Practical Guides in Radiation Oncology
Series Editors: Nancy Y. Lee · Jiade J. Lu

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Gastrointestinal Malignancies

A Practical Guide on Treatment Techniques

Springer

Practical Guides in Radiation Oncology

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The series *Practical Guides in Radiation Oncology* is designed to assist radiation oncology residents and practicing radiation oncologists in the application of current techniques in radiation oncology and day-to-day management in clinical practice, i.e., treatment planning. Individual volumes offer clear guidance on contouring in different cancers and present treatment recommendations, including with regard to advanced options such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). Each volume addresses one particular area of practice and is edited by experts with an outstanding international reputation. Readers will find the series to be an ideal source of up-to-date information on when to apply the various available technologies and how to perform safe treatment planning.

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Preface

The *Gastrointestinal Malignancies: A Practical Guide on Treatment Techniques* series is intended to be a *Practical Guide* to incorporating and delivering quality radiation therapy in the multimodality treatment of gastrointestinal malignancies *rather than a traditional textbook* addressing background and summaries of landmark clinical trials. It is designed for radiation oncologists, medical physicists, medical dosimetrists, and other oncology professionals such as medical and surgical oncologists with special interest in radiation techniques.

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Part I

Esophageal Cancer

Proximal/Cervical Esophageal Cancer

1

Anupam Rishi and Jimmy J. Caudell

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1.1 Introduction

The esophagus is a hollow, muscular tube, approximately 25 cm in length, which extends from the lower border of the cricoid cartilage to the cardiac orifice of the stomach. The American Joint Committee on Cancer (AJCC) has divided the esophagus into four regions: cervical, upper (proximal) thoracic, mid-thoracic, and lower thoracic [1]. The cervical esophagus begins at the cricopharyngeus muscle (approximately the C7 level or 15 cm from the incisors) and extends to the thoracic inlet

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(approximately T3 level or 18 cm from the incisors, at the level of the suprasternal notch). Cervical esophageal cancers differ from those at the mid- and lower esophagus or gastroesophageal junction in regard to natural history, patterns of spread, biological behavior, and management. As such, cervical esophageal cancers are managed more similarly to head and neck squamous cell carcinomas rather than for malignancies involving more distal portions of the esophagus. In this chapter, we will discuss the management principles and radiotherapy (RT) delivery techniques for cervical esophageal cancers.

1.2 Management Principles for Cervical Esophageal Cancers

The management of cervical esophageal cancer differs from that of cancers of the remaining esophagus [2]. Due to proximity to critical organs and risk of adjacent anatomical structure invasion, most cervical esophageal cancers are not amenable to surgery, as this would involve functionally devastating resections of portions of the pharynx, larynx, and cervical esophagus (pharyngo-laryngo-esophagectomy). In addition, neck dissections are often required. Therefore, surgery is associated with significant morbidity, mortality, and severely compromised quality of life [3, 4]. Based on various studies, patients treated with definitive surgery had morbidity rates of 60–70%, mortality rates of 7–11%, and a 5-year overall survival rate of 18–27% [5–8] (Table 1.1).

Therefore, RT combined with chemotherapy is preferred as chemoradiation (CRT) offers similar locoregional control and survival as compared to surgical resection, with less functional impairment and better quality of life [13–18]. The FFCD 9102 study showed that locally advanced thoracic esophageal cancer patients who responded to CRT derived no benefit from the addition of surgery after CRT as compared to continuation of additional CRT [19]. Similarly, a German trial compared induction chemotherapy followed by CRT followed by surgery against the same induction regimen (chemotherapy + RT), but without surgery. There was no significant difference in overall survival between the two treatment groups. Treatment-related mortality was significantly greater in the surgery group than in the CRT group [20]. Interestingly, a meta-analysis investigating RT versus surgery within multimodality protocols for esophageal cancer suggested that overall survival was equivalent between surgery and definitive CRT [21]. While these trials were not specific to cervical esophageal cancer, they provide a logical rationale for the selection of definitive CRT.

Table 1.1 Outcome of patients treated with surgery

Study	Year	N Cervical esophagus/ hypopharynx	5-year overall survival (%)	Morbidity *n* (%)	Hospital mortality *n* (%)
Wei et al. [9]	1998	32/37	24	34 (49)	6 (9)
Triboulet et al. [4]	2001	78/131	24	42 (33.1)	10 (4.8)
Wang et al. [10]	2006	15/26	31.5	19 (46.3)	4 (9.8)
Daiko et al. [11]	2007	74/0	33	25 (34)	3 (4)
Tong et al. [12]	2011	43/25	37.6 (2-year)	–	5 (7.1)

1.2.1 Definitive Chemoradiation

Given the location in the neck, cervical esophageal cancers are usually managed similarly to locally advanced head and neck squamous cell carcinoma (HNSCC) [13]. Due to the rarity of cervical esophageal cancers, no large randomized studies have focused exclusively on cervical cancers. The evidence of concurrent chemotherapy in improving survival over RT alone can be extrapolated from randomized trials and meta-analyses targeted to thoracic esophageal or head and neck squamous cell cancers. The landmark Radiation Therapy Oncology Group 85-01 trial using 2-D radiation therapy techniques (2DRT) compared RT alone (64 Gy in 32 fractions over 6.5 weeks) versus concurrent CRT [two cycles of infusional 5-FU (1000 mg/m^2 per day, days 1–4, weeks 1 and 5) plus cisplatin (75 mg/m^2 day 1 of weeks 1 and 5) and RT (50 Gy in 25 fractions over 5 weeks)]. The results showed a significant survival advantage for the CRT arm, i.e., 5-year survival 27% vs. 0% [14, 15, 22]. Although this study included only patients with thoracic esophageal cancer, the study results form the basis of the current non-surgical treatment of patients with esophageal cancer, including cervical esophagus. Various smaller studies of exclusive cervical esophageal cancer have reported a 5-year OS of 30–40% for patients treated with definitive CRT [16–18, 23, 24], which is comparable with OS after surgery alone (24–47%) [4, 10, 11, 13, 25–29]. Previous studies on the efficacy of RT with or without chemotherapy for treating cervical esophageal cancer have reported 3-year survival rates of 22–40% [17, 23, 30–32] (Table 1.2).

Preservation of the larynx and pharynx is an important management concern in cervical esophageal cancer due to the frequency of hypopharyngeal or laryngeal involvement. The negative physical and psychosocial impact of a permanent tracheostomy and loss of natural voice are powerful drivers for patients to choose a treatment that will preserve their laryngeal and swallowing functions. From this perspective of organ preservation, treatment approaches such as RT or concurrent RT and systemic therapy have been used to preserve the functional larynx for patients with laryngeal, hypopharyngeal, or cervical esophageal cancers [37–40]. In the RTOG 91-11 study, the larynx preservation rate was 88% using concurrent CRT [37, 38].

Although CRT for esophageal cancers usually consists of 50.4 Gy in 1.8 Gy per fraction per day, higher doses up to 66–70 Gy may be appropriate for cervical esophageal cancer analogous to the HNSCC [12, 17, 30, 32, 33, 36, 41]. Delivering an adequate RT dose to the tumor is often challenging because of the proximity of the cervical esophagus to vital structures such as the spinal cord, brachial plexus, larynx, pharyngeal constrictors, and lungs. However, with the advances in modern RT techniques, such as IMRT, Volume-Modulated Arc therapy (VMAT), or other rotational radiation delivery techniques, delivery of a more conformal dose to the tumor and improved sparing of nearby organs at risk are possible [42–50]. Preliminary single institution data from use of proton-beam RT (PBT) in cervical esophageal cancers has also shown potentially improved dose distributions [51, 52].

Table 1.2 Outcome of patients treated using radiotherapy

Study	Year	*N*	RT	Dose (Gy)	LRC	2-year overall survival (%)	5-year overall survival (%)
Stuschke et al. [30]	1999	17	2D	60–66	33 (2-year)	24	NA
Burmeister et al. [33]	2000	34	2D	50.4–65	NA	NA	55
Yamada et al. [32]	2006	27	2D	44–73.7	13 (5-year)	38	38
Uno et al. [34]	2007	21	IMRT	60–74	NA	41	27
Huang et al. [23]	2008	71	2D/3D/ IMRT	54 Gy/20 fr (n = 29) 70 Gy/35 fr (n = 42)	NA NA	41 32	NA NA
Tong et al. [12]	2011	21	2D/3D	60–68	NA	46.9	NA
Grass et al. [2]	2014	240	NA	NA	NA	40	28
Cao et al. [35]	2015	115	IMRT	59.4–80	68.3 (2-year)	47.6	NA
Cao et al. [36]	2016	64	IMRT	60–70	74.5 (2-year)	42.5	NA

IMRT intensity-modulated radiotherapy, *LRC* locoregional control

1.2.2 Concurrent Chemotherapy

As cervical esophageal cancers are often managed similar to head and neck squamous cell carcinoma, concurrent high-dose cisplatin-based chemotherapy, consisting of 100 mg/m^2 on day 1, 22, and 43 of RT, may be reasonable [23]. Other commonly used concurrent chemotherapeutic regimens include a combination of cisplatin (75 mg/m^2 day 1 of weeks 1 and 5) and 5-FU (two cycles of infusional 5-FU, 1000 mg/m^2 per day, days 1–4, weeks 1 and 5), as adapted from established regimens in lower esophageal squamous cell cancers (SCC) [53]. No difference in locoregional control and survival outcome has been observed comparing patients treated with high-dose cisplatin versus cisplatin + 5-FU or mitomycin C, but combination therapy can lead to higher toxicity rates when compared with cisplatin alone [23, 54].

Other chemotherapeutic regimens have also been studied with comparable results. Recently, the PRODIGE5/ACCORD17 randomized trial assessed the efficacy and safety of the concurrent FOLFOX regimen (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, bolus fluorouracil 400 mg/m^2, and infusional fluorouracil 1600 mg/m^2) against standard cisplatin/5FU as part of definitive CRT (50 Gy in 25 fractions) [55]. No significant differences were recorded in the progression-free survival and rates of grade 3 or 4 adverse events in both the arms. Carboplatin and paclitaxel-based chemotherapy, a regimen already used in SCC of the lower esophagus, has been used as an alternative to the cisplatin-based regimen [56].

Overexpression of EGFR has been detected in 30–90% of esophageal cancers and correlates with increased invasion, dedifferentiation, and worse prognosis [57,

58]. Cetuximab, an EGFR targeting therapy, is an established radiosensitizer in HNSCC [59], but its role in cervical esophageal cancers is not established. On the basis of the results of the SCOPE1 trial, a multicenter phase II/III randomized trial comparing CRT versus CRT + cetuximab, the use of cetuximab cannot be recommended due to treatment-limiting toxicity [60]. Recently, a phase III REAL3 trial had to be closed early due to a lack of efficacy [61]. RTOG 0436, a randomized phase III trial, evaluated concurrent chemoradiation [50.4 Gy/1.8 Gy fractions + weekly concurrent cisplatin (50 mg/m^2) and paclitaxel (25 mg/m^2) ± weekly cetuximab (400 mg/m^2 day 1 then weekly 250 mg/m^2)] in nonoperative management of esophageal carcinoma [62]. The preliminary results showed that cetuximab added to chemoradiation did not improve OS [62]. These results add to the growing body of literature, indicating no benefit for current EGFR-targeted agents, and therefore, their use is not recommended outside a trial setting.

1.3 Radiation Therapy Techniques and Planning

The design and delivery of radiation therapy for esophageal cancer requires knowledge of the natural history, anatomy, pattern of spread, and radiobiological principles. Furthermore, the use of proper equipment, implementation of methods to decrease treatment-related toxicity, and close collaboration with the physics and technology staff are essential. The cervical esophagus lies in close anatomical relation to various sensitive organs at risk such as spinal cord, brachial plexus, larynx, pharyngeal constrictors, and lungs. Therefore, key to successful radiation planning is minimizing the dose to these structures while delivering an adequate dose to the primary tumor and regional lymph nodes, which can be aided by techniques such as patient immobilization, modern imaging acquisition, CT-based treatment planning for organ identification, and RT plan optimization.

1.3.1 Setup and Immobilization

Patients are placed in a reproducible supine position with arms laterally and head hyper-extended and immobilized with a thermoplastic head/neck/shoulder mask.

1.3.2 Simulation

A contrast-enhanced Computed Tomography (CT)-based simulation scans are recommended over fluoroscopy for better delineation of target and sparing of organs at risk (OAR).

- The planning CT should encompass the entire neck starting from the base of the skull extending inferiorly through the entire esophagus length to encompass disease with margins.
- Slice thickness of $\leq$3 mm slices should be used, allowing accurate tumor characterization as well as improved quality of digitally reconstructed radiographs.

- Arterial phase IV contrast is generally used to define tumor and nodal basins and to allow the radiation oncologist to discern normal vasculature from other adjacent normal structures, potential adenopathy, etc.
- The tumor and vital structures are then outlined on each slice on the treatment planning system, enabling a 3-dimensional treatment plan to be generated.
- Unlike thoracic esophagus, breathing movements are not significant in cervical esophageal cancer and immobilization using thermoplastic head and shoulder mask sufficiently minimizes interfraction movements. Four-dimensional CT scan, respiratory gating, or breath hold techniques are not routinely recommended for cervical esophageal cancers.

1.3.3 18F-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET) Planning

As an adjunct to CT, PET-CT can be used in esophageal cancer not only as a routine part of initial staging, but also for RT planning and response assessment.

- For primary tumors, PET scans in esophageal cancer have a sensitivity ranging from 95 to 100% and a specificity of 100% [63, 64].
- Because of its higher accuracy to differentiate malignant and normal tissues, it is recommended to incorporate PET-CT into RT planning to improve the target delineation process and to adapt treatment plans [65–68]. In some studies, the use of PET-CT for tumor delineation results in a difference in target volume when compared to CT and EUS in 10–63% of patients [65]. The discordance between CT and PET-CT was due mainly to differences in defining the longitudinal extent of disease in the esophagus [69].
- If no planning PET is available at the time of simulation, a diagnostic PET can also be fused with the simulation CT to aid target delineation.

1.3.4 Treatment Planning

1.3.4.1 Field Design

- IMRT-based planning has facilitated the treatment of cervical esophageal lesions and is the authors' preferred method for treating these tumors (Fig. 1.1). Strict normal tissue constraints, including normal lung and spinal cord, are important considerations using these techniques.

1.3.4.2 Target Volume

- Supraclavicular and superior mediastinal nodes are irradiated electively. Analysis of nodal involvement in a large series of resected squamous cell carcinoma patients supports the concept of elective mediastinal and supraclavicular node coverage in locally advanced proximal tumors [70].

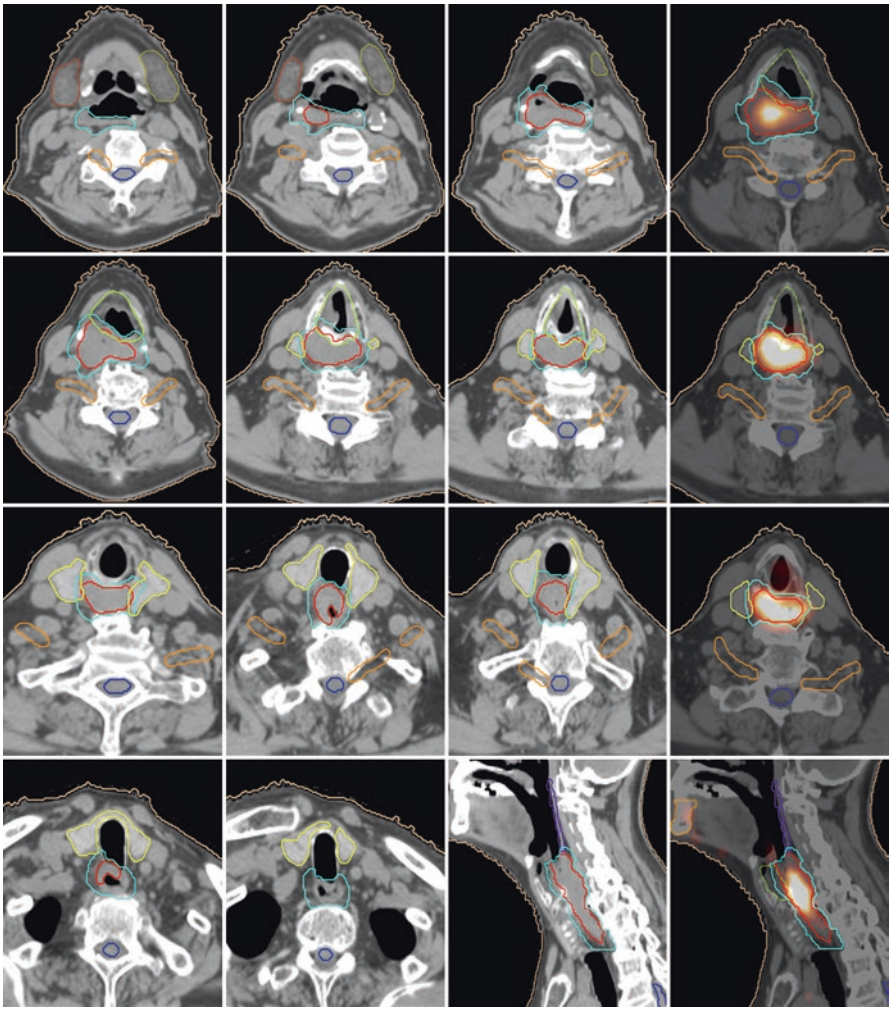

Fig. 1.1 Contouring atlas for a cT3N0M0 cervical esophageal cancer. Delineation of Gross Target Volume (GTV) (*red*), based on CT and PET; Clinical target Volume (CTV) (*skyblue*) expansion accounts for microscopic spread supero-inferiorly; Planning Target Volume (PTV) expansion (3–5 mm) around the CTV to account for setup error and may vary based on IGRT method (Table 1.3). Note the CTV expansion is manually defined to respect anatomic boundaries. *Red* = Gross Target Volume; *Skyblue* = Clinical Target Volume; Normal tissue includes: *Yellow* = thyroid; *Orange* = brachial plexus; mandible (sagittal); *Yellow-green* = larynx; *Blue* = spinal cord; *Brown* = right submandibular gland; *Olive* = left submandibular gland; *Slate blue* = pharyngeal constrictors

- In modern conformal RT practice, treatment volumes are more commonly defined based on the ICRU definitions of clinical target volume (CTV) and planning target volume (PTV). Definitions of GTV, CTV, and PTV are detailed in Table 1.3. Target delineation is shown in Fig. 1.1.

Table 1.3 Definitions of target volumes in RT for cervical esophageal cancer [71]

Type	Description
GTVp	All grossly positive disease of the primary tumor as seen on exam, laryngoscopy, diagnostic and planning CT scans, and PET/CT imaging
GTVn	All grossly involved regional lymph nodes
CTVp[a]	Cranial-caudal: GTV plus 3-cm margin for submucosal extension along the length of the esophagus; or 1 cm above any grossly involved periesophageal nodes, whichever is more cephalad. The upper border should not extend above the level of the cricoid cartilage unless there is gross disease at that level. This margin should be oriented along the esophageal mucosa, instead of being a simple geometric expansion Radially, extend by 1 cm from GTV but respecting anatomic boundaries, such as the vertebral body, trachea, pleura, and vessels, to encompass the periesophageal lymph nodes
CTVn	The nodal CTV should encompass the elective nodal regions, including bilateral levels III, IV, Vb, Vc, VI, and mediastinal nodes, variable coverage of II and Va depending on disease configuration The cranial and caudal limits of the CTV-LN were the caudal edge of the lateral process of the atlas and trachea bifurcation, respectively *Atlas of images illustrating nodal CTV and organs of risk is located at RTOG website: https://www.rtog.org/CoreLab/ContouringAtlases/HNAtlases.aspx)* [72, 73]
PTV	PTV expansion ensures adequate target coverage Defined as per ICRU-62 guidelines and may vary on IGRT method [74] • Portal imaging has been associated with a 5–6 mm setup uncertainty for radiation treatment • With use of CBCT, 3-mm PTV expansion margins appear adequate [75]

GTVp gross tumor volume of primary disease, *GTVn* gross tumor volume of nodal disease, *CTVp* clinical target volume—primary disease, *CTVn* clinical target volume—nodal disease, *PTV* planning target volume, *CBCT* cone-beam CT

[a]CTV should be delineated by radiation oncologists and automatic expansion from GTV is not an acceptable practice

1.3.5 Treatment Delivery Techniques

1.3.5.1 Intensity-Modulated Radiotherapy (IMRT)

With the advent of CT-based 3-dimensional (3D) treatment planning, better anatomic visualization and improved target delineation are feasible for the dose avoidance of normal structures. IMRT utilizes multiple beams (typically 5–9), with each beam modulated further using computer-controlled multi-leaf collimation to dynamically block the path of the radiation when the beam is on. This produces better conformity to the tumor and dose reduction to normal structures [42]. No randomized trial has compared IMRT with 3DCRT in cervical esophageal cancer; however, various studies suggest that these techniques may be useful in the treatment of cervical esophageal cancers [43–46].

1.3.5.2 Volumetric-Modulated Arc Therapy (VMAT) and Helical Tomotherapy (Accuray, Sunnyvale, CA)

Rotational radiation treatment techniques such as Tomotherapy and VMAT allow delivery of a more conformal dose distribution to the tumor and improved sparing of nearby organs at risk, providing an alternative treatment option to conventional IMRT (Fig. 1.2) [47–50]. On dosimetric analysis, tomotherapy plans showed sharper

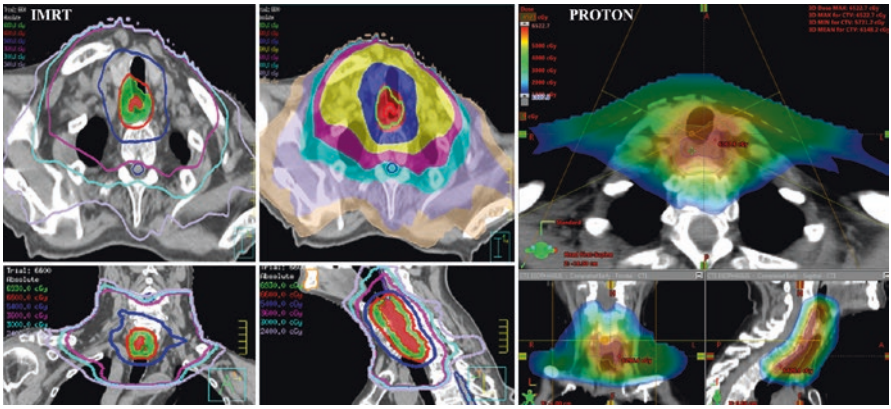

Fig. 1.2 Representative treatment plans for cervical esophagus using IMRT (VMAT) and proton-beam therapy (IMPT). (*Courtesy of Shahed Badiyan, MD, University of Maryland, Maryland Proton Treatment Center, and Michael D. Chuong, MD, Miami Cancer Institute at Baptist Health South Florida). IMRT* intensity-modulated radiotherapy, *VMAT* volumetric-modulated radiotherapy, *IMPT* intensity-modulated proton therapy

dose gradients, more conformal coverage, and better Homogeneity Index for both gross and elective target volume compared with IMRT or 3D-CRT plans. The mean V20 [percentage of the lung volume (with the subtraction of the volume involved by esophageal cancer) which receives radiation doses of 20 Gy or more] of lung was significantly reduced in tomotherapy plans [76]. Compared with static field IMRT, VMAT slightly improves OAR dose sparing and reduces NTCP and monitor units with better PTV coverage [77].

1.3.5.3 Proton-Beam Therapy (PBT)

The interaction between protons and tissue is substantially different than that of photons or electrons [78]. Unlike photon radiation, protons initially traverse matter with minimal loss in energy or attenuation, and the majority of their energy is selectively deposited in the area where they have minimal or essentially no velocity, which is known as the Bragg peak. Importantly, there is essentially no dose deposition distally. Preliminary single institution data from the use of Proton-beam RT (PBT) in proximal esophageal cancers has also shown good dose distributions as the majority of the proton energy is selectively deposited in the area where they have minimal or essentially no velocity, which is known as the Bragg peak (Fig. 1.2) [51, 52].

1.3.5.4 Intensity-Modulated Proton Therapy (IMPT)

Although PBT essentially eliminates exit dose to normal tissues compared with photon therapy, the deposition of high doses proximal to the target is not as highly conformal. In the head and neck regions, the presence of multiple nearby organs at risk that are preferably spared as much as possible makes HNC plans complex. It is therefore especially important in these patients to incorporate robustness in the proton optimization process [79]. Intensity-modulated proton therapy (IMPT) is a more recent technological advancement in which magnets steer the proton beam to cover, or "paint," the target volume layer by layer. Due to the rarity of cervical esophageal cancer, there

Table 1.4 Radiation treatment approaches for proximal/cervical esophageal cancer

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
IMRT/ VMAT/ helical tomotherapy	Definitive CRT	50–70 Gy in 25–35 fractions of 2 Gy per fraction; 5 days/week	IMRT: Multiple coplanar isocentric beams VMAT: Volumetrically modulated coplanar arcs	Concurrent Cisplatin/platinum-based chemotherapy[a]
Proton-beam therapy[b]	Definitive CRT	50–70 GyE; 2 Gy per fraction; 5 days per week	Typically, 2–3 fields (AP/PA; lateral or posterior oblique)	Concurrent cisplatin/ platinum-based chemotherapy[a]

[a]See chemotherapy details in Sect. 1.2.2
[b]May be appropriate for selected cases

is no study evaluating the role of protons or IMPT. However, the results can be extrapolated from head and neck cancer treatment. Multiple studies of head and neck cancers have shown the potential benefits of IMPT by comparing proton therapy with photon modalities [80].

Table 1.4 outlines radiation therapy techniques used for the treatment of proximal/cervical esophagus.

1.3.6 Dose and Fractionation

Although the optimal radiation dose is not well-defined, a total dose of 50–70 Gy for definitive CRT in daily 1.8–2 Gy fractions, 5 days per week, is deemed appropriate. We recommend doses of 66–70 Gy.

1.3.7 Treatment Plan Optimization

Regardless of the radiation modality utilized, treatment plans must be optimized for adequate target coverage and minimization of dose received by the dose-limiting critical structures including spinal cord, brachial plexus, larynx, pharyngeal constrictors, and lungs. Several strategies to treatment planning optimization are commonly utilized to improve dose homogeneity within the target and avoidance of high-dose regions within normal structures, including appropriate selection of beam geometry and energy, use of multiple coplanar/ non-coplanar beams, use of beam modification devices (wedges and compensators) to accommodate for irregularities of patient contour, tissue homogeneity correction (lung correction), and the use of dose sculpting techniques to achieve more conformal dose distributions using advanced radiation technologies (IMRT, VMAT, Tomotherapy, IMPT).

We summarized in Table 1.5, the clinically relevant dose-volume constraints to be incorporated as treatment planning objectives for conventional fractionation (1.8–2 Gy per fraction). This information is a “guideline” and each plan should be unique and optimized to accommodate patient and target-specific attributes.

Table 1.5 Dose-volume considerations for treatment planning optimization of conventional fractionation (70 Gy in 35 fractions; 2 Gy per fraction) [81]

Critical structure	Dose/volume parameters	Toxicity rate (%)	Toxicity endpoint
Spinal cord	Max dose (Gy, 0.03 cc) ≤ 50 Gy	0.2	Myelopathy
Lung—PTV	Mean lung dose < 20 Gy V20 ≤ 30% V10 < 40%	<20	Symptomatic pneumonitis
Brachial plexus	Max dose ≤ 66 Gy V60 < 5% (RTOG 0619)	<5	Plexopathy
Larynx	Max dose: 66 Gy Mean dose < 44 Gy V50 ≤ 27%	<20	Vocal dysfunction Aspiration
Pharynx/pharyngeal constrictors	Mean dose < 50 Gy	<20	Symptomatic dysphagia and aspiration
Thyroid	V26 < 20%		Hypothyroidism

1.4 Physics Quality Assurance

- Prospective peer review of treatment plans and detailed attention quality assurance measures before and during treatment is highly recommended.
- ICRU Reports 50, 62, and 83 on prescribing, recording, and reporting photon-beam therapy provide guidance for both 3DCRT and IMRT delivery systems.
  - The American Association of Physicists in Medicine (AAPM) has published the Task Group reports outlining recommendations on quality assurance processes for photon-based 3DCRT and IMRT/VMAT [82–85].
  - For Proton Therapy, ICRU Report 78 provides QA guidance on prescribing, recording, and reporting proton-beam therapy for both passive and scanning beam delivery systems.
  - As image guidance plays a crucial role in targeting, all components need to be comprehensively tested for accuracy [86].

1.5 Summary

- Cervical esophageal cancers are often locally advanced at the time of diagnosis, infiltrating nearby anatomical structures, and often present with lymph node metastases.
- Due to proximity to critical organs, most cervical esophageal cancers are not treatable by surgery, as this would involve functionally devastating resections of portions of the pharynx, the larynx, and portions of the proximal esophagus.
- The management of cervical esophageal cancers is more closely related to head and neck squamous cell carcinomas rather than for malignancies involving more distal portions of the esophagus, and definitive chemoradiotherapy is the standard of care.

- The recommended dose and fractionation include 50–70 Gy for definitive chemoradiation in daily 1.8–2 Gy fractions, 5 days per week.
- Optimal concurrent chemotherapeutic options include cisplatin 100 mg/m^2 IV on days 1, 22, and 43 or 40 mg/m^2 IV weekly for 6–7 weeks.
- We recommend use of newer technologies like IMRT/IGRT for routine treatment as it provides greater precision while minimizing toxicities to adjacent vital organs (spinal cord, brachial plexus, lung).
- Careful consideration should be given while planning to meet the dose constraints for critical surrounding organs without compromising the target dose.

1.6 Treatment Algorithm

See Fig. 1.3.

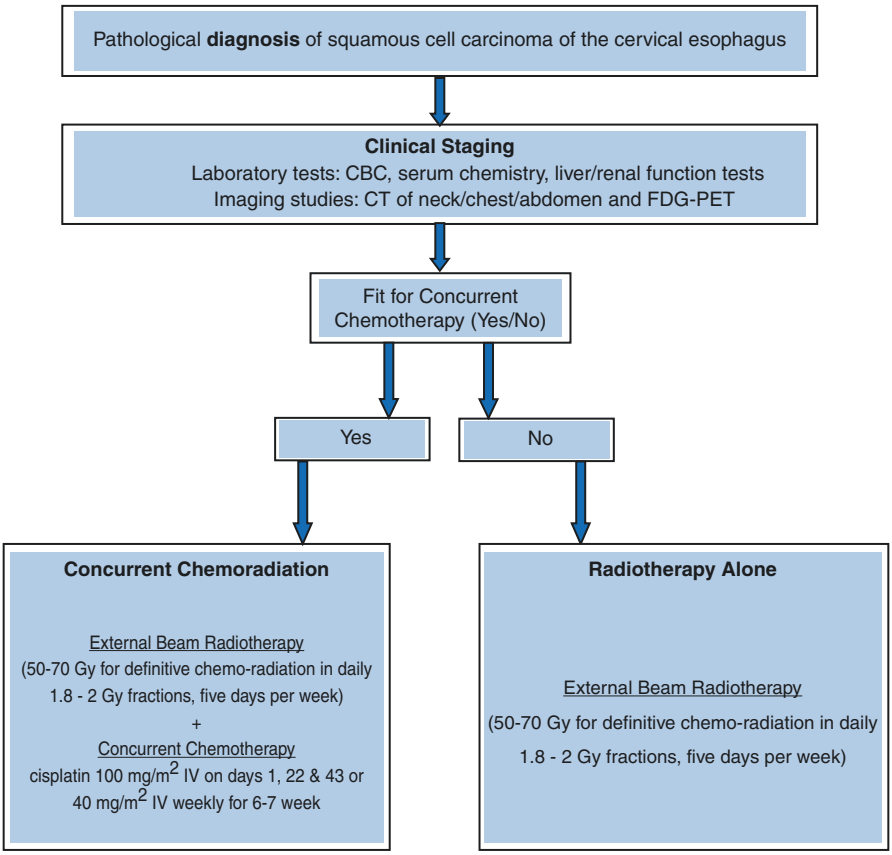

Fig. 1.3 This treatment algorithm is designed to help choose clinical scenarios appropriate for particular treatment modalities in the setting of non-metastatic cervical esophageal cancer

References

1. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC cancer staging manual: esophagus and esophagogastric junction. Ann Surg Oncol. 2010;17(7):1721–4.
2. Grass GD, Cooper SL, Armeson K, Garrett-Mayer E, Sharma A. Cervical esophageal cancer: a population-based study. Head Neck. 2015;37(6):808–14.
3. Ong GB, Lee TC. Pharyngogastric anastomosis after oesophago-pharyngectomy for carcinoma of the hypopharynx and cervical oesophagus. Br J Surg. 1960;48:193–200.
4. Triboulet JP, Mariette C, Chevalier D, Amrouni H. Surgical management of carcinoma of the hypopharynx and cervical esophagus: analysis of 209 cases. Arch Surg. 2001; 136(10):1164–70.
5. Kakegawa T, Yamana H, Ando N. Analysis of surgical treatment for carcinoma situated in the cervical esophagus. Surgery. 1985;97(2):150–7.
6. Kelley DJ, Wolf R, Shaha AR, Spiro RH, Bains MS, Kraus DH, et al. Impact of clinicopathologic parameters on patient survival in carcinoma of the cervical esophagus. Am J Surg. 1995;170(5):427–31.
7. Vigneswaran WT, Trastek VF, Pairolero PC, Deschamps C, Daly RC, Allen MS. Extended esophagectomy in the management of carcinoma of the upper thoracic esophagus. J Thorac Cardiovasc Surg. 1994;107(3):901–6. discussion 6-7
8. Wang HW, Kuo KT, Wu YC, Huang BS, Hsu WH, Huang MH, et al. Surgical results of upper thoracic esophageal carcinoma. J Chin Med Assoc. 2004;67(9):447–57.
9. Wei WI, Lam LK, Yuen PW, Wong J. Current status of pharyngolaryngo-esophagectomy and pharyngogastric anastomosis. Head Neck. 1998;20(3):240–4.
10. Wang HW, Chu PY, Kuo KT, Yang CH, Chang SY, Hsu WH, et al. A reappraisal of surgical management for squamous cell carcinoma in the pharyngoesophageal junction. J Surg Oncol. 2006;93(6):468–76.
11. Daiko H, Hayashi R, Saikawa M, Sakuraba M, Yamazaki M, Miyazaki M, et al. Surgical management of carcinoma of the cervical esophagus. J Surg Oncol. 2007;96(2):166–72.
12. Tong DK, Law S, Kwong DL, Wei WI, Ng RW, Wong KH. Current management of cervical esophageal cancer. World J Surg. 2011;35(3):600–7.
13. Ott K, Lordick F, Molls M, Bartels H, Biemer E, Siewert JR. Limited resection and free jejunal graft interposition for squamous cell carcinoma of the cervical oesophagus. Br J Surg. 2009;96(3):258–66.
14. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593–8.
15. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA. 1999;281(17):1623–7.
16. Zenda S, Kojima T, Kato K, Izumi S, Ozawa T, Kiyota N, et al. Multicenter phase 2 study of cisplatin and 5-fluorouracil with concurrent radiation therapy as an organ preservation approach in patients with squamous cell carcinoma of the cervical esophagus. Int J Radiat Oncol Biol Phys. 2016;96(5):976–84.
17. Zhang P, Xi M, Zhao L, Qiu B, Liu H, Hu YH, et al. Clinical efficacy and failure pattern in patients with cervical esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol. 2015;116(2):257–61.
18. Cao CN, Luo JW, Gao L, Xu GZ, Yi JL, Huang XD, et al. Primary radiotherapy compared with primary surgery in cervical esophageal cancer. JAMA Otolaryngol Head Neck Surg. 2014;140(10):918–26.
19. Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. J Clin Oncol. 2007;25(10):1160–8.

20. Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. J Clin Oncol. 2005;23(10):2310–7.
21. Pottgen C, Stuschke M. Radiotherapy versus surgery within multimodality protocols for esophageal cancer—a meta-analysis of the randomized trials. Cancer Treat Rev. 2012;38(6):599–604.
22. al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997;15(1):277–84.
23. Huang SH, Lockwood G, Brierley J, Cummings B, Kim J, Wong R, et al. Effect of concurrent high-dose cisplatin chemotherapy and conformal radiotherapy on cervical esophageal cancer survival. Int J Radiat Oncol Biol Phys. 2008;71(3):735–40.
24. Gkika E, Gauler T, Eberhardt W, Stahl M, Stuschke M, Pottgen C. Long-term results of definitive radiochemotherapy in locally advanced cancers of the cervical esophagus. Dis Esophagus. 2014;27(7):678–84.
25. Miyata H, Yamasaki M, Takahashi T, Kurokawa Y, Nakajima K, Takiguchi S, et al. Larynx-preserving limited resection and free jejunal graft for carcinoma of the cervical esophagus. World J Surg. 2013;37(3):551–7.
26. Sun F, Li X, Lei D, Jin T, Liu D, Zhao H, et al. Surgical management of cervical esophageal carcinoma with larynx preservation and reconstruction. Int J Clin Exp Med. 2014;7(9):2771–8.
27. Hu G, Wei L, Zhu J, Zhou J. Surgical management of carcinoma of the hypopharynx and cervical esophagus. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2004;18(6):329–31.
28. Peracchia A, Bardini R, Ruol A, Segalin A, Castoro C, Asolati M, et al. Surgical management of carcinoma of the hypopharynx and cervical esophagus. Hepato-Gastroenterology. 1990;37(4):371–5.
29. Jiang M, He X, Wu D, Han Y, Zhang H, Wang M. Reconstruction techniques for hypopharyngeal and cervical esophageal carcinoma. J Thorac Dis. 2015;7(3):449–54.
30. Stuschke M, Stahl M, Wilke H, Walz MK, Oldenburg AR, Stuben G, et al. Induction chemotherapy followed by concurrent chemotherapy and high-dose radiotherapy for locally advanced squamous cell carcinoma of the cervical oesophagus. Oncology. 1999;57(2):99–105.
31. Wang S, Liao Z, Chen Y, Chang JY, Jeter M, Guerrero T, et al. Esophageal cancer located at the neck and upper thorax treated with concurrent chemoradiation: a single-institution experience. J Thorac Oncol. 2006;1(3):252–9.
32. Yamada K, Murakami M, Okamoto Y, Okuno Y, Nakajima T, Kusumi F, et al. Treatment results of radiotherapy for carcinoma of the cervical esophagus. Acta Oncol. 2006;45(8):1120–5.
33. Burmeister BH, Dickie G, Smithers BM, Hodge R, Morton K. Thirty-four patients with carcinoma of the cervical esophagus treated with chemoradiation therapy. Arch Otolaryngol Head Neck Surg. 2000;126(2):205–8.
34. Uno T, Isobe K, Kawakami H, Ueno N, Shimada H, Matsubara H, et al. Concurrent chemoradiation for patients with squamous cell carcinoma of the cervical esophagus. Dis Esophagus. 2007;20(1):12–8.
35. Cao C, Luo J, Gao L, Xu G, Yi J, Huang X, et al. Definitive radiotherapy for cervical esophageal cancer. Head Neck. 2015;37(2):151–5.
36. Cao CN, Luo JW, Gao L, Xu GZ, Yi JL, Huang XD, et al. Intensity-modulated radiotherapy for cervical esophageal squamous cell carcinoma: clinical outcomes and patterns of failure. Eur Arch Otorhinolaryngol. 2016;273(3):741–7.
37. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med. 1991;324(24):1685–90.
38. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31(7):845–52.
39. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349(22):2091–8.

40. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst. 2009;101(7):498–506.
41. National Comprehensive Cancer Network Clinical Practice Guideline in Oncology. Esophageal and esophagogastric junction cancers (Version 2.2016). https://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf. Accessed 15 Dec 2016.
42. Wang YC, Chen SW, Chien CR, Hsieh TC, Yu CY, Kuo YC, et al. Radiotherapy for esophageal cancer using simultaneous integrated boost techniques: dosimetric comparison of helical TomoTherapy, volumetric-modulated arc therapy (RapidArc) and dynamic intensity-modulated radiotherapy. Technol Cancer Res Treat. 2013;12(6):485–91.
43. Tu L, Sun L, Xu Y, Wang Y, Zhou L, Liu Y, et al. Paclitaxel and cisplatin combined with intensity-modulated radiotherapy for upper esophageal carcinoma. Radiat Oncol. 2013;8:75.
44. Fu WH, Wang LH, Zhou ZM, Dai JR, Hu YM, Zhao LJ. Comparison of conformal and intensity-modulated techniques for simultaneous integrated boost radiotherapy of upper esophageal carcinoma. World J Gastroenterol. 2004;10(8):1098–102.
45. Fenkell L, Kaminsky I, Breen S, Huang S, Van Prooijen M, Ringash J. Dosimetric comparison of IMRT vs. 3D conformal radiotherapy in the treatment of cancer of the cervical esophagus. Radiother Oncol. 2008;89(3):287–91.
46. Zhu WG, Zhou K, Yu CH, Han JH, Li T, Chen XF. Efficacy analysis of simplified intensity-modulated radiotherapy with high or conventional dose and concurrent chemotherapy for patients with neck and upper thoracic esophageal carcinoma. Asian Pac J Cancer Prev. 2012;13(3):803–7.
47. Ma P, Wang X, Xu Y, Dai J, Wang L. Applying the technique of volume-modulated arc radiotherapy to upper esophageal carcinoma. J Appl Clin Med Phys. 2014;15(3):4732.
48. Yin Y, Chen J, Xing L, Dong X, Liu T, Lu J, et al. Applications of IMAT in cervical esophageal cancer radiotherapy: a comparison with fixed-field IMRT in dosimetry and implementation. J Appl Clin Med Phys. 2011;12(2):3343.
49. Martin S, Chen JZ, Rashid Dar A, Yartsev S. Dosimetric comparison of helical tomotherapy, RapidArc, and a novel IMRT & arc technique for esophageal carcinoma. Radiother Oncol. 2011;101(3):431–7.
50. Gary YY. Helical tomotherapy for radiochemotherapy in esophageal cancer: a preferred plan? J Thorac Dis. 2009;1(1):3–4.
51. Ishikawa H, Hashimoto T, Moriwaki T, Hyodo I, Hisakura K, Terashima H, et al. Proton beam therapy combined with concurrent chemotherapy for esophageal cancer. Anticancer Res. 2015;35(3):1757–62.
52. Lin SH, Komaki R, Liao Z, Wei C, Myles B, Guo X, et al. Proton beam therapy and concurrent chemotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2012;83(3):e345–51.
53. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol Off J Am Soc Clin Oncol. 2002;20(5):1167–74.
54. Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer. 1997;33(8):1216–20.
55. Conroy T, Galais MP, Raoul JL, Bouche O, Gourgou-Bourgade S, Douillard JY, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. Lancet Oncol. 2014;15(3):305–14.
56. Ruppert BN, Watkins JM, Shirai K, Wahlquist AE, Garrett-Mayer E, Aguero EG, et al. Cisplatin/Irinotecan versus carboplatin/paclitaxel as definitive chemoradiotherapy for locoregionally advanced esophageal cancer. Am J Clin Oncol. 2010;33(4):346–52.
57. Itakura Y, Sasano H, Shiga C, Furukawa Y, Shiga K, Mori S, et al. Epidermal growth factor receptor overexpression in esophageal carcinoma. An immunohistochemical study correlated with clinicopathologic findings and DNA amplification. Cancer. 1994;74(3):795–804.

58. Lin G, Sun XJ, Han QB, Wang Z, Xu YP, Gu JL, et al. Epidermal growth factor receptor protein overexpression and gene amplification are associated with aggressive biological behaviors of esophageal squamous cell carcinoma. Oncol Lett. 2015;10(2):901–6.
59. National Comprehensive Cancer Network. Clinical practice guidelines in oncology (NCCN guidelines). Head and neck cancers. 2015. NCCN.org.
60. Crosby T, Hurt CN, Falk S, Gollins S, Mukherjee S, Staffurth J, et al. Chemoradiotherapy with or without cetuximab in patients with oesophageal cancer (SCOPE1): a multicentre, phase 2/3 randomised trial. Lancet Oncol. 2013;14(7):627–37.
61. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AF, Okines C, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol. 2013;14(6):481–9.
62. Ilson DH, Moughan J, Suntharalingam M, Dicker A, Kachnic LA, Crane CH. The initial report of RTOG 0436: a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery. J Clin Oncol. 2014;32(15_suppl):4007.
63. You JJ, Wong RK, Darling G, Gulenchyn K, Urbain JL, Evans WK. Clinical utility of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in the staging of patients with potentially resectable esophageal cancer. J Thorac Oncol. 2013;8(12):1563–9.
64. Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Sundaresan SR, Patterson GA, et al. Staging of esophageal cancer with 18F-fluorodeoxyglucose positron emission tomography. AJR Am J Roentgenol. 1997;168(2):417–24.
65. Moureau-Zabotto L, Touboul E, Lerouge D, Deniaud-Alexandre E, Grahek D, Foulquier JN, et al. Impact of CT and 18F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2005;63(2):340–5.
66. Hong TS, Killoran JH, Mamede M, Mamon HJ. Impact of manual and automated interpretation of fused PET/CT data on esophageal target definitions in radiation planning. Int J Radiat Oncol Biol Phys. 2008;72(5):1612–8.
67. Schreurs LM, Busz DM, Paardekooper GM, Beukema JC, Jager PL, Van der Jagt EJ, et al. Impact of 18-fluorodeoxyglucose positron emission tomography on computed tomography defined target volumes in radiation treatment planning of esophageal cancer: reduction in geographic misses with equal inter-observer variability: PET/CT improves esophageal target definition. Dis Esophagus. 2010;23(6):493–501.
68. Gondi V, Bradley K, Mehta M, Howard A, Khuntia D, Ritter M, et al. Impact of hybrid fluorodeoxyglucose positron-emission tomography/computed tomography on radiotherapy planning in esophageal and non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2007;67(1):187–95.
69. Leong T, Everitt C, Yuen K, Condron S, Hui A, Ngan SY, et al. A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol. 2006;78(3):254–61.
70. Cheng J, Kong L, Huang W, Li B, Li H, Wang Z, et al. Explore the radiotherapeutic clinical target volume delineation for thoracic esophageal squamous cell carcinoma from the pattern of lymphatic metastases. J Thorac Oncol. 2013;8(3):359–65.
71. Wu AJ, Bosch WR, Chang DT, Hong TS, Jabbour SK, Kleinberg LR, et al. Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and Gastroesophageal junction cancer. Int J Radiat Oncol Biol Phys. 2015;92(4):911–20.
72. Gregoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol. 2014;110(1):172–81.
73. Brouwer CL, Steenbakkers RJ, Bourhis J, Budach W, Grau C, Gregoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG oncology and TROG consensus guidelines. Radiother Oncol. 2015;117(1):83–90.
74. Chavaudra J, Bridier A. Definition of volumes in external radiotherapy: ICRU reports 50 and 62. Cancer Radiother. 2001;5(5):472–8.

75. Chen AM, Farwell DG, Luu Q, Donald PJ, Perks J, Purdy JA. Evaluation of the planning target volume in the treatment of head and neck cancer with intensity-modulated radiotherapy: what is the appropriate expansion margin in the setting of daily image guidance? Int J Radiat Oncol Biol Phys. 2011;81(4):943–9.
76. Chen YJ, Liu A, Han C, Tsai PT, Schultheiss TE, Pezner RD, et al. Helical tomotherapy for radiotherapy in esophageal cancer: a preferred plan with better conformal target coverage and more homogeneous dose distribution. Med Dosim. 2007;32(3):166–71.
77. Yin L, Wu H, Gong J, Geng JH, Jiang F, Shi AH, et al. Volumetric-modulated arc therapy vs. c-IMRT in esophageal cancer: a treatment planning comparison. World J Gastroenterol. 2012;18(37):5266–75.
78. Patyal B. Dosimetry aspects of proton therapy. Technol Cancer Res Treat. 2007;6(4 Suppl):17–23.
79. Stuschke M, Kaiser A, Abu Jawad J, Pottgen C, Levegrun S, Farr J. Multi-scenario based robust intensity-modulated proton therapy (IMPT) plans can account for set-up errors more effectively in terms of normal tissue sparing than planning target volume (PTV) based intensity-modulated photon plans in the head and neck region. Radiat Oncol. 2013;8:145.
80. van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366–77.
81. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3):S10–S9.
82. Gibbons JP, Antolak JA, Followill DS, Huq MS, Klein EE, Lam KL, et al. Monitor unit calculations for external photon and electron beams: report of the AAPM Therapy Physics Committee Task Group No. 71. Med Phys. 2014;41(3).
83. Stern RL, Heaton R, Fraser MW, Goddu SM, Kirby TH, Lam KL, et al. Verification of monitor unit calculations for non-IMRT clinical radiotherapy: report of AAPM Task Group 114. Med Phys. 2011;38(1):504–30.
84. Ezzell GA, Galvin JM, Low D, Palta JR, Rosen I, Sharpe MB, et al. Guidance document on delivery, treatment planning, and clinical implementation of IMRT: report of the IMRT subcommittee of the AAPM radiation therapy committee. Med Phys. 2003;30(8):2089–115.
85. Low DA, Moran JM, Dempsey JF, Dong L, Oldham M. Dosimetry tools and techniques for IMRT. Med Phys. 2011;38(3):1313–38.
86. Klein EE, Hanley J, Bayouth J, Yin FF, Simon W, Dresser S, et al. Task Group 142 report: quality assurance of medical accelerators. Med Phys. 2009;36(9):4197–212.

Mid/Distal Esophageal Cancer and Gastroesophageal Junction Cancer (Siewert Type I and II)

2

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2.1 Introduction

The esophagus is a hollow, muscular tube, approximately 25 cm in length, which extends from the lower border of the cricoid cartilage at the level of C6 to the stomach. The gastroesophageal junction (GEJ) is near the lower border of vertebra T11. The upper portion of the thoracic/mid esophagus passes behind the

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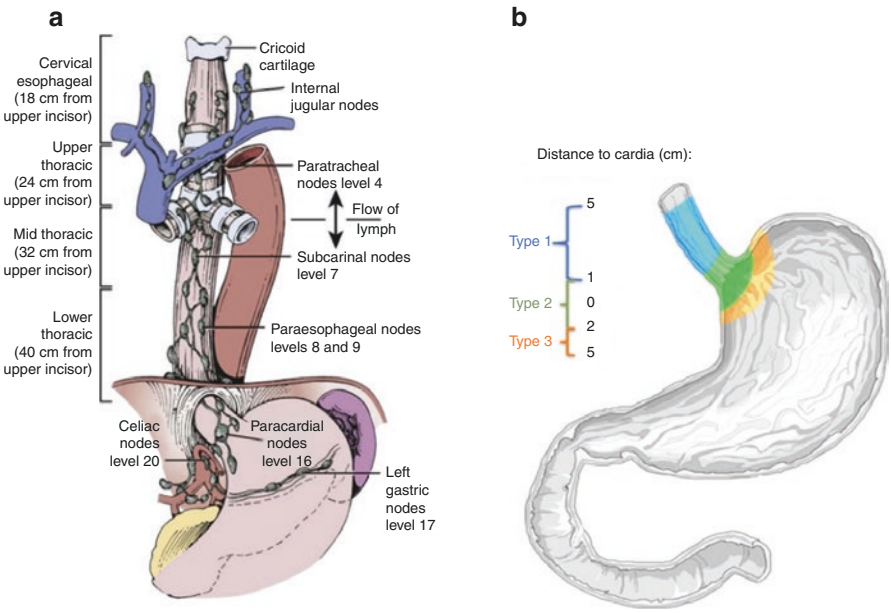

Fig. 2.1 (**a**) Esophagus anatomy (**b**) Siewert-Stein classification for gastroesophageal junction carcinoma (from Matzinger et al. 2009 [1] with permission)

tracheal bifurcation and left main stem bronchus, which corresponds endoscopically 24–32 cm from incisor, and the distal thoracic esophagus is an area approximately 6–8 cm in length from 32 to 40 cm from incisor, merging into the gastroesophageal junction (Fig. 2.1a). Tumors around the GE junction can also be divided using Siewert-Stein classification as type I (adenocarcinoma of distal part of the esophagus with center located within between 1–5 cm above the anatomic GEJ), type II (adenocarcinoma of the real cardia, i.e., within 1 cm above and 2 cm below the GEJ), and type III (adenocarcinoma of the sub-cardiac stomach, i.e., 2–5 cm below GEJ) (Fig. 2.1b). In this chapter, we will discuss the management and treatment techniques for mid/distal and GEJ cancer (Siewert type I and II). Siewert type III, which is considered as stomach cancer, will be discussed in subsequent chapters.

2.2 Management Principles for Mid/Distal Esophagus and Gastroesophageal Junction Carcinoma (Siewert Type I and II)

Surgery has been the standard of care for early-stage esophageal cancer. However, its utility as monotherapy has been challenged. Data from various surgical series report 5-year survival rates of 15–20% with surgery alone [2–5]. Exploration of various therapeutic approaches in randomized trials and meta-analysis led to the

Table 2.1 Treatment recommendation as per NCCN guidelines 2016 [6]

Stage	Recommended treatment
Tis, T1a, superficial T1b and N0	Endoscopic resection and/or ablation, esophagectomy
cT1b, N+ cT2-T4a, N0-N+ and Medically fit	Preoperative chemoradiation [radiotherapy (RT) 41.4–50.4 Gy + concurrent chemotherapy] → surgery (preferred) or Definitive chemoradiation (for medically inoperable or patients who decline surgery) [RT 50–50.4 Gy + concurrent chemotherapy] or Esophagectomy [T1b-T2 low-risk lesions: <2 cm, well-differentiated] or Preoperative chemotherapy → Esophagectomy or Perioperative chemotherapy (GEJ cancers) → Esophagectomy
cT4b	Definitive chemoradiation [RT 50–50.4 Gy + concurrent chemotherapy]

current standard of care multimodality approach with induction chemoradiotherapy followed by surgical resection for operable disease. For patients with medically inoperable esophageal cancer or who decline surgery, definitive radiotherapy is the treatment of choice for stage T1-2 N0 M0 disease, and concurrent chemoradiotherapy should be considered for locally advanced lesions. Most clinicians treat GEJ (Sievert I & II) as esophageal cancers with preoperative chemoradiotherapy. However, these tumors have been included in many of the trials examining the benefit of adjuvant and neoadjuvant chemotherapy for gastric cancer, and institutional practice varies. The recent NCCN-recommended therapeutic options in different stages are summarized in Table 2.1.

2.2.1 Curative Surgical Techniques

Surgery is usually undertaken for lesions of the mid- to lower third of the thoracic esophagus and gastroesophageal junction and involves a subtotal or total esophagectomy. Esophagectomy may be accomplished by a number of techniques, including a transhiatal esophagectomy, right thoracotomy (Ivor-Lewis), or left thoracotomy [7]. It is vital to know the type of procedure and anastomosis, especially in the context of planning for postoperative radiotherapy.

- Transhiatal Esophagectomy (THE): THE is recommended for tumors anywhere in the esophagus or gastric cardia. THE does not include a thoracotomy, and instead, the stomach is mobilized from the surrounding omentum with blunt dissection of the thoracic esophagus and patients are left with cervical anastomosis. Limitations are the lack of exposure of mid-esophagus and direct visualization and dissection of the subcarinal lymph nodes cannot be performed.

- Transthoracic Esophagectomy (Ivor Lewis procedure): This approach is mainly good for mid to upper esophageal lesions, and patients are left with thoracic or cervical anastomosis.
- Left thoracotomy: appropriate for the lower third of esophagus and gastric cardia, and patients are left with low-to-mid thoracic anastomosis [7].

The optimal surgical approach for esophageal cancer is debatable. Results of a randomized trial and a meta-analysis comparing transhiatal versus transthoracic approach in patients with adenocarcinoma of esophagus revealed no significant differences in 5-year overall and disease-free survival rates, although transhiatal esophagectomy was associated with lower morbidity [4, 8]. Another treatment option for high-grade dysplasia is esophageal mucosal resection (EMR) or esophageal mucosal dissection. EMR dissects the esophageal submucosa to better evaluate and stage early carcinoma [9].

2.2.2 Combined Modality Approach

Prior to the advent of modern radiotherapy delivery techniques and routine use of chemoradiotherapy (CRT), radiation therapy (RT) alone was used (60–66 Gy over a period of 6–7 weeks at 2 Gy per fraction) [10, 11]. Results from numerous randomized trials and meta-analysis did not show any improvement in resectability or overall survival rates from the addition of either preoperative or postoperative radiation alone as compared to surgery alone [12–16]. Five-year overall survival of 0% was seen in RT alone arm in RTOG 8501 as mentioned below [17].

2.2.2.1 Definitive Chemoradiation

For medically inoperable or locally advanced disease, the addition of concurrent chemotherapy has proven to improve survival over RT alone as demonstrated in various randomized trials and meta-analyses. The landmark Radiation Therapy Oncology Group 85-01 trial using 2-D radiation therapy techniques (2DRT) compared RT alone (64 Gy in 32 fractions over 6.5 weeks) versus concurrent CRT [two cycles of infusional 5-FU (1000 mg/m^2 per day, days 1–4, weeks 1 and 5) plus cisplatin (75 mg/m^2 day 1 of weeks 1 and 5) and RT (50 Gy in 25 fractions over 5 weeks)]. The results showed a significant survival advantage for CRT arm, i.e., 5-year survival 27 vs. 0 percent [17, 18]. The dose escalation US Intergroup Study 0123 randomized patients to CRT (cisplatin and 5-FU), but they were randomly assigned to 50.4 Gy vs. high-dose 64.8 Gy arms [19]. The dose escalation arm had higher treatment-related deaths (10% vs. 2%), while there was no difference in median survival (13 vs. 18 months), 2-year overall survival (31% vs. 40%), or locoregional failure (56% vs. 52%). One argument for why higher dose did not result in better survival or locoregional control is the use of dosimetrically inferior 2D radiation delivery techniques. Modern techniques [3-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), image-guided radiotherapy (IGRT) and protons] are associated with precise dose distribution as compared to 2D techniques, and the use of these state of art