

Radiation techniques for esophageal cancer

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Abstract: Radiotherapy plays a crucial role in the curative management of localized esophageal cancer, both as definitive and preoperative therapy. For definitive therapy, the standard radiation dose is 50.4 Gy in 28 fractions and should be delivered with concurrent chemotherapy. Chemoradiotherapy also has a well-established benefit in the preoperative setting, as established in the CROSS randomized trial. Radiation fields are typically generous, to account for subclinical extension of disease along the esophagus and to regional nodes. Three-dimensional conformal radiation is the current standard technique for esophageal cancer, though intensity-modulated radiation therapy is increasingly utilized and may improve the outcomes of esophageal radiotherapy by reducing radiation dose to critical normal tissues.

Keywords: Esophageal cancer; radiotherapy; radiation dose; target volume delineation; intensity modulated radiation therapy

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Background

Esophageal cancer is the eighth most common cancer worldwide. It is most prevalent in countries within eastern and southern Africa and eastern Asia. Three-quarters of affected patients are male. Patients with esophageal cancer have a very poor survival, with a mortality to incidence ratio of 0.88. Overall, there are an estimated 456,000 new patients and 400,000 deaths per year as estimated by GLOBOCAN 2012 (1). In the US alone, esophageal cancer will affect an estimated 16,940 new patients and cause 15,690 deaths in 2017 (2).

Esophageal cancer has two distinct histopathologic subtypes: squamous cell carcinoma and adenocarcinoma. These subtypes vary in terms of incidence, risk factors, location, and age of diagnosis. Squamous cell carcinoma used to be the dominant subtype, but since the 1970s there has been a major shift towards adenocarcinoma in the Western world. Risk factors contributing to squamous cell carcinoma include alcohol and tobacco use, while

those contributing to adenocarcinoma include tobacco use, obesity, and Barrett's metaplasia. Most squamous cell carcinoma occurs in the mid or upper esophagus, whereas close to all cases of adenocarcinoma occur in the distal esophagus and gastroesophageal junction (GEJ). Symptoms of both are similar, including dysphagia, odynophagia, unintentional weight loss, and chest pain (3,4).

Treatment options for esophageal cancer include surgery, chemotherapy, and radiation. Radiation has an established role in the definitive, neoadjuvant, and palliative settings. Early experiences treating esophageal cancer with surgery or radiation alone resulted in poor survival outcomes. In 1985, the Radiation Therapy Oncology Group (RTOG) launched a phase III study comparing concurrent chemoradiation therapy (with concurrent 5-fluorouracil and cisplatin) versus radiation monotherapy for thoracic esophageal cancer. The study was terminated early and ultimately showed a 5-year survival of 26% in the chemoradiation group compared to 0% in the radiation-alone group (5). The rate of local recurrence or persistence

remained high even with chemoradiation, at 46% (6). This study established the viability of radiation, when combined with chemotherapy, as a potentially curative treatment option for esophageal cancer.

In patients with resectable disease, preoperative chemoradiation has also been shown to improve survival, based on results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS). Conducted between 2004 and 2008, this trial randomized patients to surgery alone or preoperative chemoradiation using carboplatin, paclitaxel, and 41.4 Gy in 23 fractions. Most patients had adenocarcinoma. Both squamous and adenocarcinoma patients benefitted from chemoradiation (though effect size was greater in squamous cancers), the R0 resection rate was significantly improved, and the rate of pathologic complete response after chemoradiation was 29% (7). The locoregional recurrence rate at 5 years for patients who received neoadjuvant treatment was 14%, versus 34% for those who underwent surgery alone (8). Though conflicting evidence suggests that neoadjuvant chemotherapy alone may also offer a survival benefit, synthesis of the limited prospective data comparing preoperative chemoradiation to chemotherapy alone suggests a benefit for the inclusion of radiation (9,10). Currently, the optimal treatment paradigm for resectable esophageal cancer is widely considered to be neoadjuvant chemoradiation followed by surgery.

In sum, these analyses clearly demonstrate a survival benefit with concurrent chemoradiation for locally advanced, non-metastatic esophageal cancer, in both the operable and inoperable settings.

Radiation dose

Varying doses of radiation have been investigated for esophageal cancer. In the definitive setting, RTOG 85-01 established 50 Gy as a standard dose with concurrent chemotherapy (5,6). Due to the high rate of local recurrence and persistence even with concurrent chemotherapy, it was hypothesized that outcomes could be improved with higher radiation doses. This led to a phase III intergroup trial (INT 0123) that compared the RTOG 85-01 chemoradiation dose (slightly modified to 50.4 Gy rather than 50 Gy) to a higher dose of 64.8 Gy, using the same chemotherapy. Squamous cell carcinoma accounted for 86% of patients. This study demonstrated no difference in 2-year survival between the two groups. Notably, there were 11 treatment-related fatalities in patients randomized to high dose,

compared to 2 in the standard dose group. Seven of the 11 deaths in the high-dose group, however, occurred before those patients had received a dose of 50.4 Gy, suggesting that the failure of the high-dose strategy in this study was not due to inherent toxicity of radiation doses above 50.4 Gy (11).

Together, the results of RTOG 85-01 and INT 0123 continue to define the standard radiation dose for definitive chemoradiation as 50.4 Gy in 28 fractions. Nevertheless, there continues to be interest in higher radiation doses in hopes of achieving higher complete response rates and reducing local recurrence, particularly for patients who are medically inoperable, or have proximal or cervical tumors where surgery would entail a disfiguring laryngopharyngectomy. Cervical tumors, in particular, are nearly analogous to hypopharyngeal cancers, and despite the lack of prospective randomized data, small retrospective and prospective experiences suggest that higher radiation doses of 60Gy or more are reasonable for this situation (12-14).

In the preoperative setting, lower doses of radiation have been used in conjunction with chemotherapy. The successful CROSS trial used a dose of 41.4 Gy in 23 fractions, yielding not only a clear survival benefit but also a relatively high 29% pathologic complete response rate (7). The German Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma Trial (POET), which compared preoperative chemoradiation *vs.* preoperative chemotherapy alone for GEJ adenocarcinoma, used an even lower dose of 30 Gy in 15 fractions, and showed a non-significant advantage of chemoradiation over chemotherapy (10). Therefore, in medically fit patients where surgery after chemoradiation is the clear intention, it is reasonable to consider radiation doses less than 50.4 Gy, with 41.4 Gy as per the CROSS trial being a well-supported choice. Lower preoperative doses can also be considered if the treatment volume is anticipated to be particularly large or involve a significant portion of the stomach. Because of the excellent results of the CROSS trial, carboplatin and paclitaxel is our standard recommendation for concurrent chemotherapy with radiotherapy in both the definitive and preoperative settings.

Though lower pre-operative radiation doses are acceptable, we continue to recommend 50.4 Gy as a standard preoperative dose, which has been shown to be a tolerable and effective preoperative dose in previous CALGB trials (15). In practice, many patients with esophageal cancer may be borderline candidates for

surgery due to medical comorbidity. Additionally, some operative candidates are nevertheless strongly motivated to pursue non-operative management if an apparent complete response to chemoradiation is achieved, an approach which has been examined by the RTOG in a single-arm prospective trial (16). Therefore, using the same dose of 50.4 Gy for preoperative-intent as for definitive-intent patients allows the final decision regarding surgery to be made after completion of chemoradiation, when tumor response and patient fitness at that juncture can be considered.

Radiation treatment planning

Radiation treatment volumes for esophageal cancer have traditionally been generous to account for subclinical disease extension via longitudinal spread and regional nodal involvement. The initial treatment fields for RTOG 85-01 included the entire esophagus, extending from the supraclavicular fossa to the GEJ, with an ensuing boost field extending at least 5 centimeters above and below the tumor (5). In the more modern era, treatment fields have been revised to encompass smaller target volumes. For example, the INT 0123 trial no longer included the entire esophagus in the field, but defined superior and inferior field borders 5 cm from the primary tumor, and radial field border at least 2 cm beyond the primary tumor to encompass the paraesophageal lymph nodes. The supraclavicular lymph nodes were also included in the treatment field if the tumor was in the cervical esophagus (11). The CROSS treatment fields were further reduced with superior and inferior field borders of 4 cm and radial border of 1.5 cm, and in the scenario in which the tumor extended into the stomach, the inferior border was reduced to 3 cm (7). Pathologic studies indicate that a 3 cm margin is likely sufficient to encompass microscopic disease extension beyond gross tumor (17).

With the advancement of imaging techniques, better localization of the tumor volume is now possible. For example, pre-treatment position emission tomography (PET) scans, now standard in the evaluation of esophageal cancer, are particularly helpful in localizing the gross tumor volume (GTV) of the primary tumor as well as the involved nodes. Defining the superior and inferior extent of the GTV is relatively straightforward with integrated PET-CT scans, compared to CT alone. Information from esophagogastroduodenoscopy (EGD), however, should also be reviewed and incorporated in

GTV delineation, particularly in cases where PET-based delineation alone may not be entirely clear due to factors such as low FDG avidity of the tumor, or the presence of overlapping physiologic FDG uptake (particularly common in the stomach) that make distinguishing tumor borders challenging.

Recently, an expert panel developed and published consensus contouring guidelines for esophageal cancer, intended for use with intensity modulated radiation therapy (IMRT) and other conformal techniques (18). It was recommended that GTV be defined using a combination of pre-treatment PET scan, computed tomography (CT) scan, and endoscopy report. The superior border of the clinical target volume (CTV) was an expansion of 3–4 cm above the gross tumor or 1cm above any grossly involved paraesophageal lymph node, whichever was more superior. The inferior border was defined as either 3–4 cm below the gross disease, or at least 2 cm along clinically uninvolved gastric mucosa if the tumor was distally located to reduce radiation dose to normal stomach, assuming a standard radiation dose of 50.4 Gy. Radially, a 1–1.5 cm margin was recommended to include the periesophageal lymph nodes, with exception of smaller margins of 0.5 cm in areas that interfaced with uninvolved cardiac and hepatic tissue.

Regarding elective nodal irradiation, it was recommended that for distal tumors, the celiac lymph nodes as well as paraaortic and gastrohepatic lymph nodes between the GEJ and celiac axis is included in the CTV. The inclusion of the gastrohepatic lymph nodes in particular is supported by pathologic data indicating that nodes in these stations (in particular, the paracardial, lesser curvature, and left gastric nodes) are among the most frequently involved in distal and GEJ adenocarcinomas (19,20). Celiac nodes are less frequently involved but still appear to be affected at a frequency that justifies elective coverage (21). For tumors above the carina, bilateral supraclavicular lymph nodes should be included in the CTV, as well as anterior mediastinal nodes. Finally, planning target volume (PTV) should be a uniform 0.5–1 cm expansion from the CTV in all directions (18).

An additional consideration when defining target volumes is the effect of respiratory motion, which is most important for distal tumors and those involving the GEJ (22,23). Multiple techniques that control or account for respiratory motion are available. One of the most straightforward is measurement of respiratory motion using 4-dimensional CT (4D-CT) at the time of simulation, in which case the magnitude of respiratory excursion can be

incorporated into the choice of PTV margin. If the target volumes are displaced more than 1cm due to respiratory motion, it may be preferable to employ techniques such as respiratory gating, deep inspiration breath hold (DIBH), or abdominal compression to avoid excessive normal tissue dose. Daily image-guidance and endoscopic placement of fiducial markers can also be employed to facilitate the use of smaller PTV margins while maintaining target coverage. Of note, differential gastric filling may lead to both displacement of target volumes as well as inter-fraction dose variations to the stomach, although this effect did not seem to be significant for the most part in small retrospective and prospective series (24,25). To minimize the effect of variations in gastric filling, we recommend patients fast for 2–3 hours prior to treatment.

Radiation techniques

There are several external beam radiation treatment techniques available for treatment of esophageal cancer, including 3-dimensional conformal radiation therapy (3DCRT), IMRT, volumetric modulated arc therapy (VMAT), and proton therapy. The current standard of care for esophageal cancer treatment is 3DCRT. A common 3DCRT arrangement for esophageal cancer consists of four static treatment fields (“4-field box”): anterior-posterior (AP), posterior-anterior (PA), left lateral (LL), and right lateral (RL). With advancements in treatment planning, it is now common to employ a greater number of fields and/or employ different beam arrangements with 3DCRT. The goal of advanced radiation treatment planning is to deliver more conformal treatment with optimal dose coverage to the target volumes and decreased dose to the normal tissues. Avoiding damage to the spinal cord, liver, and kidneys is crucial but also relatively straightforward to achieve with 3DCRT; as such, complications involving those organs are exceedingly rare from radiotherapy for esophageal cancer. More challenging is reducing dose and toxicity risk to lungs, heart, stomach, and small bowel, since there is not a clear threshold dose that predicts radiation-related toxicity in those organs.

IMRT has become increasingly popular for treatment of esophageal and other cancers because it has the capacity to deliver even more conformal treatment than 3DCRT. This is due to its ability to modulate the intensity of the radiation given within a single treatment field by either creating a series of smaller fields or by dynamically changing the shape of the field while the radiation is being

delivered. IMRT has been shown to significantly reduce dose to the lungs (26) and the heart (27,28) in esophageal cancer radiotherapy, and has been associated with a lower risk of grade 3 or higher non-hematologic toxicities (29), and other-cause and cardiac-related deaths (30). Although IMRT has not yet emerged as a clear standard of care for esophageal cancers generally, it is clearly preferable for cervical esophagus, both because of the proximity to other radiosensitive normal structures in the head and neck, and because of the higher radiation doses commonly used in this setting. In cervical esophageal cancer, IMRT has shown improved coverage of the target volume with decreased dose to the normal structures (31), and a recent small series has suggested that IMRT and dose escalation may predict for increased survival (32). VMAT is essentially a variation of IMRT where the radiation beam is constantly being delivered and modulated while traveling in one or more arcs around the patient. VMAT has been shown to deliver similarly conformal radiation to the target as IMRT, with decreased treatment time (33,34).

Proton therapy is an emerging treatment technique in esophageal cancer. In contrast to 3DCRT and IMRT, proton beams are composed of charged particles that deliver most of their energy at a specific depth within a tissue, a phenomenon which is termed the “Bragg peak”. As such, proton therapy lacks the exit dose that is characteristic of photon therapy and therefore can be used to limit the dose to the surrounding tissues. Dosimetric comparisons of proton therapy versus IMRT and 3DCRT showed that with proton therapy, the volumes and/or dose of irradiated lung, stomach, liver, spinal cord, left anterior descending artery, left ventricle, pericardium, and heart can be reduced without sacrificing coverage of the target volumes (35). No randomized comparisons of proton therapy to 3DCRT or IMRT have been reported. However, retrospective series and comparisons have suggested that proton therapy may reduce the rate of pulmonary complications such as respiratory insufficiency (36). In the neoadjuvant setting with concurrent chemotherapy, proton therapy was shown to have tolerable side effects with less than 10% post-operative complications and a comparable 28% pathologic complete response rate (37). In lung cancer, recent randomized data has shown that heart dose is an important predictor of survival, and that IMRT may improve outcomes by reducing heart dose relative to 3DCRT (38). As radiation therapy for esophageal cancer (particularly distal and GEJ tumors) deals with similar anatomic and dosimetric constraints as lung cancer, IMRT and proton

therapy may prove beneficial by reducing the risk of serious cardiopulmonary complications, and may also provide a better platform for future studies involving dose escalation as well.

Conclusions

Radiotherapy plays an integral role in the curative management of esophageal cancer, both as a definitive local therapy as well as an adjunct to surgical resection. For definitive therapy, radiotherapy to a dose of 50.4 Gy with concurrent chemotherapy is standard. For preoperative therapy, we prefer a dose of 50.4 Gy with concurrent chemotherapy though lower doses such as 41.4 Gy are also reasonable if there is a clear intention for subsequent surgery. 3DCRT is the current standard radiation technique for esophageal cancer, but IMRT may be preferred in certain situations such as cervical tumors. Advanced radiation techniques such as IMRT, VMAT, and protons offer the promise of improved outcomes via lower normal tissue toxicity.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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