Radiation Therapy for Esophageal Squamous Cell Carcinoma

16

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Abstract

Radiotherapy is indicated for the treatment of esophageal cancer both with curative intent and with palliative intent. Concurrent chemoradiotherapy is the standard treatment for patients in good condition who can receive chemotherapy, based on the results of randomized trial compared chemoradiotherapy with radiotherapy alone. For locally advanced unresectable esophageal cancer, definitive chemoradiotherapy is standard therapy with potentially curative intent. And for resectable esophageal cancer, definitive chemoradiotherapy is a treatment option in an attempt to preserve the esophagus from favorable results of clinical trials. These results are supported by salvage treatment in cases of residual or recurrent disease after chemoradiotherapy. However, high mortality rate of salvage surgery and high incidence of late toxicities after chemoradiotherapy with higher radiation dose are important problems to be solved. Neoadjuvant chemoradiotherapy is the standard treatment for locally advanced esophageal cancer in Western countries, however, it is investigational in Japan. Recently, prophylactic chemoradiotherapy for patients with pT1b or pT1a involving lymphovascular invasion after endoscopic resection could be a treatment option from favorable result of a clinical trial. Combination chemotherapy of new agents and new radiotherapy techniques such as intensity-modulated radiation therapy, proton-beam therapy, and heavy-particle radiotherapy have been evaluated in clinical trials to improve the treatment results including efficacy and toxicity.

Keywords

Esophageal cancer · Radiotherapy · Chemoradiotherapy · Brachytherapy · Treatment planning

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16.1 Indications of Radiotherapy

Although surgery is the principal curative therapy for resectable esophageal cancer, definitive chemoradiotherapy is a treatment option in an attempt to preserve the esophagus since favorable treatment results were reported from clinical trials [1–5]. And resection of a cervical esophageal cancer would require a laryngoesophagectomy, so definitive chemoradiotherapy is also a treatment option in an attempt to preserve the larynx in addition to the esophagus. For locally advanced unresectable esophageal cancer (T4 cases), definitive chemoradiotherapy is a standard therapy from favorable results [6–8]. Recently, prophylactic chemoradiotherapy for patients with pT1b or pT1a involving lymphovascular invasion after endoscopic resection could be a treatment option from favorable result of clinical trial [9]. And radiotherapy alone is a treatment option since many patients with esophageal cancer are elderly, of poor PS or have metastases at presentation. Radiotherapy is also useful to palliate dysphagia or pain.

16.2 Radiation Therapy Techniques

16.2.1 Simulation

During simulation, the patient lies supine with arms by their sides or with arms above their head in the case of considering to use the lateral or oblique beam arrangements. For cervical esophageal tumor, an immobilization mask should be used to minimize variation in daily setup. Computed tomography (CT)-based planning is recommended. The patient is placed on the CT simulator in the treatment position, and a scan of the entire area of interest with margin is obtained. At minimum, 3–5-mm slices should be used, allowing accurate tumor characterization, as well as improved quality of digitally reconstructed radiographs. The tumor and normal tissue structures are then outlined on each slice on the treatment planning system, enabling a three-dimensional treatment plan to be generated. Four-dimensional (4D) CT scan may be appropriate to assess tumoral motion, facilitating appropriate margin placement on the target volumes.

16.2.2 Treatment Planning

16.2.2.1 Target Volume Delineation

Gross Tumor Volumes (GTV)

The primary tumor in the esophagus is defined as GTVp based on the examinations including barium swallow, upper esophagogastroduodenoscopy (EGD), endoscopic ultrasonography (EUS), and CT scan. The endoscopic diagnosis with iodine staining is essential for detecting the superficial cancer and intraepithelial spread of the advanced cancer. In the treatment of the superficial cancer, endoscopic metal

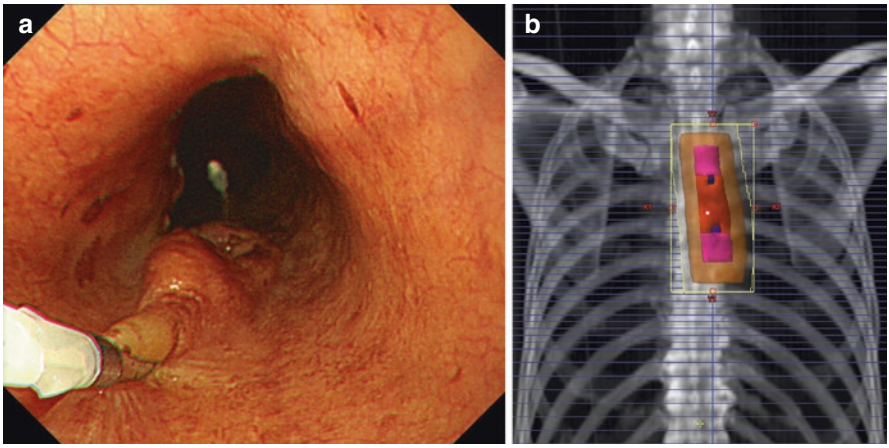


Fig. 16.1 (**a**, **b**) Example 3D-treatment planning for a cT1bN0 middle thoracic esophagus tumor. (**a**) Endoscopic insertion of metal clips in the esophageal wall near the proximal and distal end of the primary tumor. (**b**) Target volume of local radiotherapy planning. Metal clips (blue), GTV of primary tumor (red), CTV of primary tumor (pink); GTV plus 2-cm margin proximally and distally along the length of the esophagus, PTV (orange)

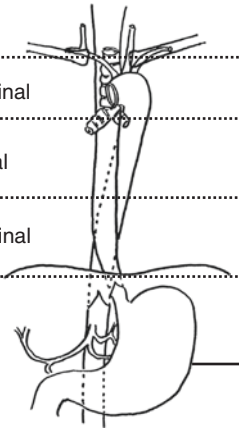
clips are inserted in the esophageal wall near the proximal and distal end of the primary tumor as fiducial markers before radiotherapy treatment planning (Fig. 16.1a). Diagnostic PET/CT has more recently been integrated into radiation treatment planning of esophageal cancer and definition of GTV [10]. The metastatic lymph nodes are defined as GTVn mainly based on the CT scan and palpitation. Similarly, EUS may detect enlarged nodes that need to be included. It is difficult to evaluate the metastatic lymph nodes accurately by the tumor size. In a study from Kyoto University, the optimal size criterion for both CT and MR in the detection of cervical and mediastinal lymph node metastases is 5 mm for short-axis diameter [11].

Clinical Target Volume (CTV)

CTVp is defined as the GTVp with 2–4 cm expansion proximally and distally along the length of the esophagus. The intent is to extend the margin along the length of the esophagus to provide a margin for coverage of the submucosal extension of the tumor. One pathological analysis of 34 surgical specimens of ESCC showed the mean microscopic spread beyond the gross tumor was 10.5 ± 13.5 mm proximally and 10.6 ± 8.1 mm distally and placement of a 3-cm margin proximally and distally on the primary tumor would cover microscopic disease extension in 94% of cases [12].

CTVn is defined as the GTVn with 0–0.5 cm margin in all directions.

The regional lymph nodes are defined as CTVsubclinical (CTVs) for each primary site in the treatment of elective nodal irradiation. Several pathological analyses of surgical specimens of ESCC reported that the rate of positive lymph nodes per number of cases were 47–70% and patterns of involved nodal spread were



	Primary site		
	Upper thoracic tumor	Middle thoracic tumor	Lower thoracic tumor
Cervical	46.3%	29.2%	27.2%
Upper mediastinal	46.3%	35.7%	29.6%
Mid-mediastinal	22.0%	32.7%	39.5%
Lower mediastinal	7.3%	16.1%	35.8%
Abdominal	12.2%	39.9%	74.1%

Fig. 16.2 Location and frequency of nodal involvement (%) by ESCC according to the site of primary site (From Akiyama H, et al. [13])

Table 16.1 Regional lymph nodes defined as CTVs for each primary site

Primary site	Regional lymph nodes
Cervical esophagus	Mid jugular lymph nodes, supraclavicular lymph nodes, superior mediastinal lymph nodes, subcarinal lymph nodes
Upper thoracic esophagus	Supraclavicular lymph nodes, superior mediastinal lymph nodes, subcarinal lymph nodes
Middle thoracic esophagus	Superior mediastinal lymph nodes, middle mediastinal lymph nodes, lower mediastinal lymph nodes, perigastric lymph nodes
Lower thoracic esophagus	Superior mediastinal lymph nodes, middle mediastinal lymph nodes, lower mediastinal lymph nodes, perigastric lymph nodes, celiac lymph nodes

different from each primary site [13–15] (Fig. 16.2). Even if clinical T1bN0 cases, the rate of positive lymph node was 27.0% based on the pathological analysis of surgical specimens of ESCC [16]. Retrospective analysis from Japan showed that elective nodal irradiation was effective for regional lymph node failure [17]. Guidelines 2016 for the treatment of esophageal cancer in Japan show the inclusion of regional lymph nodes in CTVs for each primary site (Table 16.1) (Fig. 16.3a–d). Typically, the regional lymph nodes include bilateral supraclavicular fossae, superior mediastinal, and subcarinal lymph nodes for carcinoma of the cervical esophagus and upper thoracic esophagus (Fig. 16.4a). Mid jugular lymph nodes are also included for carcinoma of the cervical esophagus. And the regional lymph nodes include superior mediastinal, subcarinal, middle mediastinal, lower mediastinal, and perigastric lymph nodes for carcinoma of the middle or lower thoracic esophagus (Fig. 16.4b). Celiac axis lymph nodes are also included for carcinoma of the

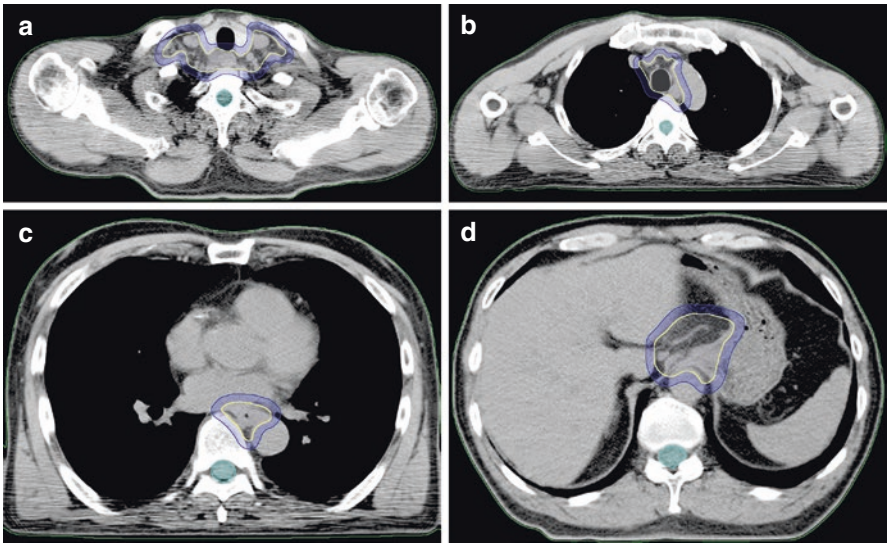


Fig. 16.3 Example of target volume delineation of CTV of the elective nodal region. CTVs (yellow) and PTVs (blue)

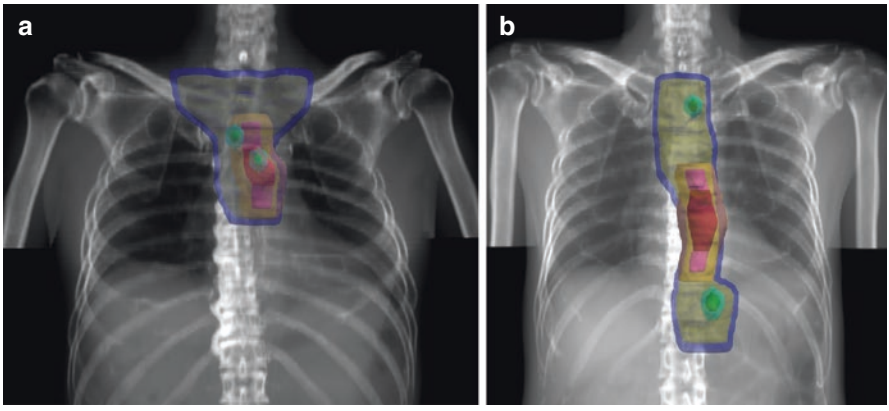


Fig. 16.4 (**a**, **b**) Examples of the target volume with the elective nodal region in the 3D-treatment planning for cT3N1 thoracic esophagus tumor. (**a**) For cancer of the upper thoracic esophagus. (**b**) For cancer of the middle or lower thoracic esophagus. GTV of primary tumor (red), GTV of metastatic lymph nodes (green), CTV of primary tumor (pink), CTV of elective nodal region (yellow), and Initial PTV (blue), boost PTV (orange and cyan)

lower thoracic esophagus. There is no consensus about inclusion of regional lymph nodes in CTVs for each primary site. Although elective nodal irradiation yields to prevent or delay regional node failure, a recent review reported that its impact on survival remains less clear [18].

Planning Target Volume (PTV)

Planning Target Volume (PTV) is defined as Clinical Target Volume (CTV) with 1–2 cm margin in craniocaudal direction and 0.5–1 cm margin in the lateral direction to account for respiratory organ motion and daily setup error. Report of evaluating the respiratory motion of distal esophageal tumor using 4D-CT showed that a radical margin of 0.8 cm and an axial margin of ±1.8 cm would provide tumor motion coverage for 95% of the cases [19].

16.2.2.2 Field Design

In the treatment of target to the primary tumor and involved lymph nodes only, beam arrangement in 3D-CRT uses a multi-field technique such as a three- to six-field arrangement (Fig. 16.1b). By contrast in the treatment including the elective nodal irradiation, anteroposterior (AP)/posteroanterior (PA) fields is used up to 40–45 Gy followed by off-cord boost fields. For cervical esophageal tumor, right anterior oblique (RAO) and left anterior oblique (LAO) with wedged pairs is usually used as off-cord boost fields. For upper, middle, and lower esophageal tumor, RAO and left posterior oblique (LPO) is usually used as off-cord boost fields. At the beginning of initial treatment for a middle or lower thoracic esophagus tumor, a multi-field technique such as a four-field arrangement (AP/PA/RAO/LPO) is recommended considering the cardiac toxicity (Fig. 16.5). However, it is necessary to minimize the volume of the irradiated lung (beam weight; AP/PA >> obliques) as to the lung toxicity. In the case of exist of hot spot such as >110% of the prescribed radiation dose, the field-in-field technique is considered to improve the conformity of the dose distribution. More recently, intensity-modulated radiotherapy (IMRT) has been considered, particularly cervical lesions. IMRT can further improve the conformity of the dose distribution by sparing the adjacent normal strictures such as spinal cord to help meet dose constraints (Fig. 16.6). Diametric comparisons of IMRT versus 3D conformal therapy in cervical esophageal cancer have demonstrated superior target volume coverage and conformality with decreased normal tissue dose [20]. A potential disadvantage of IMRT is the possibility of delivering

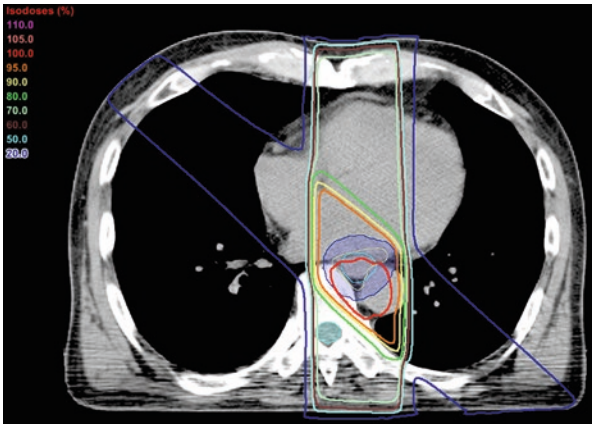


Fig. 16.5 Example of dose distribution treated with a four-field technique for a middle thoracic esophagus tumor (beam weights arrangement of 180 cGy per fraction; anterior 60 cGy, posterior 70 cGy, obliques 25 cGy). Daily heart dose: <80% of the prescribed dose, Daily lung dose: <30% of the prescribed dose

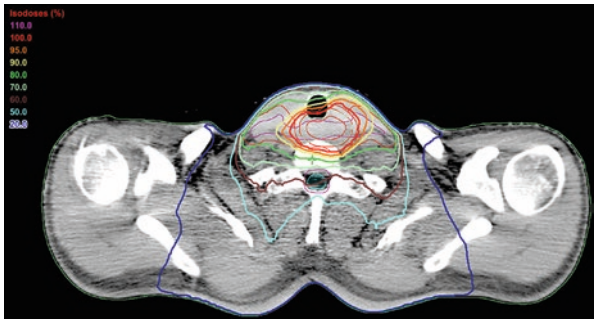


Fig. 16.6 Dose distribution of IMRT plan for a cervical esophagus tumor

low doses of radiation therapy to normal tissue areas. The influence of this on toxicity (low-dose pulmonary irradiation and development of lung toxicity) remains uncertain. Several clinical trials of definitive chemoradiotherapy using IMRT for cervical or thoracic esophageal cancer are now ongoing.

16.2.2.3 Dose and Fractionation

Conventional daily dosing at 1.8–2.0 Gy fraction is standard. In the treatment of radiotherapy alone, 60–70 Gy at 1.8–2 Gy per fraction is standard radiation dose. In the treatment of chemoradiotherapy, based on the result of a randomized trial intergroup (INT) 0123 demonstrated that no significant difference in overall survival and local/regional control between the 50.4 Gy arm and the 64.8 Gy arm among patients (85% SCC) treated with concurrent 5-FU and cisplatin chemotherapy for nonsurgical therapy [21], standard dose of radiotherapy for esophageal cancer is usually 50–50.4 Gy at 1.8–2 Gy per fraction in the definitive setting. Meanwhile, the Pattern of Care Study reported that median total dose of external radiotherapy was 60 Gy for definitive chemoradiotherapy patients in Japan [22]. In the neoadjuvant setting, 40–50.4 Gy at 1.8–2 Gy per fraction is standard radiation dose. And in the prophylactic setting, 41.4 Gy at 1.8 Gy per fraction is used in clinical trial [9].

16.2.2.4 Dose Constraints

In radiotherapy treatment planning of esophageal cancer, normal-tissue tolerance should always be considered. Accurate delineation of adjacent organs, including lungs, spinal cord, heart, kidneys, and liver is important. And it is necessary to evaluate the dose-volume histogram (DVH) analyses for each organ (Fig. 16.7). Max dose of the spinal cord is generally limited to 45 Gy using 1.8 Gy fractions. Several studies have demonstrated that dosimetric parameters derived from DVH are associated with organ toxicity after treatment of esophageal cancer [23–27]. In the treatment of esophageal cancer using a neoadjuvant regimen of 45 Gy with concurrent chemoradiotherapy, a lung V10 (a percentage of lung volume receiving at least 10 Gy) of 40% or greater, and a V15 of 30% or greater, was shown to be predictive of significantly greater pulmonary complications (pneumonia and acute respiratory distress syndrome [ARDS]) [26]. Investigators from the United States reported that the volume of lung spared from doses of 5 Gy or higher (VS5) was the factor most strongly associated with postoperative pulmonary complications

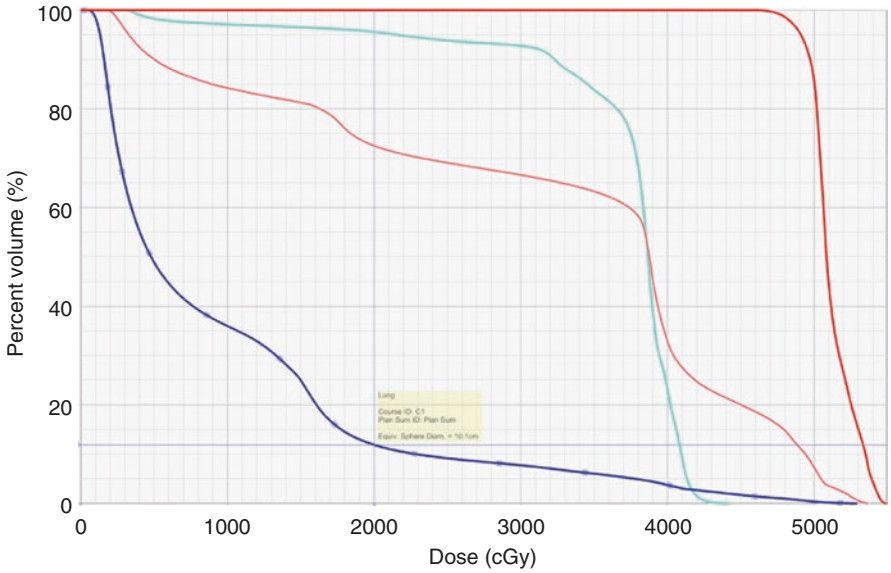


Fig. 16.7 DVH analysis of a four-field technique for a middle thoracic esophagus tumor (50.4 Gy in 28 fraction with elective nodal irradiation of 41.4 Gy). Boost PTV (red), Total lung (blue), Heart (pink), and Spinal cord (cyan)

(pneumonia and ARDS) for esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery [27]. In the treatment of esophageal cancer using definitive regimen of 60 Gy with concurrent chemoradiotherapy, investigators from Japan reported that the optimal V20 threshold to predict symptomatic radiation pneumonitis (grade2) was 30.5% [23]. Konski and colleagues proposed thresholds for symptomatic cardiac toxicities (pericardial effusion, myocardial infarction, and sick sinus syndrome) for whole-heart V20 of 70%, V30 of 65%, and V40 of 60% [25]. Fukada and colleagues reported that mean pericardial doses of 36.5 Gy and V45 of 58% were selected as optimal cutoff values for predicting symptomatic pericardial effusion [24]. For lower esophageal cancers, it is recommended that mean liver dose should be limited to less than 28 Gy, and mean dose of bilateral whole kidneys should be limited to less than 15–18 Gy [28].

16.2.3 Brachytherapy

Brachytherapy involves intraluminal placement of a radioactive source into the esophagus with an intraorally or intranasally inserted applicator and permits treatment of a localized area of the esophagus to high radiation doses with relative sparing of surrounding structures. This technique may be used alone or in combination with external beam radiotherapy with or without chemotherapy. The indication of brachytherapy is the treatment of superficial esophageal cancer for curative intent in

Japan (local control rate: 79–85%) [29–35], on the other hand it is used to relief symptom such as dysphagia for palliative intent in the treatment of advanced esophageal cancer in Western countries [36, 37]. Brachytherapy can be administered by two general methods; Low-dose rate (LDR) brachytherapy, High-dose rate (HDR) brachytherapy. Modern HDR brachytherapy equipment delivers radiation much faster than 12 Gy/h, permitting the delivery of a planned dose within minutes compared with LDR sources, which require many hours or days. As a general rule of HDR brachytherapy, the diameter of the balloon applicator should be 15–20 mm. The whole length of the tumor and 2 cm above and below the lesion are included in the target volume. The reference dose point is set at a depth of 5 mm of the esophageal submucosa (5 mm beyond the wall of the balloon surface). There is no definite consensus about the optimal dose of intraluminal brachytherapy for esophageal cancer. In Japan, 50–60 Gy external beam radiotherapy followed by 8–12 Gy in two-four fractions (3–4 Gy per fraction) HDR brachytherapy is generally used. It was reported that a higher dose per fraction associated with the risk of esophageal ulcer and perforation [29]. Dose of 4 Gy or less per fraction by HDR brachytherapy and dose of 6 Gy or less per fraction by LDR brachytherapy once or twice a week is recommended in Japan [31]. The American brachytherapy society (ABS) recommends an HDR dose of 10 Gy in two fractions, prescribed at 1 cm from the source, to boost 50 Gy EBRT [38]. Figure 16.8 illustrates the dose distribution and 3D-view in the treatment planning of HDR-brachytherapy.

16.3 Treatment Results

16.3.1 Radiotherapy Alone

Radiation therapy alone has been usually delivered when lesions are deemed inoperable because of tumor extent or medical contraindications. In general, patients receiving radiation as a sole treatment modality have a median survival of 6–12 months and 5-year survival of <10%. In a review of 49 early series involving more than 8400 patients (100% SCC) treated with radiation therapy alone, overall survival rates at 1, 2, and 5 years were 18%, 8%, and 6%, respectively [39]. Okawa and colleagues reported 5-year survival rates by stage (100% SCC) [40]. For patients with stage I disease, the 5-year survival rate was 20%; stage II, 10%; stage III, 3%; and stage IV, 0%. Five-year overall survival rate (OS) was 9%. For cervical esophageal lesions treated with radiation alone, the cure rates are comparable with those in patients treated with surgery alone. As a result of clinical trial, Radiation Therapy Oncology Group (RTOG) trial (RTOG8501) comparing combined chemotherapy with 5-FU and cisplatin with radiotherapy (50 Gy) versus radiotherapy alone (64 Gy) showed that 3-year survival with radiotherapy alone was 0% [1–3]. In a prospective trial of radiotherapy alone (66 Gy) for patients older than 80 years old with T1-3N0M0 squamous cell carcinoma of the thoracic esophagus, median survival time and 3-year overall survival rate were 30 months

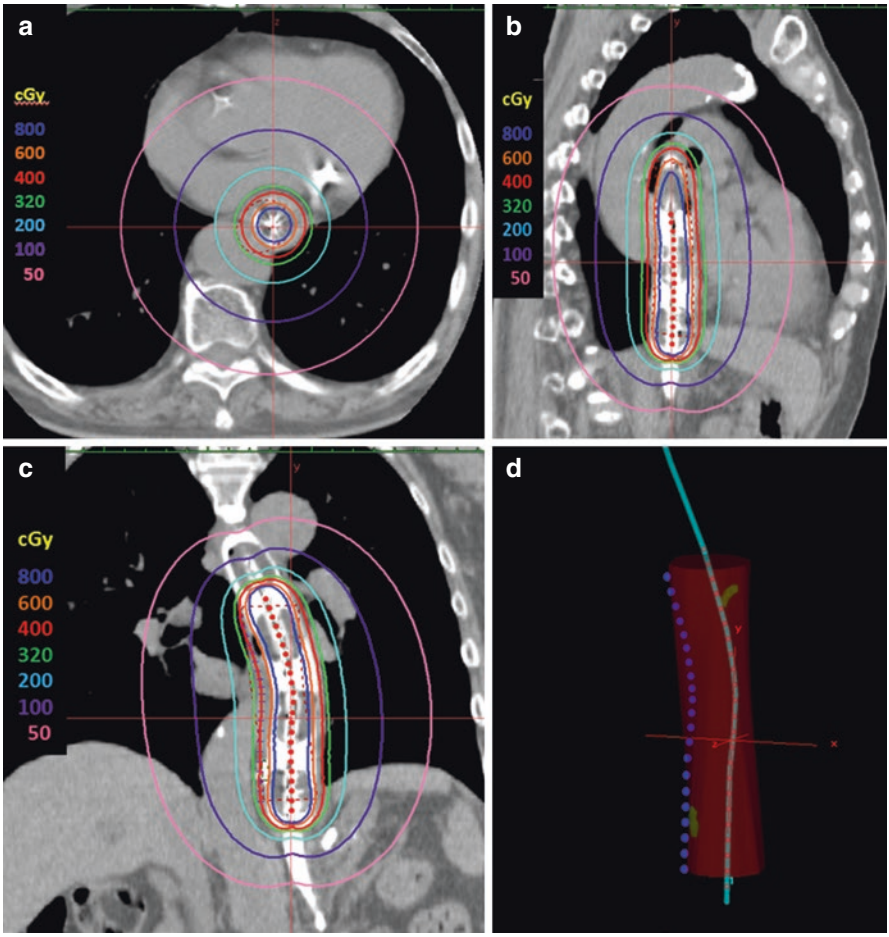


Fig. 16.8 (**a–d**) Dose distribution of intraluminal brachytherapy for a cT1bN0 middle thoracic esophagus tumor. Prescription dose: 400 cGy at a depth of 5 mm of the esophageal submucosa as the reference dose point. (**a**) axial view. (**b**) Sagittal view. (**c**) Coronal view, (**d**) 3D-view. Metal clips (green), High-risk CTV (red): GTV plus 2 cm margin proximally and distally along the length of the esophagus, reference dose point (blue), catheter (cyan), and dwell points (red)

and 39%, respectively [41]. This favorable results were due to patient selection including earlier stage (non-T4N0; 35% T1N0) compared to RTOG8501.

16.3.2 Chemoradiotherapy

The landmark trial establishing the superiority of concurrent chemoradiotherapy to radiation therapy alone was RTOG8501. Herskovic and colleagues reported the results of this randomized trial comparing combined chemotherapy with 5-FU and

cisplatin with radiotherapy (50 Gy) versus radiotherapy alone (64 Gy) for esophageal cancer (88% SCC) [3]. The median survival in patients treated by radiation alone was 8.9 months compared with 12.5 months for those treated with combined therapy, with 2-year survival rate 10% versus 38%; the incidence of local recurrence decreased from 24% to 16%, and the 2-year distant metastasis rate decreased from 26% to 12%. Updated results showed that at 5 years, survival rates were 26% and 0%, respectively, for chemoradiotherapy and radiation therapy alone [1, 2].

16.3.2.1 Chemoradiotherapy for Unresectable Locally Advanced Esophageal Cancer

For locally advanced unresectable esophageal cancer, chemoradiotherapy is standard treatment with potentially curative intent. Results of clinical trials of definitive chemoradiotherapy for T4 tumor is shown in Table 16.2 [6–8, 21, 42–52]. INT0123, a randomized clinical trial compared standard-dose 50.4 Gy to high-dose 64.8 Gy with both concurrent 5-FU and cisplatin chemotherapy for patients with clinical T1-4N0-1M0 esophageal cancer [21]. This study was closed after an interim analysis showed no probability of superiority in the high-dose arm. No significant difference in median survival (18.1 vs. 13 months), 2-year survival (40% vs. 31%), or local-regional failure/persistence of disease (52% vs. 56%) was seen between the standard-dose and high-dose arms. In a single institute phase II trial of chemoradiotherapy with 5-FU and cisplatin and 60 Gy irradiation for patients with clinical T4 and/or M1 lymph node ESCC, complete response (CR) rate was 33% and median survival time and 3-year survival rate was 9 month and 23%, respectively [8]. Another clinical trials of 5-FU and cisplatin and 60 Gy irradiation for patients including clinical T4 showed that CR rate was 15–33% and 2-year, 3 year survival rates were 27%–46% and 23%–30%, respectively [6, 7, 42–44]. Other combination regimens using new drugs (paclitaxel, docetaxel, oxaliplatin, S-1, capecitabine, cetuximab, and nimotuzumab) with concurrent radiotherapy have been evaluated [46–54]. Recently, another treatment strategy including intensive induction chemotherapy (docetaxel, cisplatin, and 5-FU) have been evaluated [55, 56]. Multidisciplinary treatment in which surgery or chemoradiotherapy was performed after intensive induction chemotherapy has been shown to yield good short-term results with a 1-year overall survival rate of 67.9% [52]. JCOG1510, randomized control trial compared this multidisciplinary treatment to definitive chemoradiotherapy is now ongoing.

16.3.2.2 Chemoradiotherapy for Resectable Esophageal Cancer

Definitive chemoradiotherapy is a treatment option in an attempt to preserve the esophagus for resectable esophageal cancer. Results of clinical trials of definitive chemoradiotherapy for resectable esophageal cancer is shown in Table 16.3 [1–5, 55–60]. For stage I esophageal cancer, Japan Clinical Oncology Group (JCOG) 9708, a phase II trial of chemoradiotherapy with 5-FU and cisplatin and 60 Gy irradiation against primary tumor only was conducted (Fig. 16.1b). CR rate was 87.5% and the 5-year overall survival rate was 75.5% [4]. Recently, results of the parallel group controlled trial of esophagectomy versus chemoradiotherapy for stage I (T1b)

Table 16.2 Results of clinical trials of definitive CRT for ESCC including T4

Author	cStage	Pathology: rate of SCC (%)	No. of pt.	Regimen	CR rate (%)	Survival
INT0123 [21] (USA)	T1-4N0-1 (T4: 8%)	86	109 109	FP + 50.4 Gy FP + 64.8 Gy	NR NR	2y: 31% 2y: 40%
Ohtsu [8] (Japan)	T4/M1Lym (T4: 67%)	100	54	FP + 60 Gy	33%	1y: 41% 3y: 23%
JCOG9516 [6] (Japan)	T4/M1lym (T4: 100%)	100	60	FP + 60 Gy	15	2y: 31.5%
Nishimura [7] (Japan)	T4/M1Lym (T4: 100%)	100	28	FP + 60 Gy	32	Stage III; 2y: 27% Stage IV; 1y: 23%
JCOG0303 [42] (Japan)	T4/M1lym (T4: 75%)	100	71 71	FP + 60 Gy Low dose FP + 60 Gy	0[a] 1.4[a]	3y: 30% 3y: 26%
KROSG0101/JROSG021 [43, 44] (Japan)	Stage II–IVA (T4: 44%)	100	46 45	FP + 60 Gy Low dose FP + 60 Gy	NR NR	2y: 46%, 5y: 35% 2y: 44%, 5y: 22%
Shahl [45] (Germany)	T3-4N0-1 (T4: 17%)	100	86 86	FLEP → EP + 60 Gy FLEP → EP + 40 Gy + S	NR NR	3y: 55% 3y: 58%
PRODIGE5/ACCORD17 [46] (France)	Stage I–IVA (T4: NR)	86	133 134	FP + 50 Gy FOLFOX + 50 Gy	43 43	3y: 26.9% 3y: 19.9%
SCOPE1 [47] (UK)	Stage I–III (T4: NR)	73	129 129	CP + 50 Gy CP + Cetuximab + 50 Gy		2y: 56.0% 2y: 41.3%
RTOG0436 [48] (USA)	T1N1/ T2-4N0-1/ M1a (T4: 18%)	37	169 159	Cisplatin + PTX + 50.4 Gy Cisplatin + PTX + Cetuximab + 50.4 Gy	57.9 56.3	2y: 44.0%, 3y: 27.9% 2y: 44.9%, 3y: 33.8%

KDOG0501 [49] (Japan)	T4/M1lym (T4: 69%)	100	42	DCF + 50.4 Gy, 61.2 Gy	52.4	1y: 66.1%, 3y: 43.9%
NICE trial [50] (Brazil)	T3-4N0-1/ M1a (T4: 33%)	93	107	FP + 50.4 Gy FP + Nimotuzumab + 50.4 Gy	33.3[b] 47.2[b]	MST: 11.5 months MST: 15.9 months
Sateke [51] (Japan)	T4/M1lym (T4: 61%)	100	33	DCF → FP + 60 Gy	39.4	1y: 78.8%, 3y: 40.4%
Yokota [52] (Japan)	T4/M1lym (T4: 90%)	98	48	DCF →CS if resectable →FP + 60 Gy → CS if resectable	23.5 (no CS group)	1y: 67.9%

[a]Only one point assessment of tumor response

[b]Endoscopic complete response

CRT chemoradiotherapy, *SCC* squamous cell carcinoma, *CR* complete response, *INT* intergroup, *JCOG* Japan Clinical Oncology Group, *KROSG* Kyoto Radiation Oncology Study Group, *JROSG* Japanese Radiation Oncology Study Group, *PRODIGE* Partenariat de Recherche en Oncologie Digestive, *ACCORD* Actions Concertées dans les Cancers Colo-Rectaux et Digestifs, *SCOPE* Study of Chemoradiotherapy in OesoPhageal cancer with Erbitux, *KDOG* Kitasato digestive disease & oncology group, *S* surgery, *FP* 5-FU + cisplatin, *FLEP* 5-FU + leucovorin + etoposide + cisplatin, *FOLFOX* 5-FU + oxaliplatin + leucovorin, *EP* etoposide + cisplatin, *CP* capecitabine + cisplatin, *DCF* docetaxel + cisplatin + 5-FU, *NR* not reported, *MST* median survival time, *CS* conversion surgery

Table 16.3 Results of clinical trials of definitive CRT for resectable ESCC

Author	cStage	Pathology: rate of SCC (%)	No. of pt.	Regimen	CR rate (%)	Survival
RTOG8501 [1–3] (USA)	T1-3N0-1	88	62 134	64 Gy FP + 50 Gy	NR NR	2y: 10%, 5y: 0% 2y: 38%, 5y: 26%
Bedenne [55] (France)	T3N0-1	89	130	FP + 30 Gy or 46 Gy →FP + 15 Gy or 20 Gy	NR	3y: 34%
			129	FP + 30 Gy or 46 Gy →S	NR	3y: 29%
JCOG9708 [4] (Japan)	Stage I	100	72	FP + 60 Gy	87.5	4y: 80.5%
JCOG0502 [56] (Japan)	Stage I (T1b)	100	159	FP + 60 Gy	87.3	3y: 93.1% 5y: 85.5%
JCOG9906 [5] (Japan)	Stage II/III	100	76	FP + 60 Gy	62.2	3y: 44.7% 5y: 36.8%
Kato [57] (Japan)	Stage II/III	98	51	FP + 50.4 Gy	70.6	1y: 88.2% 3y: 63.8%
JCOG0604 [54] (Japan)	Stage II/III	100	44	S-1 + cisplatin + 50.4 Gy	59.5	3y: 61.9%
RTOG0246 [58, 59] (USA)	Stage II/III	27	41	TPF → FR + 50.4 Gy + selective S	36.6	1y: 71% 5y: 36.6%
JCOG0909 [60] (Japan)	Stage II/III	100	94	FP + 50.4 Gy ± salvage treatment	58.5	3y: 74.2%

CRT chemoradiotherapy, *SCC* squamous cell carcinoma, *CR* complete response, *RTOG* Radiation Therapy Oncology Group, *JCOG* Japan Clinical Oncology Group, *FP* 5-FU + cisplatin, *S* surgery, *TPF* Paclitaxel + cisplatin + 5-FU, *NR* not reported

esophageal cancer (JCOG0502) were reported [56]. Chemoradiotherapy consisted of 5-FU and cisplatin and 60 Gy irradiation against primary tumor only the same as JCOG9708 regimen. The 3- and 5-year overall survival rates were 94.7% and 86.5% in esophagectomy arm (209 patients), and 93.1% and 85.5% in chemoradiotherapy arm (159 patients) which results were comparable with esophagectomy. CR rate was 87.3% and 3- and 5-year esophagectomy-free survival rates were 88.7% and 80.4% in chemoradiotherapy arm. Most of residual or recurrent diseases after chemoradiotherapy were curatively resected by endoscopy or surgery. Several reports showed the efficacy of these salvage treatment after definitive chemoradiotherapy [61–64]. For stage II/III esophageal cancer, JCOG9906, a phase II trial of

chemoradiotherapy with 5-FU and cisplatin and 60 Gy irradiation with elective lymph nodal irradiation showed promising activity with 62.2% of CR rate and 36.8% of 5-year overall survival rate [5]. Acute toxicities were mild, but there were four treatment-related death (5.3%) caused by late toxicities. Moreover, 8–15% of high mortality rate was seen in patients who underwent salvage surgery to residual or recurrent disease after chemoradiotherapy [62, 63]. Late toxicity and higher mortality rate might be caused by the extensive radiation field and daily treatment of AP/PA opposite fields. Therefore, a phase II trial of chemoradiotherapy with 5-FU and cisplatin and concurrent radiotherapy 50.4 Gy using of multiple field technique with reducing both the radiation dose and the volume of heart within the radiation field for stage II/III esophageal cancer was conducted [57]. At a median follow up of 29.4 months, late toxicities which were greater than grade 3 were observed in 5.9% of pneumonitis only. And CR rate was 70.6% and 3-year overall survival rate was 63.8%. As a development of the esophagus-preserving approach, a phase II study of induction chemotherapy followed by definitive chemoradiotherapy with selective salvage surgery for stage II/III esophageal cancer (27% SCC) was conducted (RTOG0246) [58, 59]. CR rate was 36.6%. Salvage surgery was performed in 44%. Treatment-related death after surgery occurred in 4.8%. The 1- and 5-year overall survival rates were 71% and 36.6%. Recently, a single-arm confirmatory study of definitive chemoradiotherapy including salvage treatment for stage II/III esophageal carcinoma (JCOG0909) was reported [60]. Chemoradiotherapy consisted of 5-FU and cisplatin and 50.4 Gy irradiation with elective nodal irradiation of 41.4 Gy. For residual or recurrent disease after chemoradiotherapy, salvage endoscopic resection or surgery was performed based on the prespecified criteria. CR rate was 58.8%. Salvage endoscopic resection and surgery were performed in 5% and 27%. R0 resection of salvage surgery was achieved in 76%. Treatment-related death after surgery occurred in 4.0%. 3-year overall survival rate and 3-year esophagectomy-free survival rates were 74.2% and 63.6%, respectively. Grade 3 late toxicities were observed in 9.6% only.

16.3.2.3 Prophylactic Chemoradiotherapy

Recently, a single-arm confirmatory study of endoscopic resection followed by selective chemoradiotherapy for stage I esophageal carcinoma (JCOG0508) was reported [9]. Patients with cT1bN0 (SM1-2) esophageal cancer, which was estimated to be treatable endoscopically, were treated with endoscopic resection, and prophylactic chemoradiotherapy was performed for patients with pathologically confirmed complete resection who had pT1a with positive vascular invasion or pT1b. Chemoradiotherapy consisted of 5-FU and cisplatin and 41.4 Gy irradiation for regional lymph nodes. The 3-year overall survival rate of 90.7%. Grade 3 late toxicities were observed in 3.1% only.

16.3.2.4 Neoadjuvant Chemoradiotherapy

Several randomized trials comparing surgery alone to neoadjuvant chemoradiotherapy were conducted and the results were conflicting (Table 16.4) [65–72]. Bosset and colleagues reported an European Organisation for Research and Treatment of

Table 16.4 Results of clinical trials of neoadjuvant chemoradiotherapy for ESCC

Author	Pathology: rate of SCC (%)	Regimen	No. of patients	MST (months)	*p*-value
Bosset [65] (France)	100	S FP + 37 Gy + S	139 143	18.6 18.6	N.S.
Urba [66] (USA)	25	S FP + VBL + 40 Gy + S	50 50	17.6 16.9	N.S.
Lee [67] (Korea)	100	S FP + 45.6 Gy (HF) + S	51 50	27.3 28.2	N.S.
Burmeister [68] (Trans-Tasman)	38	S FP + 35 Gy + S	128 128	19.3 22.2	N.S.
Tepper [69] (USA)	25	S FP + 50.4 Gy + S	30 26	21.6 54	0.002
Van Hagen [70, 71] (Netherland)	23	S PTX + CBDCA + 41.4 Gy + S	188 178	24.0 48.6	0.003
Hashimoto [72] (Japan)	100	FP + 41.4 Gy + S	31	3y OAS: 70.8%	–

SCC Squamous cell carcinoma, *MST* median survival time, *S* surgery, *FP* 5-FU + cisplatin, *VBL* vinblastine, *HF* hyperfraction, *PTX* paclitaxel, *CBDCA* carboplatin, *OAS* overall survival, *NS* not significant

Cancer (EORTC) trial randomizing 282 patients with squamous cell carcinoma of the esophagus to either surgery alone or preoperative therapy using concurrent cisplatin chemotherapy with radiation therapy [65]. Outcomes showed patients receiving neoadjuvant therapy experienced a significant improvement in disease-free survival, cancer-related mortality, margin-negative resection, and local control; however, no improvement in overall survival was seen versus patients undergoing surgery alone. Recently, results of the largest randomized trial assessing neoadjuvant chemoradiotherapy in the treatment of esophageal cancer (23% SCC) showed a significant survival benefit in patients receiving preoperative chemoradiotherapy [71]. A pathologic complete response rate was 29% in patients receiving preoperative therapy. Median survival was 49.4 months in patients receiving chemoradiotherapy versus 24.0 months in surgery alone, with a significant improvement in 3-year survival (58% vs. 44%). Updated results showed that at 5 years, survival rates were 47% and 33%, respectively, for neoadjuvant chemoradiotherapy and surgery alone [70]. Several meta-analyses have been performed concerning neoadjuvant therapy for esophageal cancer. Gebski and colleagues demonstrated an absolute 2-year overall survival benefit of 13% with the use of neoadjuvant chemoradiotherapy when compared to surgery alone [73]. Sjoquist and colleagues performed an updated meta-analysis of neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy [74]. All-cause mortality for neoadjuvant chemoradiotherapy trials estimated an absolute survival benefit at 2 years of 8.7%, with survival benefits similar between squamous cell carcinoma and adenocarcinoma patients. Recently, another

meta-analysis demonstrated that neoadjuvant chemoradiotherapy significantly increased rates of pathologic complete response/R0 resection rates in both adenocarcinoma and squamous cell carcinoma patients compared to neoadjuvant chemotherapy alone. A significant increase in 3-year survival was seen only in squamous cell carcinoma patients (56.8% vs. 42.8%), whereas in adenocarcinoma patients, no significant difference was seen (46.3% vs. 41%) [75]. Currently, neoadjuvant chemoradiotherapy is accepted as the standard treatment for locally advanced esophageal cancer in Western countries. However, there is no randomized trial performed compared neoadjuvant chemoradiotherapy to surgery alone or neoadjuvant chemotherapy in Japan. Therefore, neoadjuvant chemoradiotherapy for resectable esophageal cancer is investigational in Japan. Hashimoto and colleagues conducted a first mutli-institutional phase II trial of neoadjuvant chemoradiotherapy for stage II/III esophageal cancer in Japan and reported promising activity with 41% of pathological CR rate and 77.4% of 2-year overall survival [72]. JCOG1109, three-arm randomized control trial compared neoadjuvant 5-FU and cisplatin to neoadjuvant 5-FU and cisplatin and radiotherapy or neoadjuvant docetaxel and cisplatin and 5-FU is now ongoing [76].

16.3.3 Palliative Therapy

Palliative radiotherapy is also useful for the purpose of relief of symptoms such as dysphagia and pain, and impair of the patient's quality of life. Palliative treatment regimens range from 30 Gy over 2 weeks to 50 Gy over 5 weeks or up to 60 Gy over 6 weeks, with up to 80% relief of pain and dysphagia [77]. Many studies report a 60% to >80% rate of relief from dysphagia with radiation. Coia and colleagues reported that nearly half of patients with baseline dysphagia experienced an improvement in swallowing within 2 weeks of treatment initiation [78]. By the completion of the sixth week, 80% or more of patients experienced improvement. A median time to maximal improvement was approximately 1 month. Palliative chemoradiotherapy is likely preferable to radiation alone for patients with advanced-stage esophageal carcinoma who have a good performance status. Retrospective analysis showed that 75% of stage IVB patients treated with 5-FU and cisplatin and 40 Gy irradiation improved dysphagia score [79]. Recently, Penniment and colleagues reported a Trans-Tasman Radiation Oncology Group (TROG) trial (TROG 03.01) randomizing 220 patients with advanced/metastatic esophageal cancer (26% SCC) to receive 35 Gy in 15 fractions (or alternatively 30 Gy in 10 fractions) with or without the addition of concurrent cisplatin and fluorouracil [80]. No significant differences in dysphagia relief (45% vs. 35%) and median overall survival (6.9 vs. 6.7 months) were seen between the chemoradiotherapy group and the radiotherapy group. As to toxicity, there were significant differences in grade 3–4 acute toxicity (36% vs. 16%) between the chemoradiotherapy group and the radiotherapy group. Intraluminal brachytherapy has also been used for palliation of dysphagia [38]. The previously described randomized trial from the Netherlands comparing intraluminal brachytherapy to stent placement showed that although patients undergoing stenting

experienced a more rapid improvement in dysphagia, long-term palliation was significantly improved in patients treated with brachytherapy [37]. A meta-analysis of prospective studies of brachytherapy encompassing 623 patients concluded that brachytherapy was a highly effective and relatively safe treatment option that was currently underused. However, the severe adverse event rate was 23% (stenosis 12%, fistula development 8%) [81].

16.4 Toxicity of Radiotherapy

Acute adverse events are esophagitis, dermatitis, weight loss, fatigue, and anorexia. Nausea and vomiting are relatively common, particularly in patients with lower esophageal tumor. Most patients experience esophagitis and dysphagia. Many symptoms resolve within 1–2 weeks of treatment completion. Radiation pneumonitis is subacute, generally occurs 2–6 months after radiation therapy completion. Usually, most patients have no symptoms. Common symptoms include nonproductive cough, fever, dyspnea, and, more uncommonly, respiratory distress. Late adverse events are pericardial effusion, pleural effusion, esophageal strictures, fistula formation, and hemorrhage [82]. And hypothyroidism may occur in case of including the thyroid within radiation field [44]. In a Japanese study, long-term analysis of 78 patients with complete remission treated with definitive chemoradiotherapy (cisplatin and 5-FU with 60 Gy) for squamous cell carcinoma revealed grade 2, 3, and 4 late pericarditis occurring in 6%, 5%, and 1% of patients, respectively; grade 4 heart failure in 2 patients; grade 2, 3, and 4 pleural effusion development in 5%, 6%, and 0% of patients, respectively; and grade 2, 3, and 4 radiation pneumonitis development in 1%, 2%, and 0% of patients, respectively [83]. Another analysis from Japan using fields inclusive of supraclavicular, mediastinal, and celiac regions up to a dose of 60 Gy with concurrent cisplatin and 5-FU showed a 2-year cumulative incidence of late, high-grade cardiopulmonary toxicities for patients ≥75 years of 29% versus 3% in younger patients. They concluded that older patients may not tolerate extensive radiation fields [84]. In JCOG9906, late toxicities included grade 3/4 esophagitis (13%), pericardial (16%), and pleural (9%) effusions, and radiation pneumonitis (4%), which caused 4 deaths [5]. These high incidences of late toxicities might be caused by extensive radiation field and daily treatment of AP/PA opposite fields. Recently, to reduce the late cardiac toxicity, use of multiple field technique with reducing both the radiation dose and the volume of heart within the radiation field is recommended while keeping the volume of the irradiated lung at a lower percentage [9, 57, 60]. About half of the esophageal strictures are due to local persistent or local recurrence. For benign strictures, dilation results in palliation in the majority of patients. Tumor involvement of the trachea or aorta or lung can lead to fistula formation during or after radiotherapy. In regard to brachytherapy, combination chemoradiotherapy with HDR-brachytherapy was associated with a high risk of life-threatening toxicities including esophageal ulcer, fistula, and perforation [34, 85–87]. And intubation with metallic stents before or during radiotherapy was associated with a high risk of life-threatening complications (Grade 3–5: 51%, Grade 5:

21%) such as hematemesis, esophageal fistula, and pneumonitis [88]. Samual and colleagues reported the outcome of patients with and without esophageal stenting before radiotherapy treated with concurrent chemoradiotherapy at a median dose of 50.4 Gy [89]. Of the 103 patients, there were significant differences in grade 3 or higher acute toxicities including esophagitis, dehydration, and anorexia between the stent group and no-stent group (71% vs. 27%). And after propensity score matching, the stent patients had a worse median overall survival compared with the no-stent patients (11.5 vs. 22.0 months).

16.5 New Radiation Treatment Modalities

New radiotherapy techniques such as IMRT, proton-beam therapy, and heavy-particle radiotherapy permit concentration of the radiation dose on the tumor with avoidance of critical organs such as the heart, lung, and spinal cord. These techniques may allow dose escalation in the treatment of esophageal cancer. Proton-beam treatment and heavy-particle radiotherapy take advantage of Bragg peak property to allow dose localization at the tumor while avoiding critical organs. In addition, carbon-ion radiotherapy that utilizes heavy-ion beams has a high relative biological effectiveness (RBE) with high linear transfer. Report from Japan using protons with or without photons to a median total dose of 76 GyE for 46 patients with ESCC showed the 5-year local control rate was T1: 83%; T2–4: 29%; and survival T1: 55%; T2–4: 13% [90]. Mizumoto and colleagues reported the results of locally advanced ESCC using protons with or without photons to a total dose of 70–98 GyE [91]. Of 51 patients, 40 (78%) showed a complete response (T1, T2: 100%; T3: 77%; T4: 38%). And the 5-year local control rate was 38.0% and 5-year overall survival rate was 21.1%. As a late toxicity, one patient died due to hemorrhage from an esophageal ulcer at the site of irradiation without recurrence. However, there were no other non-hematologic toxicities of grade ≥3 including lung and heart toxicity. Lin and colleagues reported the toxicities and outcomes of 62 patients treated with proton-beam therapy to a median total dose of 50.4 Gy with concurrent chemotherapy for esophageal cancer (22.6%SCC) [92]. A total of 29 patients (46.8%) received preoperative CRT. The pathologic complete response rate for surgical cohort was 28%, and the CR and near CR rates (0%–1% residual cells) were 50%. The 3-year overall survival rate was 51.7% and local-regional control rates were 56.5%. There was one case each of grade 2, 3, 5 radiation pneumonitis and another one patient died due to cardiac toxicity. Ishikawa and colleagues also reported the toxicities and outcomes of 40 patients treated with proton-beam therapy concurrently combined with chemotherapy consisting of cisplatin and 5-FU for esophageal cancer [93]. A total dose of 60 GyE was delivered and an additional boost of 4–10 GyE was given when residual tumors were suspected. Of 40 patients, 31 (78%) showed a complete response (stage I: 88%; stage II: 89%; stage III: 56%). And the 2-year local control rate was 66.4% and 2-year overall survival rate was 75.1%. As a late toxicity, no cardiopulmonary toxicities of grade 3 or higher were observed. Akutsu and colleagues conducted a phase I/II clinical trial of preoperative

carbon-ion radiotherapy for ESCC [94]. Thirty-one patients were enrolled and the radiation dose was escalated from 28.8 GyE up to 36.8 GyE. 12 (38.7%) patients achieved a pathological CR. The overall 3- and 5-year survival rates in the stage I cases were 81% and 61%, and were 85% and 77% for the stage II, and 43% and 29% for the stage III cases, respectively. One case (3.2%) in 35.2 GyE presented Grade 3 of postoperative acute respiratory distress syndrome (ARDS), and there were no late toxicities. However, these new approaches remain investigational, so further research is necessary to evaluate the efficacy and safety of new techniques and technology in a prospective trial.

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