what could be achieved with EBRT may improve local control. To this end, there are several published retrospective studies evaluating EBRT without chemotherapy followed by BT boost. These trials have used EBRT doses of 40 to 60 Gy followed by a BT boost dose of 8 to 12 Gy prescribed out from 0.5 to 1 cm from the source axis.[71-74] Five-year rates were 33% to 69.5% for OS, 57% to 77% for local control, and 6% to 26% for late complications. The Japanese Society

of Therapeutic Radiology and Oncology performed a randomized trial to establish the optimal irradiation method in radical radiation therapy for esophageal cancer.[68] The study consisted of 94 patients with SqCC of the esophagus who received 60 Gy EBRT and then were randomized to either an additional 10 Gy EBRT boost or 10 Gy BT in 2 fractions. Most patients had T2-3 disease. The 5-year cause-specific survival rates were 27% in the EBRT-only arm and 38% in the BT arm ($P = .385$). However, in patients with a lesion smaller than 5 cm, the difference was statistically significant favoring the BT arm ($P = .025$).

Since the results of the RTOG 8501 randomized trial, which demonstrated a survival advantage of concomitant chemoradiation over radiation alone,[3,4] several studies have evaluated EBRT with concurrent chemotherapy followed by BT boost. Vuong et al[67] retrospectively analyzed 53 patients treated with 20 Gy BT in 4 fractions followed by 50 Gy EBRT with cisplatin/5-FU. They found a 2-year local control rate of 75% and a 5-year survival rate of 28%, with a fistula rate of 1.2%. This local control rate compared favorably with larger chemoradiation trials without BT. A second retrospective study[75] evaluated 53 patients with predominantly SqCC of the esophagus treated with chemoradiation therapy to a dose of 40 to 61 Gy followed by a BT boost of 8 to 24 Gy in 2 to 4 fractions. These patients were compared with 116 patients who were treated in a similar manner except without chemotherapy. They experienced only 1 fistula. The local control rates for those who received chemotherapy compared with those who did not receive chemotherapy were 60% and 42%, respectively ($P = .029$).[75] Severe late toxicities (grades 3 and 4) occurred in 15% of patients receiving chemoradiotherapy compared with 2.5% in those in the RT-only

group and were only in patients who received a boost dose of 16 Gy or higher.

Calais et al[65] published one of the first prospective reports that involved treating patients with esophageal cancer with chemoradiation followed by a BT boost. A total of 53 patients with stage IIB or III disease were recruited and received 60 Gy at 2 Gy per fraction with concomitant cisplatin, 5-FU, and MMC followed by BT boost of 10 Gy in 2 fractions. The researchers found a grade 3 or 4 toxicity of 23% and 7%, respectively, which was mostly hematologic. Local control and actuarial survival rates were 74% and 27%, respectively. A second prospective trial, RTOG 9207,[66] evaluated 50 patients (92% SqCC) who received 50 Gy EBRT with concomitant cisplatin and 5-FU followed by a BT boost of 15 Gy (n = 40), which was later revised to 10 Gy (n = 10). They found a grade 4 or 5 toxicity of 26% and 8%, respectively, with a fistula rate of 12%. The 12-month survival rate was 48%. The investigators concluded that survival was no different with the addition of BT and should be cautioned given their fistula rate. However, this study has been criticized for its high BT dose that was delivered during the chemotherapy as opposed to after chemotherapy.

In summary, there is a clear role for BT as palliative treatment for tumor-related dysphagia and bleeding in patients esophageal cancer. A dose of either 16 Gy in 2 fractions or 18 Gy in 3 fractions is acceptable. BT with EBRT as a boost should be considered in patients being treated without chemotherapy, particularly those with smaller tumors and SqCC pathology. With those patients being treated with concomitant chemotherapy, BT boost does appear to improve local control rates, but doing so increases toxicity. The increased rate of fistulas appears to be avoidable if the BT boost given does not overlap with the chemotherapy and higher doses are to be avoided. In addition, we do not typically offer BT in our practice as a boost to chemoradiation therapy for patients with a KPS lower than 70, with tumors at or above the carina or those that extend into the stomach. Our standard dose regimen is 10 Gy in 2 fractions or 12 Gy in 3 fractions depending on the EBRT dose. BT boost is usually given 1 week after chemotherapy EBRT completion. At the time of publication, we have not experienced any fistulas or grade 4 or higher toxicity. Lastly, the benefit is unclear in patients with AC — the predominant esophageal tumor variant in the United States — because most of the studies reviewed included SqCC.

Staging

The ability to accurately stage esophageal cancer in patients is critical for ensuring that the appropriate treatment options are discussed with the patient. Various imaging modalities to assess the locoregional extent of disease as well as to rule out distant metastasis are required for proper staging. Diagnostic imaging techniques have evolved over time. Computed tomography (CT), PET, and EUS are now considered to be part of a standard staging workup and collectively offer a comprehensive assessment of the locoregional as well as distant extent of disease. These imaging techniques are complementary; the use of any single imaging modality alone is not adequate to properly stage patients with esophageal cancer.

Because of its capacity to distinguish the layers of the esophageal wall, EUS plays a primary role in determining the local extent of tumor involvement. The accuracy of EUS for T (tumor stage) and N (nodal stage) diagnosis has been reported as 85% to 90% and 75% to 80%, respectively.[76-79] Fine-needle aspiration biopsy can increase N stage accuracy to approximately 87%.[77] Zhang et al[79] showed EUS to be more accurate than CT in diagnosing T and N stages. These authors compared pretreatment staging by CT and EUS with the pathological stage. In patients who had not received neoadjuvant therapy, T and N stage accuracy for EUS was 79% and 74% compared with 62% and 53% for CT, respectively.

The ability to accurately determine whether a patient has distant metastatic disease is crucial for appropriately offering patients curative or palliative treatment. As technology has evolved, diagnosis of distant metastasis has become more accurate. Prior to the era of routine PET staging, early autopsy studies of patients with esophageal cancer demonstrated that many had metastatic disease that had not been detected previously.[80] A 2004 meta-analysis[81] demonstrated PET to have a specificity of 97% and a sensitivity of 67% for diagnosis of distant metastasis. Flamen et al[82] showed the specificity and sensitivity of PET for identifying distant metastasis to be 90% and 74%, respectively. By contrast, the specificity and sensitivity for the combined use of CT and EUS were only 47% and 78%, respectively. Moreover, treatment were altered in 22% of patients after adding PET to CT and EUS. Finally, prospective studies have shown that PET can detect distant metastases in approximately 15% of patients that are not visualized by other staging modalities such as CT.[82,83]

Although multiple imaging modalities are useful for staging patients with esophageal cancer, it is unclear whether there is an optimal sequence for staging imaging. In theory, patients who first undergo a PET scan that demonstrates distant metastatic disease may not need to undergo additional staging studies. Schreurs et al[84] performed a logistic regression analysis of 216 operable patients and calculated the likelihood ratios of CT, PET, and EUS to determine the resectability based on different staging characteristics.

They determined PET to be the strongest predictor of curative resectability and suggested that PET be performed as the first staging procedure, reserving EUS for clearly resectable disease.

Advanced Technologies

Historically, radiation to the esophagus was delivered with 2D techniques that treated a large volume of normal tissue. This significantly changed with the advent of CT scans and computer software since patients, for the first time, could be scanned in the treatment position and the intended dose could be shaped three-dimensionally to maximize the dose to the intended target and minimize the dose to the healthy tissue. Mackley et al[85] reported that three-dimensional (3D) CT-based radiotherapy planning (3D CTP) reduces acute esophagitis in patients receiving multimodality therapy for esophageal cancer without compromising clinical outcomes compared with 2D planning. They also found that the 3D CTP plans had significantly smaller field sizes by area ($P < .0001$). The capability of integrating volumetric data into radiation treatment planning has resulted in the ability of the radiation oncologist to evaluate each patient's treatment dose distribution with respect to how much volume of the target is being represented. In modern radiotherapy, these dose-volume histograms are routinely used to determine the treatment plan that has the best balance between optimal tumor target coverage and minimal normal tissue dose.

When treating esophageal cancers with chemoradiation prior to resection, normal tissue complications are of prime concern. One of the most feared potential late sequelae of intrathoracic irradiation is radiation pneumonitis, a clinical syndrome that can occur weeks to months after radiotherapy, leading to respiratory compromise and potentially even death. Multiple studies have evaluated the dose-volume histogram parameters that the radiation oncologist can use to predict a patient's potential risk of pneumonitis.[86-88] In addition to potential radiation damage to the lung, there is also the potential for adverse effects to the heart.[89] Indeed, 3D CTP now provides the ability to evaluate parameters predictive of pericardial effusions.[90] With cancers of the gastroesophageal junction, there are additional concerns about minimizing dose to the liver, kidneys, and bowel. In a disease where multimodality therapy is common, treatment teams must be judicious in the adoption of any new treatment modality to ensure that tumor coverage is not increased at the expense of the underlying healthy tissue.

This concern has been extensively evaluated with the next generation of technologies beyond 3D conformal radiotherapy (3D CRT). With IMRT, there is not one individual beam of uniform dose as in 3D CRT but rather a series of individual beamlets each programmed to vary the dose intensity across the target/normal tissue interface. This technique can be delivered on a standard linear accelerator or on a tomotherapy unit in which the patient is treated on a machine that resembles a CT scanner, capable of delivering a dose in a 360-degree rotational fashion.[91] However, this increased precision has its price; therefore, to avoid underdosing potential disease with a resultant "marginal miss," it becomes more important than ever to optimize delineation of the target volumes and the planned delivery parameters.[92] Prior to the modern era, radiation oncologists were informed by their gastrointestinal endoscopic oncology colleagues as to where the superior and inferior extent of visible disease was at the time of upper endoscopy, and they used this information combined with a barium swallow to design 2D treatment fields. This contrasts sharply to the present day in which tumor delineation arsenals include CT, magnetic resonance imaging, PET/CT, four-dimensional (4D) PET/CT, and endoscopic placement of fiducial markers.

The question remains as to how we can best characterize the extent of locoregional disease. Comparing CT-generated volumes with PET/CT-generated target volumes, Muijs et al[93] showed that the PET/CT target was inadequately covered by the CT-based treatment plan in 36% of patients and that treatment plan modifications resulted in significant changes in dose distribution to the lungs and heart. Mamede et al[94] reported the potential validity of using a 3D tumor segmentation method for PET delineation, noting that the fluorodeoxyglucose-PET–derived tumor metabolic length in a series of patients naive to treatment correlated well with surgical pathology results. An additional concern in the chest is respiratory-associated esophageal tumor motion, which can now be quantified with a 4D CT scan that is routinely used at many centers for treatment planning.[95-97] Since the intended esophageal target is thus "moving," the question becomes whether a 4D PET/CT scan that shows the fluorodeoxyglucose avid areas in different phases of respiration is a better measure of defining the full physiologic extent of disease and whether this could improve treatment planning.[98] At our institution, we ask our colleagues to endoscopically place coiled wire fiducial markers into the submucosa to delineate the superior and inferior extent of endoscopic tumor that we can then image on 4D treatment planning scans.[99,100] We have not seen any significant migration issues with this technique. If possible, we then proceed with a treatment planning PET/CT as well, with the fiducial markers in place.

Concerns about respiratory-associated tumor motion are particularly important in the setting of gastroesophageal junction tumors. Multiple investigators

have demonstrated increasing radial esophageal motion as the tumor location becomes more distal.[95,101] Moreover, Zhao et al[102] reported that tumors in the left chest may be displaced with cardiac motion. With advanced technology such as IMRT, there is concern that motion may affect the dose distribution. In fact, Kim et al[103] reported that respiratory motion can reduce the delivered dose by up to 30% in lung tumors that move approximately 1 cm. Motion-management strategies should be considered if using IMRT to prevent potential tumor underdosage. Abdominal compression with a device placed to decrease diaphragmatic excursion used daily has been shown to decrease the superior to inferior motion by approximately one-half.[100] Another strategy involves a solid IMRT approach whereby brass compensators are placed into the pathway of each treatment field to prevent the potential tumor motion mismatch with a static beamlet.[104] Finally, there is also the possibility of incorporating respiratory-gating techniques so that the treatment machine beams "on" only during a specified phase of the breathing cycle.

An additional concern is the variability in day-to-day stomach motion due to differences in gastric filling with tumors at the gastroesophageal junction. Bouchard et al[105] reviewed an analysis of 8 patients who were instructed to fast for 3 hours before daily treatment. The treatment was planned on both a full stomach initial CT scan and an empty stomach initial scan and re-measured with weekly repeated CT scans during treatment. The results showed that the full stomach volumes were a mean of 3.3 (range, 1.7–7.5) times larger than empty stomach volumes. Stomach filling was found to have a negligible impact on target coverage. However, the investigators also analyzed plans with patients receiving a simultaneous boost to the tumor each day and found that, in this situation, the coverage to the primary tumor was compromised.

These data emphasize the importance of daily treatment verification when utilizing advanced technologies, a technique termed image-guided radiation therapy. This technique can be incorporated with a daily CT scan on the treatment machine itself, termed a cone beam CT, which can be fused with the planning CT to ensure that the setup can be reproduced. With fiducials, a cone beam CT can be used to verify the position of the intended target. Fluoroscopy is available on treatment units and can be used to quantify the amount of motion if fiducials have been implanted into the esophagus. Finally, daily kilovoltage images of the spine can also be viewed and matched to the initial scan. All of these techniques improve the setup accuracy and may allow for smaller treatment margins to protect additional normal tissue.

Modern radiation oncologists must decide which conformal technique to utilize to plan patient treatment. With IMRT and helical tomotherapy, treatment-planning studies have shown improved dose distributions with better coverage of the intended target and better sparing of the healthy tissues compared with 3D CRT.[106-108] Clinical data are now emerging to support the role of IMRT in esophageal cancer.

Our group recently analyzed the outcomes of patients with esophageal cancer treated with IMRT chemoradiation.[109] Patients evaluated were treated between 2006 and 2011 with either preoperative or definitive IMRT chemoradiation to 50 to 60 Gy prescribed to the gross tumor volume and 45 to 50.4 Gy to the clinical target volume concurrently with chemotherapy. IMRT techniques included multifield-segmented step and shoot, compensator-based, and volumetric arc therapies. We identified 108 patients with a median follow-up of 19 months. Median OS and DFS were 32 and 21.6 months, respectively. A total of 58 patients (53.7%) underwent surgical resection. There was no difference in OS or DFS in patients who underwent surgery compared with patients who were definitively treated without surgery. Median weight loss was 5.5%, and rates of hospital admissions, feeding tube placement, stent placement, dilation, and radiation pneumonitis were 15.7%, 7.4%, 4.6%, 12%, and 1.9%, respectively. Long-term radiation pneumonitis was observed in 6 (5.6%) patients. The benefits of IMRT over 3D radiation planning are better target conformality and sparing of the surrounding normal tissues.

Moreover, Kole et al[110] showed that IMRT significantly reduced the dose to the heart compared with 3D CRT. They analyzed 19 patients treated with IMRT and compared 3-field and 4-field 3D CRT plans on those same patients. They showed a significant reduction in mean dose (22.9 vs 28.2 Gy) and V30 (24.8% vs 61.0%; $P < .05$) and a significant improvement in the target conformity with IMRT as measured by the conformality index (ratio of total volume receiving 95% of prescription dose to the planning target volume receiving 95% of prescription dose), with the mean conformality index reduced from 1.56 to 1.30 using IMRT. Nguyen et al[108] analyzed 9 patients in a feasibility study to compare lung and heart doses between 3D CRT and tomotherapy. Mean lung dose (7.4 vs 11.8 Gy; $P = .004$) and heart ventricle dose (12.4 vs 18.3 Gy; $P = .006$) were significantly reduced with tomotherapy. Nicolini et al[111] compared volumetric modulated arc therapy (VMAT) with multifield IMRT and 3D CRT plans in patients with esophageal cancer, showing that VMAT and IMRT provided similar target coverage and were superior to 3D CRT. The conformity indexes were 1.2 for VMAT and IMRT and 1.5 for 3D CRT. The mean lung doses were 12.2 for IMRT, 11.3 for VMAT, and 18.2 for 3D CRT, and the V20 values were 23.6% for IMRT, 21.1% for VMAT,

and 39.2% for 3D CRT. However, an analysis from India[112] of 45 patients with esophageal cancer treated with either 3D CRT or IMRT resulted in higher rates of radiation pneumonitis in patients receiving IMRT, which correlated with higher V20 and V30 values.

Recently, interest has re-emerged about the potential role of proton therapy for patients with esophageal cancer. Unlike photon beams generated on traditional treatment units, protons are produced by cyclotrons and have an advantage in the characteristic of the beam such that there is a sharp fall off between high- and low-dose areas due to what is termed the Bragg peak.[113] Thirty years ago Japanese investigators began describing ongoing work with particle radiation therapy using protons.[114] They subsequently reported that high-dose irradiation with protons could lead to improved local control and long-term survival without excessive risk to normal tissues in patients with esophageal cancer.[115,116] With improved technologies enabling more accessibility to proton treatment centers, radiation oncologists are now exploring the results with modern proton treatment. Dosimetric studies have reported improved planning parameters with respect to IMRT.[117,118] Since many treatment failures are within the areas of gross esophageal disease, considerable interest revolves around performing dose escalation with lower normal tissue toxicity. Prospective studies are ongoing to explore the clinical outcomes in the modern era with this form of treatment delivery to determine whether results will be superior to other conformal techniques.

Conclusions

Neoadjuvant chemoradiotherapy provides a significant benefit over surgery alone for both adenocarcinoma and squamous cell carcinoma. Preoperative chemoradiation trends toward increased survival over preoperative chemotherapy alone. The benefit of surgery after chemoradiation remains controversial. Data to support the use of radiation alone for curative intent are limited; therefore, it should be reserved for the palliative setting. Chemoradiotherapy has no effect on Barrett's esophagus and should be addressed with surgery or ablative techniques, such as cryotherapy, to prevent new esophageal primary cancers from forming. Brachytherapy provides better long-term relief of dysphagia than self-expanding metal stents provides. The role of brachytherapy in the curative setting is controversial and must be individualized to patient response to initial therapy. The role of positron emission tomography and endoscopic ultrasonography in staging has dramatically improved our ability to stratify patients who will benefit from surgery, chemotherapy, and/or radiation therapy. We await the results of the RTOG 0436 randomized trial that is analyzing the effect of biologic therapy against epidermal growth fac-

tor receptor. Future directions will study molecular signatures predicting response to chemotherapy and radiation to determine who should have upfront resection rather than neoadjuvant therapy. Modern improvements in metabolic imaging have led to the better delineation of target volume localization. With higher confidence in defining the extent of disease in the esophagus and the advances in improved computed tomography-based software, planning and delivering radiation can be more precise than ever before. Daily cardiac- and respiratory-associated tumor motion can be quantified and treatment position verified prior to each fraction. These advances translate to fewer acute adverse events during treatment and the hope that better outcomes may be possible. Current evidence documents these improved treatment planning parameters, but the data confirming improved clinical outcomes with possible superior pathological response and overall survival are not yet available.

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