Esophageal Cancer

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Epidemiology

For squamous cell carcinoma (SCC), lifestyle risk predisposing factors include dose-dependent smoking and alcohol consumption; alcohol consumption could be synergistic with smoking. Dietary risk factors include low intake of vegetables, fruits, fish, poultry, and vitamins but high in take of red meat and processed foods. Tylosis and Plummer-Vinson syndromes are predisposing genetic factors for SCC of the esophagus. Gastroesophageal reflux disease and Barrett's esophagitis are known risk factors for dysplasia leading to invasive adenocarcinoma, mainly at the distal esophagus or gastroesophageal junction (GEJ). Human papillomavirus is an infectious contributing factor; *Helicobacter pylori* is a risk factor for gastric cancer, but not for esophageal cancer. Injury from lye ingestion, achalasia, and esophageal diverticuli are other possible risk factors.

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Pathological and Biological Features

SCC and adenocarcinoma are the two major types of esophageal cancer. Over the past 3 decades, the proportions have shifted from about 90 % being SCC to about 50 % being adenocarcinoma [2]. Adenocarcinoma arises mostly at the distal esophagus or GEJ, and SCC arises mostly at the mid-esophagus or above.

Staging

The esophagus has an endoscopic length of approximately 40 cm from the upper incisor teeth and the cricoid cartilage at the level of vertebra C7 and extending past the diaphragm to join with the stomach (generally at the lower border of vertebra T11). Workup for the initial evaluation and disease staging is summarized in Table 13.1. The tumor location affects classification, lymphatic drainage, and options for management [3, 4]: general sections are the cervical esophagus (from the level of the cricopharyngeus muscle to the level of the sternal notch), the upper thoracic esophagus (to the azygos arch inferiorly), the middle thoracic esophagus (to the level of the inferior pulmonary vein), and the lower thoracic esophagus (to the lower esophageal sphincter at the esophagogastric junction). According to the seventh edition of the AJCC staging system (Table 13.2), the tumor position is determined by the upper edge of the tumor in the esophagus, not where the tumor volume is largest. Tumors at the esophagogastric junction are staged as esophageal cancer when the tumor's epicenter is within the lower thoracic esophagus, at the esophagogastric junction, or within the proximal 5 cm of the stomach with extension into the esophagus [4, 5].

The length of the primary tumor, although critical for target delineation, is not included in the current staging system. The seventh edition has the same T1–T3 classifications, but the T4 classification has been changed to either resectable T4a (invasion of the pleura, pericardium, or diaphragm) or unresectable T4b (invasion of the aorta, carotid vessels, azygos vein, left main bronchus, vertebral body, or trachea) [4]. The revised manual defines regional lymph nodes to include any paraesophageal lymph nodes, from cervical to celiac, owing to the longitudinal nature of lymphatic drainage. The N classification is also based on the number of involved nodes (N1, one or two; N2, three to six; N3, seven or more). Besides the communication of the caval and the portal venous systems within the submucosa of the esophagus [6], a rich network links the lymphatics in the lamina propria and submucosa and the lymphatics in the muscularis propria and adventitia. Therefore, extensive intramucosal and submucosal spread beyond a grossly visible tumor is not surprising and should be an important consideration in defining the clinical target volume (CTV) in esophageal cancer. Generally all three groups of upper, middle, and lower lymphatic trunks drain into the paraesophageal lymph nodes adjacent to the esophagus; the cervical nodes drain into the internal jugular and upper tracheal nodes; the thoracic nodes into the superior, middle, and lower mediastinal nodes; and

Table 13.1 Workup at initial evaluation

Workup		
History	Screen for family history	
Physical examination		
Complete blood count and comprehensive blood chemistry		
Upper GI endoscopy	Biopsy	
Chest/abdominal CT with oral and IV contrast	If M0	If M1
	Positron emission tomography-computed tomography (PET-CT)	Biopsy of metastatic focus
		HER2–neu testing if adenocarcinoma
	Endoscopic ultrasound (EUS)	
	Endoscopic resection (ER) if early stage	
	Bronchoscopy for tumors at or above the carina	
Assign Siewert category for esophagogastric junction (EGJ) adenocarcinomas	Type I: distal esophageal tumor centered within 1–5 cm above the anatomic EGJ	
	Type II: cardia tumor centered within 1 cm above and 2 cm below the EGJ	
	Type III: subcardial carcinoma centered between 2 and 5 cm below the EGJ, infiltrating the EGJ and the distal esophagus from below	
Smoking cessation	Advice, counseling, pharmacotherapy	
Nutritional assessment and counseling	Consider nutritional support with nasogastric or J-tube but not percutaneous endoscopic gastrostomy (PEG)	

the abdominal nodes into the superior gastric artery, celiac axis, common hepatic artery, and splenic artery nodes.

The revised seventh edition manual also defined separate stage groupings based on the histology of the tumor (Table 13.3) [4, 5].

Evidence-Based Treatment Approaches

The tumor histology (squamous or adenocarcinoma) currently does not influence the choice of therapy, but it does influence the location of the tumor. Epidemiological evidence suggests that adenocarcinoma tends to arise from Barrett's dysplasia in the lower esophagus or GEJ, whereas most SCC arises in the upper esophagus.

Table 13.2 Comparison of changes in sixth and seventh editions of AJCC

	Comparison of TNM staging system	
	Sixth edition	Seventh edition
Tumor	Tis: carcinoma in situ	Tis: high-grade dysplasia
	T1: invasion of lamina propria, muscularis mucosae, or submucosa	T1a: tumor invades lamina propria or muscularis mucosae
		T1b: tumor invades submucosa
	T2: invasion of muscularis propria	Same
	T3: invasion of adventitia	Same
	T4: invasion of adjacent structures	T4a: resectable (pleura, pericardium, or diaphragm)
		T4b: unresectable (aorta, vertebral body, or trachea)
Node	N0: absent	Same
	N1: present	N1: 1–2 regional LNs
		N2: 3–6 regional LNs
		N3: ≥7 regional LNs
	M0: absent	Same
Metastasis	M1a: cervical LN (in upper esophageal cancer) or celiac LN (in lower esophageal cancer)	M1: present
	M1b: all other distant metastases	
LN: lymph node		

Standard treatment options in clude esophagectomy for surgically resectable tumors or concurrent chemoradiotherapy for surgically unresectable tumors. However, the rates of local-regional failure after surgery (37–59 %), radiotherapy (68 %), preoperative chemotherapy and surgery (27–58 %), chemoradiotherapy (46–58 %), and preoperative chemoradiotherapy and surgery (23 %) all remain high, as does the rate of distant metastasis; indeed, the 5-year overall survival (OS) rates are low at 20–27 % [7, 8].

Because radiotherapy is a vital part of the overall management strategy, clinicians must understand the natural course of tumor dissemination to accurately delineate the treatment target for precise delivery of the dose so as to eradicate the tumor and yet spare the surrounding organs at risk. Radiotherapy has evolved greatly over time, from two-dimensional external beam radiotherapy, which had major uncertainties in dose distribution and lack of normal tissue sparing, to three-dimensional conformal radiotherapy and on to intensity-modulated radiotherapy, which has much more desirable dose conformality, which minimizes irradiation of critical normal structures and reduces toxicity. This form of radiotherapy has shown promise for improving treatment efficacy by providing better tumor coverage and reducing toxic effects on normal tissue, possibly allowing escalation of the radiation dose.

The major goal of treatment is to provide the longest possible OS and disease-free survival (DFS), by R0 resection if surgery is used and by complete pathological response if nonsurgical methods such as chemoradiotherapy are used. Summarized

Table 13.3 Stage groupings for squamous cell carcinoma and adenocarcinoma

Stage groupings for squamous cell carcinoma					
TM category	N0		N1	N2	N3
	G1	G2–G3			
T1M0	IA	IB	IIB	IIIA	IIIC
T2M0			IIB	IIIA	IIIC
LE	IB	IIA			
UME	IIA	IIB			
T3M0			IIIA	IIIB	IIIC
LE	IB	IIA			
UME	IIA	IIB			
T4M0			IIIC		
T4a	IIIA				
T4b	IIIC				
IIIC					
Any T, M1	IV				
G histologic grade, *LE* lower esophagus, *UME* upper and middle esophagus					
Stage groupings for adenocarcinoma					
TM category	N0		N1	N2	N3
	G1–G2	G3			
T1M0	IA	IB	IIB	IIIA	IIIC
T2M0	IB	IIA	IIB	IIIA	IIIC
T3M0	IIB		IIIA	IIIB	IIIC
T4M0			IIIC		
T4a	IIIA				
T4b	IIIC				
Any T, M1	IV				

below is current evidence supporting the choice of treatment according to the type and extent of the tumor.

Superficial Tumors

The advent of routine endoscopic surveillance for patients with Barrett's esophagus has led to an increase in the global incidence of superficial (T1) esophageal cancer. The two major treatment options for early esophageal cancer, balancing the risk of nodal metastases and procedural risk based on the depth of tumor invasion into the esophageal wall are surgical esophagectomy and endoscopic resection. Submucosa invasion or muscularis mucosa invasion with lymphovascular invasion increases nodal metastasis risk which precludes pure eligibility for endoscopic therapy alone [9, 10]. For fit patients with submucosal (T1b) cancer, esophagectomy will maximize the chance for cure. Evidence on the use of radio therapy or chemoradiotherapy as definitive treatment for superficial esophageal cancer is very limited, and

therefore such treatment should be reserved for patients with medical contraindications for surgery or patients who are ineligible for endoscopic therapy because of varices, previous perforation, or severe cervical spine disease.

Locoregional Cancer (Stages I–III)

All patients with potentially resectable localized thoracic esophageal cancer (>5 cm from the cricopharyngeus) and intra-abdominal esophageal or EGJ cancer should be evaluated in a multidisciplinary setting for to consider esophagectomy. Esophagectomy should be done by experienced surgeons, and nodal dissection must be adequate (at least 15 lymph nodes, ≥30 if possible) for a significant reduction in mortality [11, 12].

Only an R0 resection provides substantial long-term survival for patients treated surgically for localized esophageal cancer because of the risk of microscopically positive margins, which confer a disappointing prognos is, even when preoperative chemotherapy is used (Table 13.4) [13]. The Radiation Therapy Oncology Group trial 8911 (Intergroup 113) compared chemotherapy plus surgery (216 patients) versus surgery alone (227 patients) for localized esophageal cancer. The rates of R0

Table 13.4 Perioperative chemotherapy trials

Preoperative chemotherapy plus surgery versus surgery trials						
		Median	1 year	2 year	3 year	5 year
Trials and References		Survival (months)	OS Rate (%)	OS Rate (%)	OS Rate (%)	OS Rate (%)
Kelsen et al.; RTOG 8911 (INT-0113) [7]	Surgery alone	14.9 m	60	37		R0 32 vs R1 5
Preoperative chemotherapy	Cisplatin and fluorouracil ×3 pre- and ×2 post-op	16.1 m	59	35		
MRC trial [14]	Surgery alone	13.3		34		
Preoperative chemotherapy	Cisplatin 80 mg/m^2 + fluorouracil 1,000 mg/m^2 ×2 cycles	16.8		43		
Cunningham et al.; MAGIC [8]	Surgery alone					23
Preoperative chemotherapy	Epirubicin, cisplatin, and infused fluorouracil					36
Ando et al.; JCOG 9907 [15]	Surgery alone					
Preoperative chemotherapy	Two courses of cisplatin plus fluorouracil					55
Postoperative chemotherapy						43

resection were 59 % for the surgery-only group and 63 % for the neoadjuvant chemotherapy group ($P=0.5137$); 32 % of patients with R0 resections were alive and free of disease at 5 years in comparison with only 5 % of those with an R1 resection [13]. Thus RTOG 8911 showed that postoperative chemoradiotherapy could offer the possibility of long-term disease-free survival to a small percentage of patients, even after an R1 resection.

For cervical or cervicothoracic tumors less than 5 cm from the cricopharyngeus, the recommended treatment is definitive chemoradiation. Preoperative chemoradiotherapy is recommended (41.4–50.4 Gy + concurrent chemotherapy) for non-cervical T1b, N+ and T2–T4a, N0–N+ esophageal cases [16–21], and definitive chemoradiotherapy is the recommended treatment for cervical esophageal cancer and T4b cases, and is an option for patients with non-cervical esophageal cancer who decline surgery (50–50.4 Gy + concurrent chemotherapy) [22, 23]. Radiotherapy alone produces inferior results for both SCC and adenocarcinoma histology relative to chemoradiotherapy according to RTOG 85-01, a randomized trial of chemoradiotherapy (four cycles of fluorouracil and cisplatin given concurrently with 50 Gy in 2 Gy/fraction/day) versus radiotherapy alone (64 Gy in 2 Gy/fraction/day), each without resection [24, 25]. Median survival times were 14 vs 9 months; 5-year OS rates were 27 % (projected 8- and 10-year OS rates of 22 % and 20 %) vs 0%. Local failure as the first site of failure was also higher in the radiotherapy-only group (47 % vs 65 %). The subsequent INT 0123 (RTOG 94-05) trial assessed radiotherapy dose escalation with the same concurrent cisplatin-fluorouracil regimen (64.8 Gy vs 50.4 Gy) and reported no significant difference between the high-dose or standard-dose groups in median survival times (13 vs 18 months), in 2-year OS rates (31 % vs 40 %), and in rates of locoregional persistence or failure (56 % vs 52 %) [26]. The value and efficacy of definitive chemoradiotherapy for locally advanced esophageal cancer have been confirmed in subsequent trials [27–29], in which overall response rates were higher to docetaxel and cisplatin for SCC (71 % complete response) [27] and favorable but not significantly different for FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) compared with CF [29].

Although preoperative chemoradiotherapy followed by surgery is generally agreed to be the most appropriate treatment for resectable esophageal cancer (Table 13.5), debate is continuing in light of the challenging results of the phase III CROSS and FFCD 9901 trials [19, 30]. CROSS, the largest trial of esophageal cancer (368 patients with T2–3, N0–1, M0 esophageal or EGJ cancer in which the length and width of the primary tumor ≤8 cm; 75 % adenocarcinoma and 23 % SCC), revealed that preoperative chemoradiotherapy with concurrent carboplatin and paclitaxel produced significantly improved OS (median survival times 49 vs 24 months; 1-, 2-, 3-, and 5-year OS rates 82 %, 67 %, 58 %, and 47 % vs 70 %, 50 %, 44 %, and 34 %) and DFS versus surgery alone, in addition to higher R0 resection rates (92 % vs 69 %), higher pathologic complete response rates in SCC than in adenocarcinoma (49 % vs 23 %; $P=0.008$), and lower rates of locoregional recurrence (14 % vs 34 %; $P=<0.001$) [19, 20]. On the other hand, FFCD 9901 showed higher rates of postoperative mortality (11.1 % vs 4 %; $P=0.049$) from preoperative chemoradiotherapy with concurrent cisplatin-fluorouracil versus surgery alone, and no improvement in

Table 13.5 Preoperative chemoradiotherapy trials

Trial and Reference	Median Survival (months)	1 year OS (%)	2 year OS (%)	3 year OS (%)	5 year OS (%)
Urba et al. [62]	17.6	58		16	
Surgery alone					
Preoperative chemoradiotherapy schedule: cisplatin 20 mg/m^2/day on days 1 through 5 and 17 through 21, fluorouracil 300 mg/m^2/day on days 1 through 21, and vinblastine 1 mg/m^2/day on days 1 through 4 and 17 through 20; concurrent with 45 Gy as 1.5 Gy/fraction twice daily in 15 weekdays	16.9	72		30	
Walsh et al.[63]	11	42	26	6	
Surgery alone					
Preoperative chemoradiotherapy schedule: two courses of chemotherapy in weeks 1 and 6 (fluorouracil 15 mg/kg/day for 5 days, and cisplatin 75 mg/m^2 on day 7); concurrent with 40 Gy, as 2.66 Gy/fraction in 15 weekdays	16	57	37	32	
Tepper J; CALGB 9781 [21]	1.79				16
Surgery alone					
Preoperative chemoradiotherapy schedule: cisplatin 100 mg/m^2 and fluorouracil 1,000 mg/m^2/d for 4 days on weeks 1 and 5; concurrent with 50.4 Gy as 1.8 Gy/fraction in 28 weekdays	4.48				39
Mariette et al.; FFCD 9901 [30]				47.5	
Surgery alone					
Preoperative chemoradiotherapy schedule: two courses of fluorouracil 800 mg/m^2 and cisplatin 75 mg/m^2; concurrent with 45 Gy as 1.8 Gy/fraction in 25 weekdays				53	
Van Hagen et al.; Dutch CROSS [19]	24	70	50	44	34
Surgery alone					
Preoperative chemoradiotherapy schedule: weekly carboplatin (area under curve of 2 mg/ml/min) and paclitaxel (50 mg/m^2) for 5 weeks; concurrent with 41.4 Gy as 1.8 Gy/fraction in 23 weekdays	49.4	82	67	58	47

OS rates (3 years, 47.5 % vs 53 %; $P = 0.94$) or R0 resection rates (93.8 % vs 92.1 %), for patients with localized stage I-II esophageal cancer [30, 31]. The prospective randomized trial CALGB 9781 enrolled only 56 patients, but also concluded from an intent-to-treat analysis that trimodality therapy (chemoradiotherapy with cisplatin-fluorouracil) versus surgery alone for stage I–III esophageal cancer showed a significant survival advantage favoring trimodality therapy (median 4.5 vs 1.8 years; 39 % vs 16 % at 5 years) [21]. Recent meta-analyses confirmed that preoperative

chemoradiotherapy plus surgery led to significant reductions in mortality and locoregional recurrence at 3 years [16, 17]; the hazard ratio (HR) for all-cause mortality for neoadjuvant chemoradiotherapy versus surgery alone was found to be 0.78 (95 % confidence interval [CI] 0.70–0.88; $P < 0.0001$), 0.80 ($P = 0.004$) for SCC and 0.75 ($P = 0.02$) for adenocarcinoma, whereas the HR for neoadjuvant chemotherapy was 0.87 (0.79–0.96; $P = 0.005$), 0.92 ($P = 0.18$) for SCC and 0.83 ($P = 0.01$) for adenocarcinoma [18]. The poorly accruing POET has been the only phase III trial to compare neoadjuvant chemotherapy with chemoradiotherapy. This trial enrolled only 126 patients with Siewert I or II/III adenocarcinoma of the GEJ [32]; preoperative chemoradiotherapy was found to produce higher complete response rates (15.6 % vs 2.0 %), lower local recurrence rates (59.0 % vs 76.5 %; $P = 0.06$), and longer absolute survival rates (3-year OS, 47.7 % vs 27.7 %) but none of these apparent differences reached statistical significance.

Esophagectomy is the preferred next step after preoperative chemoradiotherapy, but close surveillance is appropriate for selected cases with no evidence of residual disease [33]. Salvage esophagectomy is recommended for disease that persists after definitive chemoradiotherapy [33, 34]. Preoperative chemotherapy is another option [7, 8, 14, 15]. Esophagectomy for patients with non-cervical esophageal cancer without preoperative treatment may be an option for low-risk, well-differentiated lesions smaller than 2 cm [35]. For patients who underwent esophagectomy without preoperative treatment, fluoropyrimidine-based chemotherapy is recommended for R1 or R2 resection, or no adjuvant treatment for R0 resection [35]. For patients who undergo preoperative chemotherapy followed by esophagectomy, fluoropyrimidine-based is also recommended for R1 or R2 resection, or surveillance for an R0 resection [7, 8, 14, 15, 35].

Postoperative chemoradiotherapy for node-positive or T3–T4 resectable adenocarcinoma of the stomach or EGJ (20 % of 556 stage IB–IV, M0 patients, 1988 AJCC) was investigated in the SWOG 9008/INT-0116 trial [36]. Compared with surgery alone, postoperative chemoradiotherapy with fluorouracil and lecovorin led to significantly improved OS (median survival times, 36 vs 27 months, $P = 0.005$; and OS rates 50 % vs 41 % at 3 years) and relapse-free survival rates (48 % vs 31 % at 3 years) without any increase in late toxicity [37]. Postoperative CRT was also shown retrospectively to be associated with survival benefit for patients with node-positive locoregional esophageal cancer [38, 39]. A DFS benefit was also found (37 % vs 24 % at 3 years for patients with node-positive EGJ adenocarcinoma who did not receive neoadjuvant chemotherapy) [40].

The potential effect of postoperative radiotherapy after radical surgery for esophageal carcinoma was investigated by Xiao et al. in their pre-PET-CT staging era cohort of 495 patients with SCC (200 got postoperative radiotherapy and 275 got surgery alone) [41]. The postoperative radiotherapy covered the entire mediastinum and bilateral supraclavicular areas (midplane dose 50–60 Gy, 25–30 fractions, 5–6 weeks) and led to a nonsignificant benefit in OS at 5 years (31.7 % for surgery alone vs 41.3 % for postoperative radiotherapy, $P = 0.4474$) at with a highly significant survival benefit for stage III patients (13.1 % vs 35.1 %, $P = 0.0027$) [41]. This group also retrospectively analyzed the role of postoperative

radiotherapy for 549 patients (274 got postoperative radiotherapy and 275 got surgery alone) based on nodal positivity (269 with N0 159 with 1–2 positive nodes and 121 with ≥3 positive nodes) [42]. Both nodal positivity and receipt of postoperative radiotherapy significantly affected OS [42]; postoperative RT reduced the incidence of intrathoracic recurrence and supraclavicular lymph node metastasis in all patients. For patients with T3 tumors, the 5-year survival rates were 50.6 % for those with N0 disease, 29.3 % for those with 1–2 positive nodes, and 11.7 % for those with 3 or more positive nodes ($P=0.0000$); OS rates for node-positive patients were 17.6 % for 1–2 nodes and 34.1 % for 3 or more nodes ($P=0.0378$) [42]. Schreiber et al. used the Surveillance, Epidemiology, and End Results database to analyze the effect of adjuvant radiotherapy on 1,046 patients (683 with surgery alone and 363 with postoperative radiotherapy) [43]. For patients with stage III disease, postoperative radiotherapy conferred significant improvement in median OS time and 3-year OS rates ($P<0.001$) and disease-specific survival rates regardless of tumor histology ($P<0.001$). On the other hand, other series have found no survival benefit from postoperative radiotherapy, one in 221 patients (102 surgery only, 119 surgery with postoperative radiotherapy) with SCC of the middle to lower third of the esophagus [44], and the other with 30 surgery and 30 surgery and postoperative radiotherapy [45].

For patients who are medically unfit for surgery but can tolerate chemotherapy or chemoradiation, definitive chemoradiotherapy is the preferred option (50–50.4 Gy + fluoropyrimidine-based chemotherapy) [46–49], but single-modality chemotherapy or radiotherapy could be used for patients with poor performance status [50–53]. Palliative radiotherapy and best supportive care are viable options for patients who are medically unfit for surgery and cannot tolerate chemotherapy or chemoradiation [50, 54–56].

For inoperable locally advanced or recurrent or metastatic adenocarcinoma of the esophagus or EGJ, adding trastuzumab therapy in addition to chemotherapy is being considered for patients with HER2-neu overexpression in the ToGA trial [57].

Should Every Patient Undergo Esophagectomy? Selecting Patients Best Suited for Chemoradiotherapy Alone

Two randomized trials, both almost exclusively with patients with SCC, have been done to evaluate the necessity of surgery after definitive chemoradiotherapy [58, 59]; neither found any survival advantage from adding surgery after definitive chemoradiotherapy. One trial tested trimodality therapy consisting of induction chemotherapy (3 cycles of fluorouracil, leucovorin, etoposide, and cisplatin), followed by chemoradiotherapy (40 Gy with cisplatin and etoposide), followed by surgery and compared that with the same induction chemotherapy, followed by chemoradiotherapy with dose escalation to at least 65 Gy without surgery [58]. Adding surgery to chemoradiotherapy improved local tumor control (2-year progression-free survival rates were 64.3 % for trimodality with surgery vs 40.7 % for chemoradiotherapy, HR] 2.1, $P=0.003$) but not survival. Treatment-related mortality rates were

significantly higher for the surgery group (12.8 % vs 3.5 %), $P=0.03$), and response to induction chemotherapy was a favorable prognostic factor for both groups of high-risk patients (HR 0.30, 95 % CI, 0.19–0.47; $P<0.0001$). The other trial, FFCD 9102 (89 % SCC) randomized 259 of 444 eligible patients with T3N0-1M0 thoracic esophageal cancer to receive surgery or continuation of chemoradiation (three cycles of fluorouracil/cisplatin with either conventional [20 Gy] or split-course [15 Gy] radiotherapy) if the patients responded to neoadjuvant chemoradiotherapy of (two cycles of fluorouracil/cisplatin on days 1–5 and 22–26 with concomitant conventional radiotherapy (46 Gy in 4.5 weeks) or split-course radiotherapy (15 Gy, days 1–5 and 22–26) [59]. Adding surgery to chemoradiotherapy improved local tumor control rates at 2 years (66.4 % for trimodality with surgery vs, 57 % for chemoradiotherapy, HR 2.1, $P=0.003$) and reduced the needs for stents (5 % for trimodality with surgery vs 32 % chemoradiotherapy, $P<0.001$) but did not improve survival (2-year survival rates 34 % for trimodality with surgery vs 40 % for chemoradiotherapy, $P=0.44$). Moreover, treatment-related mortality at 3 months was significantly higher in the surgery group (9.3 % vs 0.8 %, $P=0.002$).

SCOPE1, a multicenter UK phase II–III trial of 258 patients (65 adenocarcinoma, 188 SCC, and 5 undifferentiated pathology), tested intensification of treatment without surgery, as definitive chemoradiotherapy with 50 Gy in 25 fractions plus four cycles of cisplatin/capecitabine, with or without the epidermal growth factor receptor antagonist cetuximab [60]. No benefit was found from adding cetuximab to chemoradiotherapy, with more treatment failures at 24 weeks and shorter median survival (22.1 months vs 25.4 months, $P=0.035$). Chemoradiotherapy alone, with careful follow-up and salvage surgery, seems to be a sound approach for patients with SCC who achieve a pathologic complete response, but the lack of data on patients with adenocarcinoma suggests that nonsurgical approaches be avoided in such patients [61].

Surveillance Salvage

Surveillance, with salvage treatment as needed, is less common among patients undergoing trimodality therapy than among those treated with bimodality therapy [34]. In one analysis of 518 patients who received trimodality therapy (chemoradiotherapy followed by surgery), 27 patients (5 %) had local-only failure, but 188 (36 %) had distant failure, with or without local failure. Salvage therapy was ultimately beneficial to only 2 % of the 518 patients. On the other hand, salvage strategies were more effective for patients treated with definitive chemoradiotherapy without surgery [33]. In that analysis of 276 patients who did not have surgery within 6 months of chemoradiotherapy had local recurrence rates of 91 % within 2 years and 98 % within 3 years. First relapses were local only in 64 patients (23.2 %), distant (with or without local) in 120 patients (43.5 %), and 92 patients (33.3 %) had no relapses. Final relapse rates were 33.3 % none, 14.5 % local only, 15.9 % distant only, and 36.2 % distant and local. Among the 64 patients with local-only relapse, disease in 36 % could be salvaged with surgery (8 % of all patients), with corresponding median OS times of 58.6 months versus 9.5 months for those who did not have surgical salvage.

Recommended Algorithm for Treatment of Esophageal Cancer

The recommended treatment algorithm for esophageal cancer is summarized in Table 13.6.

Target Volume Determination and Delineation Guidelines

The normal anatomy of the esophagus, with its submucosal network and longitudinal direction of lymph drainage, tends to promote "skip" metastases. Which presents an ongoing challenge in defining the CTV, particularly in light of ongoing

Table 13.6 Recommended algorithm for treatment of esophageal cancer

Tis or T1a	ER ± ablation		
	Esophagectomy if extensive or nodular disease		
T1bN0	Medically fit for surgery	Esophagectomy	
	Medically unfit for surgery	ER ± ablation	
		ER ± ablation	
		Cervical esophagus	First choice: definitive CRT
			First choice:
	Medically fit for surgery		preop CRT + esophagectomy
T1b, N+		Non-cervical esophagus	Definitive CRT if declines surgery
Or			Preoperative C + esophagectomy (if adenocancer)
T2–T4a, N0–N+	Medically unfit for surgery		Esophagectomy if low-risk well-differentiated <2 cm tumors
		First choice: definitive CRT	
		Chemotherapy	
		RT	
		Palliative/best supportive care	
	First choice: definitive CRT		
	Chemotherapy alone if invasion of trachea, great vessels, heart		
T4b	Palliative/best supportive care		
Unresectable			

ER endoscopic resection, *CRT* concurrent chemoradiotherapy, *C* chemotherapy

efforts to standardize contouring [64]. Our current recommendation is to create planning target volume that extend 5 cm proximally and distally, with a, 2-cm radial margin around the gross tumor (Table 13.7).

Radial invasion in esophageal cancer is common owing to the lack of serosa, which typically serves as a barrier of local extension. Local invasion of the adjacent organs and structures such as the pericardium, heart, great vessels, trachea, and vertebral bodies should be evaluated carefully.

Nodal spread mainly depends on tumor location; the paraesophageal nodes are the first-echelon nodal drainage stop. Regional nodes are the supraclavicular and cervical nodes for tumors of the cervical esophagus, mediastinal paratracheal and subcarinal nodes for tumors of the thoracic esophagus, and left gastric and celiac axis nodes for tumors of the distal esophagus.

Simulation

Simulation and treatment should be done while the patient's stomach is empty (i.e., nil per os for at least 3 h). The simulation procedure for esophageal cancer is similar to that for lung cancer, including the use of comfortable but strict immobilization for supine patients with their arms over their head (moving arms away from any possible beam

Table 13.7 Summary of site- and technique-specific coverage and treatment planning details

Tumor location	iGTV/GTV to CTV margin	ITV/CTV to PTV margin	Elective nodal coverage	Neoadjuvant dose	Definitive dose
Upper esophagus, above the carina	3 cm craniocaudally, 8 mm circumferentially	No 4DCT/motion management and daily IGRT: 1–1.5 cm	Supraclavicular and periesophageal	41.4–50.4 Gy in 23–28 fractions	50.4–66/70 (at the cervical esophagus) Gy in 1.8–2.0 Gy per fraction
		4DCT/motion management or daily IGRT: 0.5–1 cm			
		Both 4DCT/motion management and daily IGRT: 0.5 cm			
Distal esophagus and GEJ, below the carina	Same	Same	Periesophageal and celiac ± perigastric, splenic hilum, left gastric, porta hepatis, SMA due to extension into the stomach	41.4–50.4 Gy in 23–28 fractions	

IGRT image-guided radiotherapy, *GEJ* gastroesophageal junction, *SMA* superior mesenteric artery

angles), holding a T-bar if possible, and with the neck slightly extended and supported by a custom-made cushion for stability. The simulation computed tomography (CT) images should preferably be in ≤3-mm slices. Intravenous and oral contrast is recommended. Four-dimensional CT (4D-CT) is preferred for simulation [65, 66]. Because distal esophageal tumors have significantly greater superior-inferior and anteroposterior motion than do proximal or mid-esophageal tumors, procedures to estimate the internal motion of intrathoracic structures and total extent of motion of the target and critical structures are crucial (Fig. 13.1), particularly if 4D-CT is not available. Alternatives include maximal inspiration and expiration CT scans or slow helical CT scans [67].

Gross Tumor Volume The GTV should include the gross disease at the primary disease site including any extension through the wall, any part of the esophagus wall that is thicker than 0.5 cm, and any grossly involved lymph nodes (nodes that are >1 cm in diameter or have a necrotic center or are positive on PET), which should be delineated on CT, MRI, or PET-CT scans (highly recommended; see Fig. 13.2), as well as findings from clinical examinations, endoscopic ultrasonography, barium swallow, and endoscopy.

Internal Target Volume or Internal GTV Contouring for the GTV should be based on 4D-CT data (respiratory data sets are "binned" by phase: 0–100 % at 10 % interval) in addition to all previously gathered information, and the iGTV is contoured by using the maximum intensity projection (MIP) settings, with modifications based on visual verification of contours in individual respiratory phases (Fig. 13.3) [65].

The GTV can be subdivided into the primary [tumor] site (GTV-P) and the grossly involved lymph nodes (GTV-N). Thorough contouring of the GTV-P is required based on the exact pattern of spread:

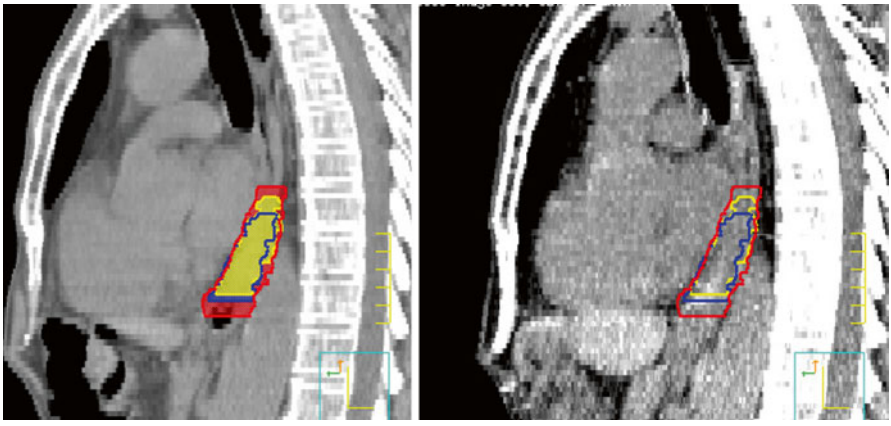

Fig. 13.1 4D-CT estimates internal motion in all extents, especially for the superior-inferior and anteroposterior motion of a distal esophageal tumor. *Blue* contours, conventional CT; *yellow* contours, PET-CT fusion; *red* contours, 4D-CT MIP-based delineation

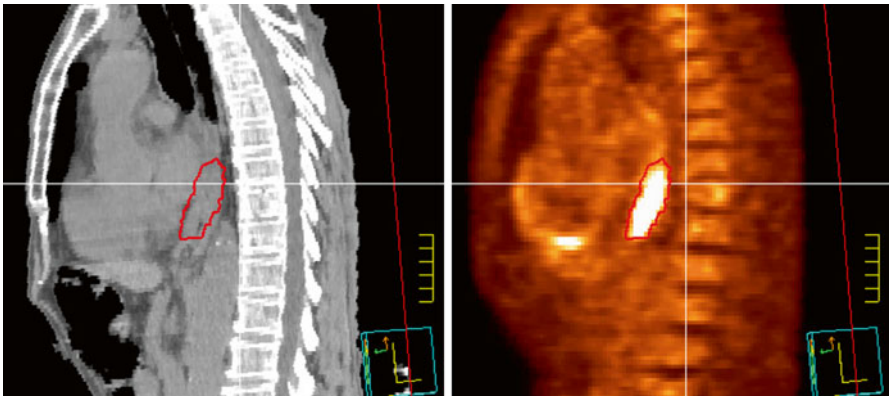

Fig. 13.2 Registering a PET-CT scan to a simulation CT scan can help with GTV delineation

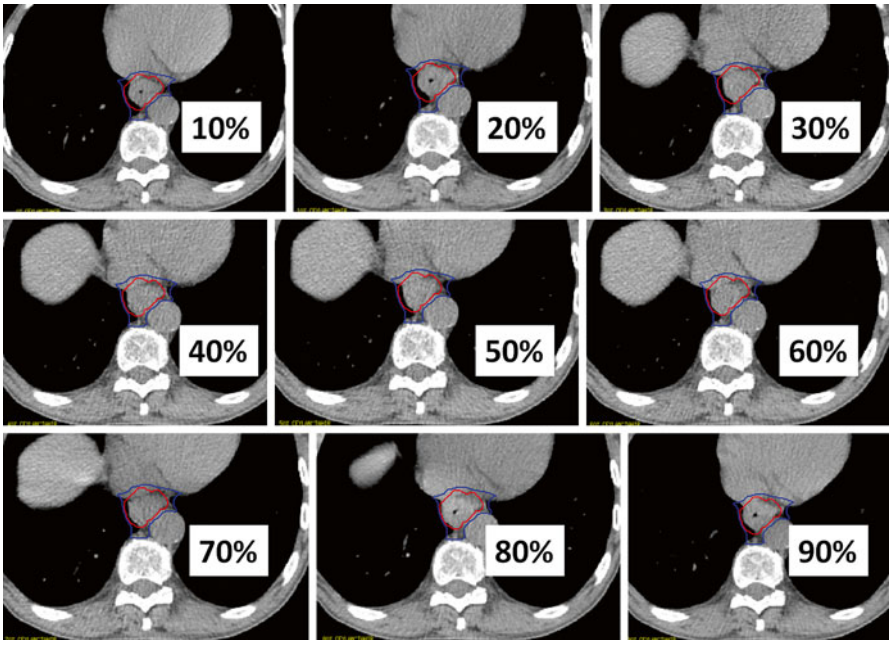

Fig. 13.3 iGTV contouring based on 4D-CT including respiratory data sets "binned" by phase (0–100 % at 10 % intervals); phase delineation at maximum intensity projection (MIP) also generally covers all movement in all phases

Radial and Local

- Is there pericardium invasion (T4a)?
- Is there pleural invasion (T4a)?
- Is there diaphragm invasion (T4a)?
- Is there tracheal invasion (T4b)?
- Is there lung invasion (T4b)?

- Is there great vessel/heart invasion (T4b)?
- Is there liver/pancreas/spleen invasion (T4b)?

Nodal
- What is the highest-echelon nodal disease?
- Is nodal disease regional or non-regional?
- Cervical esophagus: lower cervical and supraclavicular nodes
- Proximal third: paraesophageal and supraclavicular nodes
- Middle third: paraesophageal nodes
- Distal third: paraesophageal, perigastric lesser curvature and celiac axis nodes

Clinical Target Volume Because esophageal cancer can be multicentric or include submucosal "skip" metastases at considerable distances from the primary tumor [68], delineation of the CTV requires generous proximal and distal margins as well as confidence in knowing the extent of disease. Following the recommendations at the time to treat the entire esophagus because of the risk of marginal failure [25, 69, 70], RTOG 85-01 required that the entire esophagus be included in the radiotherapy portals, which led to severe toxicity when radiotherapy was given with concurrent chemotherapy [24]. The subsequent, RTOG 94-05 trial thus recommended 5-cm proximal and distal margins and a 2-cm lateral margin from the lateral border of the GTV [71], based on pathological evidence suggesting that microscopic spread within the esophagus was <3 cm about 94 % of cases except for distal microscopic spread in GEJ adenocarcinoma, which was generally <5 cm [72]. In current practice, most CTVs include an expansion of at least 3-cm following the esophageal mucosa. CTV margins should be modified to avoid irradiating nearby critical normal structures (Fig. 13.4). Whether the radiotherapy is to given before surgery or as

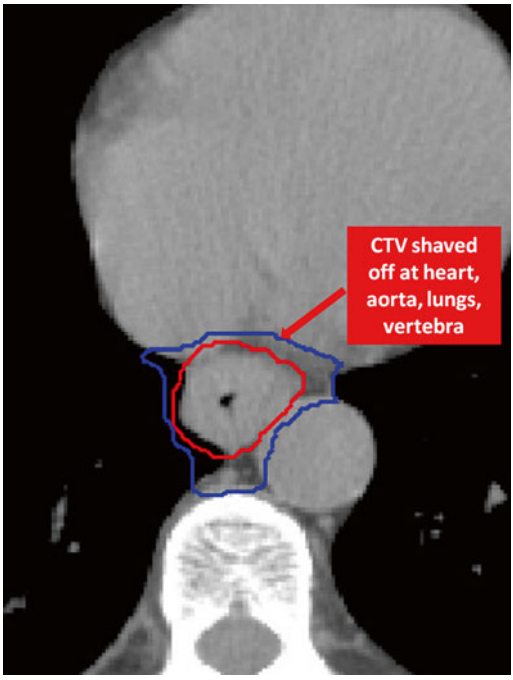

Fig. 13.4 The CTV is generated with an 8-mm expansion radially along the esophagus, which should be modified of "shaved off" to avoid irradiating critical normal structures

definitive treatment, the CTV should include the primary tumor and involved nodes, plus elective primary and nodal regions at risk:

- *Cervical esophageal tumors*: The CTV should encompass the lower cervical, supraclavicular, and superior mediastinal nodes, which generally extend from the laryngopharynx to the upper two-thirds of the esophagus, to cover submucosal spread longitudinally with a 3-cm expansion on the GTV craniocaudally and an 8-mm expansion radially along the esophagus.
- *Mid- and upper thoracic esophageal tumors*: The CTV should encompass the periesophageal and mediastinal lymph nodes plus any submucosal spread longitudinally, with a 3-cm expansion of the GTV craniocaudally and an 8-mm expansion radially along the esophagus. Supraclavicular lymph nodes should be included in the CTV for tumors above the carina.
- *Distal esophageal and GEJ tumors*: The CTV should include the periesophageal and the celiac lymph nodes plus the submucosal spread longitudinally, with a 3-cm expansion of the GTV craniocaudally at the distal esophagus, a 3-cm expansion cranially, and a 5-cm expansion caudally at the GEJ, and an 8-mm expansion radially. Regardless of the location of the primary tumor, the CTV expansion must not be a simple geometric expansion from the GTV; rather, it should follow the shape and course of the esophageal mucosa.

Planning Target Volume The PTV includes an extra margin around the CTV to compensate for variability and uncertainties in treatment setup (internal organ motion is handled with 4D-CT or alternatives). It is especially important to account for respiratory motion for tumors involving the distal esophagus or GEJ. Margins over the CTV are established in accordance with the techniques used for simulation (encompassing internal motion or not), and use of daily imaging (KV, cone beam CT, etc.). Using advanced modalities could allow some margins to be reduced. If the treating institution has not defined the appropriate magnitude of the PTV, a minimum of 5 mm in all directions should be used for each PTV. Acceptable margins for CTV to PTV are as follows:

- −1.5 cm if without 4D-CT or alternative simulation and without daily imaging
- 0.5–1.0 cm if with 4D-CT or alternative simulation and without daily imaging
- 0.5 cm if both with 4D-CT or alternative simulation and daily imaging

Contouring: A Case Example

Delineation of an iGTV and a CTV on a conventional CT scan for a patient with a T3N0M0 distal esophageal SCC is presented in Fig. 13.5.

Treatment Planning

Delineation guidelines for organs at risk have been standardized and are available in RTOG atlases; one exception is the larynx, which also needs to be delineated [73]. Normal tissue constraints can be based on the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines with normal tissue complication probability (NTCP) models (Figs. 13.6 and 13.7) (Table 13.8) [74].

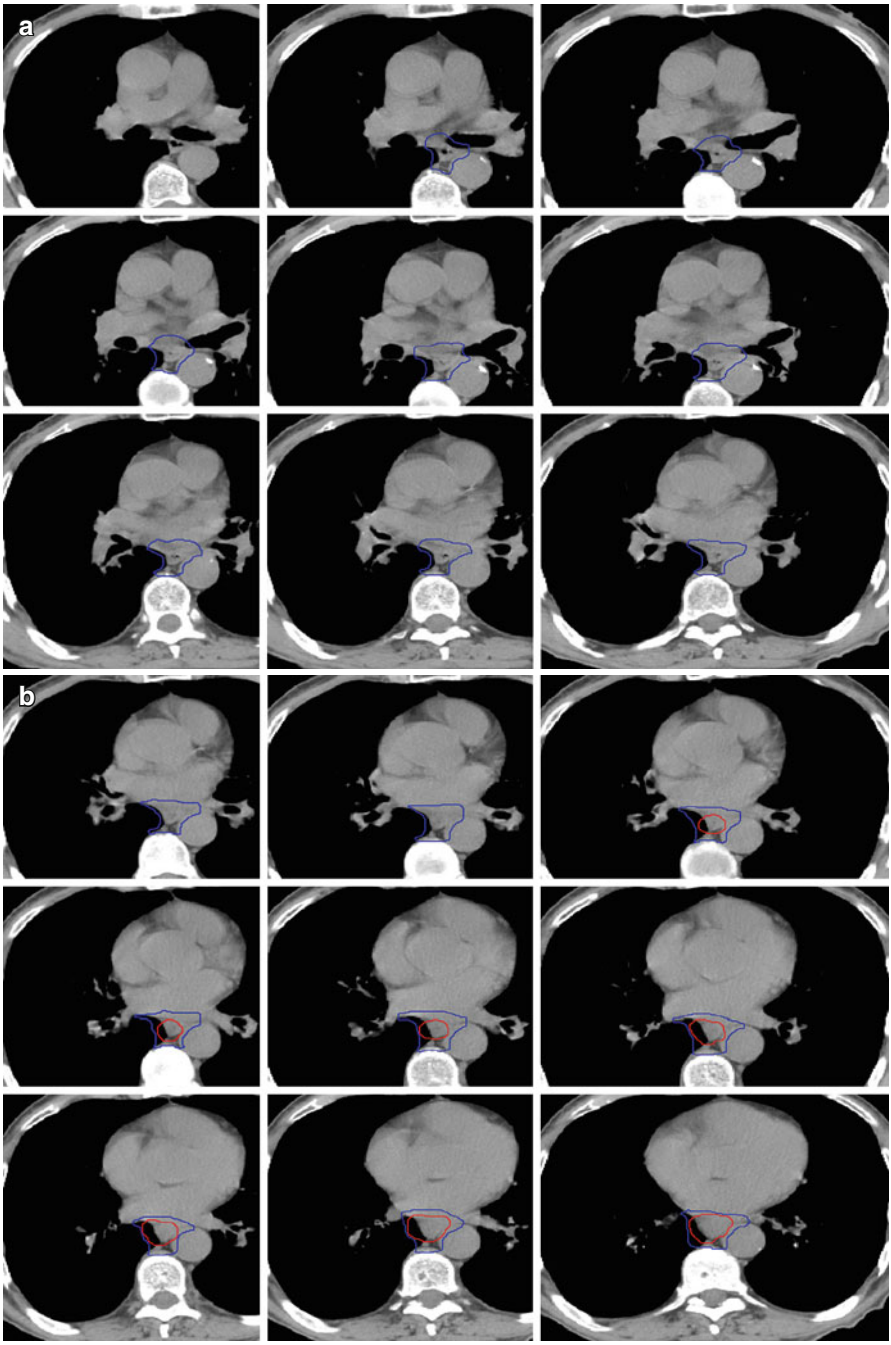

Fig. 13.5 Target delineation for a T3N0M0 SCC of the distal esophagus with coverage of the periesophageal nodes and elective coverage of the celiac nodes (*red*, iGTV; *blue*, CTV)

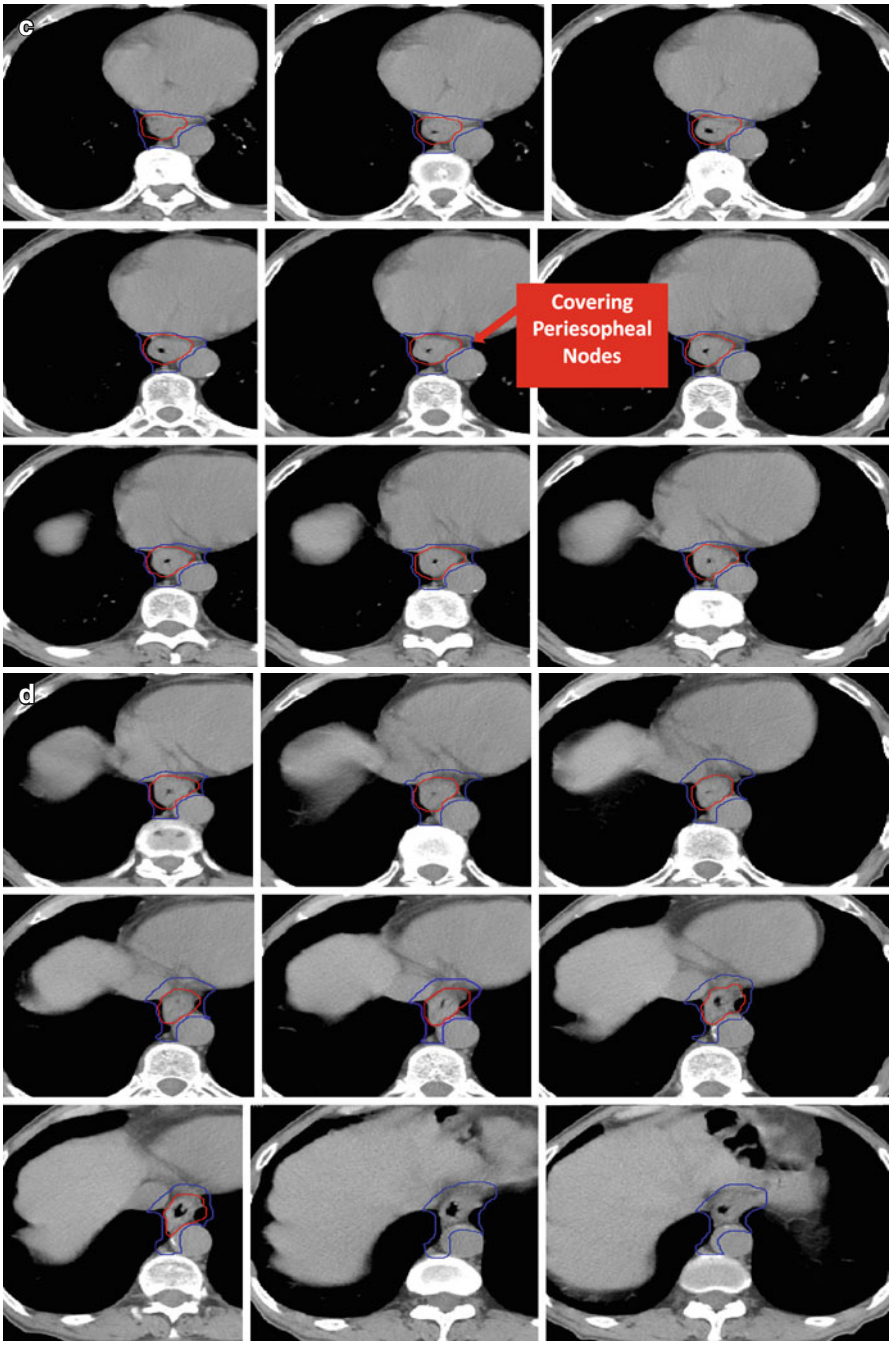

Fig. 13.5 (continued)

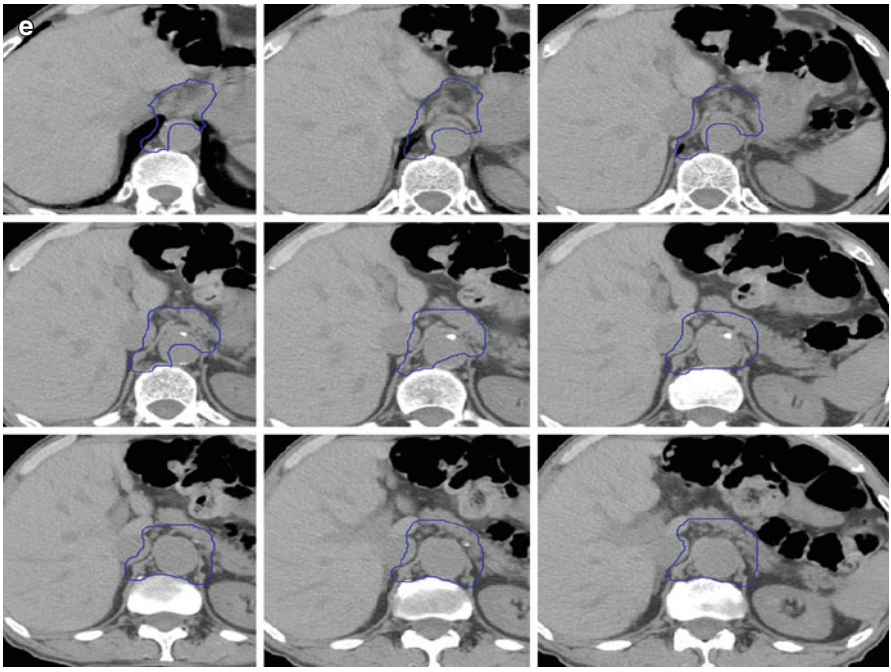

Fig. 13.5 (continued)

Treatment Planning Assessment

Our institutional standard is to deliver 100 % of the prescribed dose to the GTV and 95 % of the prescribed dose to the PTV:

- *Step 1*: Check whether the targets are adequately covered: All plans should be normalized to cover at least 95 % of the volume of the PTV by the prescribed isodose surface, and 99 % of the PTV needs to be at or above 93 % of prescribed dose.
- *Step 2*: Check for the presence of large hot spots: No more than 20 % of the PTV is to be at or above 107 % of prescribed dose, and no more than 5 % of PTV is to be at or above 114 % of the prescribed dose.
- *Step 3*: Check whether the normal tissue constraints are met.
- *Step 4*: Check the placement of any hot/cold spots (slide by slide by looking at isodose distribution): hot spots need to be located in the GTV.

Recommended Algorithm for Follow-Up Surveillance of Esophageal Cancer

The recommended algorithm for surveillance of esophageal cancer after treatment is summarized in Fig. 13.8 [20, 33, 34, 77].

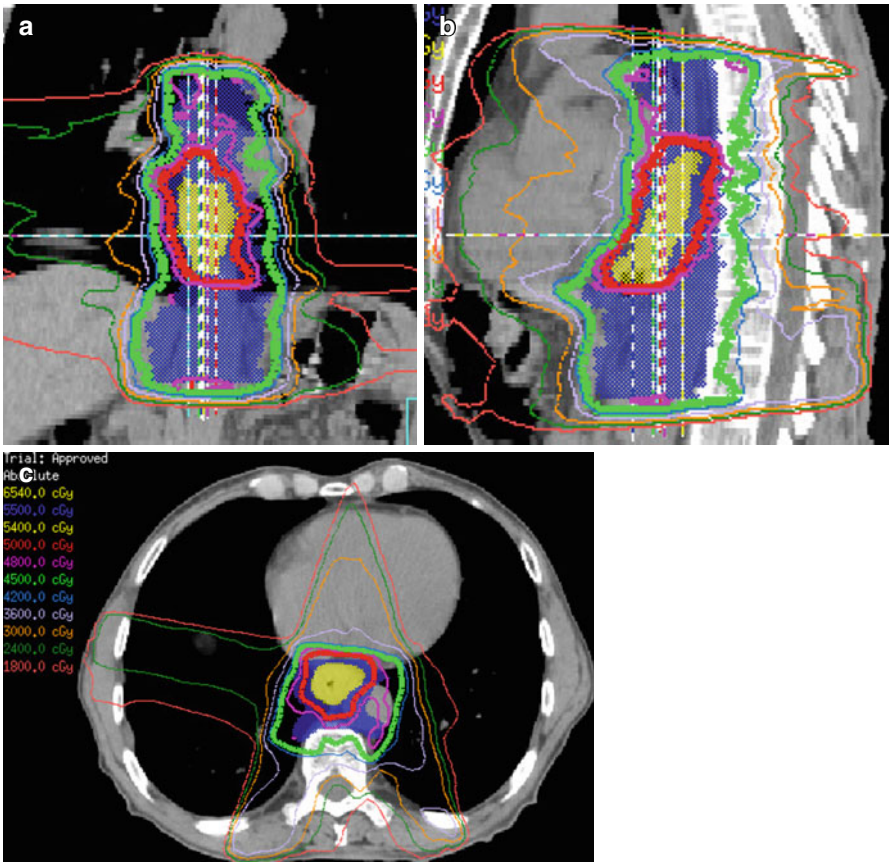

Fig. 13.6 A simultaneous integrated intensity-modulate radiotherapy plan for a distal esophageal tumor. The prescribed dose was 50 Gy (2 Gy/fraction/day) to the iGTV and 45 Gy (1.8 Gy/fraction/day) to the PTV; (**a**) coronal, (**b**) sagittal, and (**c**) axial images

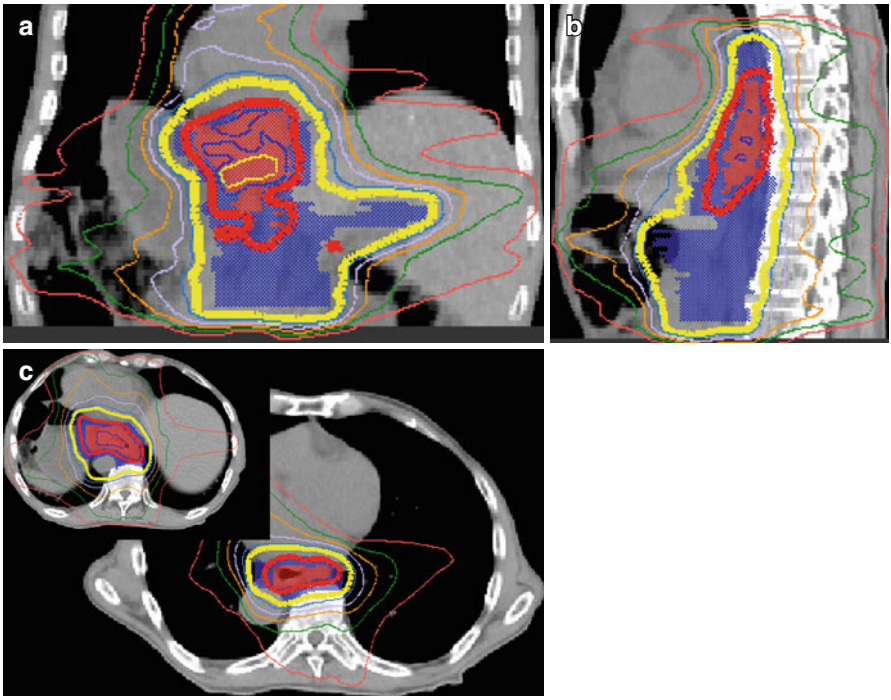

Fig. 13.7 A simultaneous integrated volumetric modulated arc therapy plan for an esophagogastric tumor with situs inversus totalis; the prescribed dose was 50 Gy (2 Gy/fraction/day) to the iGTV and 45 Gy (1.8 Gy/fraction/day) to the PTV; (**a**) coronal, (**b**) sagittal, and (**c**) axial images

Table 13.8 Guidelines for normal tissue constraints

Organ	Constraints [74]		
Larynx	Mean dose <44 Gy		
	D_{max} <66 Gy		
	V_{50} <27 %[75]		
Spinal cord	D_{max} <45 Gy		
	D_{max} <40 Gy if 3 Gy/fraction		
	Even the tumor too close, D_{max} should be <60 Gy		
Lung	Mean dose <20 Gy		
	Mean dose <8 Gy if post-pneumonectomy		
	RT alone	RT with concurrent chemotherapy	Neoadjuvant treatment before surgery [76]
	V_{20} ≤40 %	V_{20} ≤35 %	V_{20} ≤30 %
		V_{10} ≤45 %	V_{10} ≤40 %
		V_5 ≤65 %	V_5 ≤55 %
	V20 <10 % and V5 <60 % if post-pneumonectomy		

Table 13.8 (continued)

Organ	Constraints [74]
Heart	Mean dose <26 Gy
	V_{30} ≤45 %
Esophagus	Mean dose <34 Gy
	D_{max} ≤80 Gy
	V_{70} <20 %
	V_{50} <50 %
Kidney	20 Gy <32 % of bilateral kidney
Liver	Mean dose <30 Gy
	V30 <40 %

Dmax maximal dose, *GTV* gross tumor volume, *RT* radiotherapy

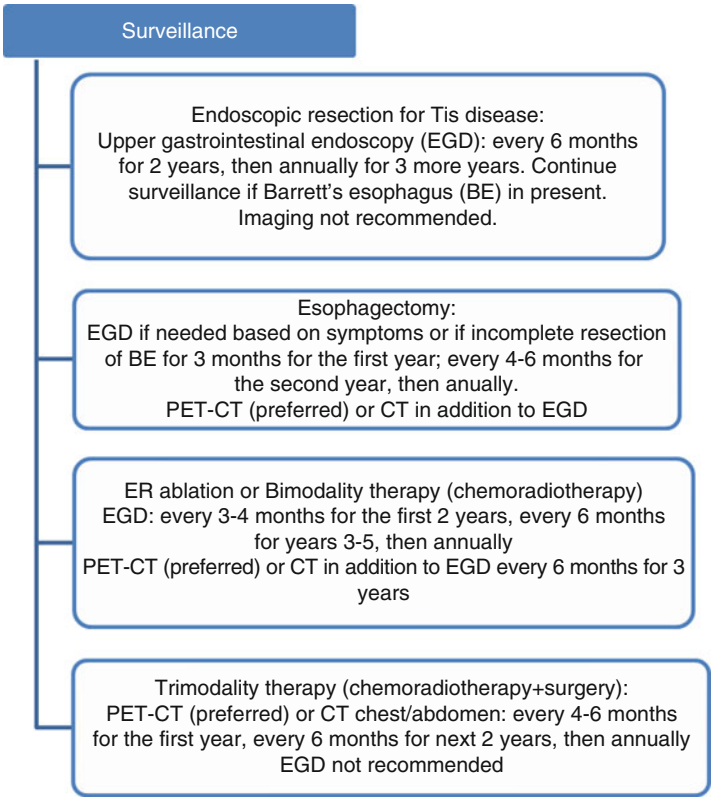

Fig. 13.8 Recommended algorithm for follow-up

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