Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2012 January 1; 82(1): 468–474. doi:10.1016/j.ijrobp.2010.10.023.

Esophageal Cancer Dose Escalation using a Simultaneous Integrated Boost Technique

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Abstract

Purpose—We previously showed that 75% of radiation therapy (RT) failures in patients with unresectable esophageal cancer are in the gross tumor volume (GTV). We performed a planning study to evaluate if a simultaneous integrated boost (SIB) technique could selectively deliver a boost dose of radiation to the GTV in patients with esophageal cancer.

Methods and Materials—Treatment plans were generated using four different approaches (two-dimensional conformal RT [2D-CRT] to 50.4 Gy or 64.8 Gy, intensity-modulated RT [IMRT] to 50.4 Gy, and SIB-IMRT to 64.8 Gy) and optimized for 10 patients with distal esophageal cancer. All plans were constructed to deliver the target dose in 28 fractions using heterogeneity corrections. Isodose distributions were evaluated for target coverage and normal tissue exposure.

Results—The 50.4-Gy IMRT plan was associated with significant reductions in mean cardiac, pulmonary, and hepatic doses relative to the 50.4-Gy 2D-CRT plan. The 64.8-Gy SIB-IMRT plan produced a 28% increase in GTV dose and the same normal tissue doses as the 50.4-Gy IMRT plan; compared with the 50.4-Gy 2D-CRT plan, the 64.8-Gy SIB-IMRT produced significant dose reductions to all critical structures (heart, lung, liver, and spinal cord).

Conclusions—The use of SIB-IMRT allowed us to selectively increase the dose to the GTV, the area at highest risk of failure, while simultaneously reducing the dose to the normal heart, lung, and liver. Clinical implications warrant systematic evaluation.

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Conflicts of Interest Notification: The authors declare no conflicts of interest.

Keywords

IMRT; dosimetry

INTRODUCTION

Trimodality therapy (surgery, chemotherapy, and radiation) for esophageal cancer has led to apparent improved treatment outcomes, with the administration of concurrent chemotherapy and radiation therapy (RT) believed to contribute to improvements in local control and survival in the bimodality setting^{1,2}. Although techniques for radiation planning, tumor imaging, and radiation delivery have advanced rapidly over the past several decades, the radiation techniques and doses used for treating esophageal cancer have remained relatively unchanged. In a previous single-institution review, we evaluated patterns of treatment failure among 66 patients with unresectable esophageal cancer given chemoradiation therapy with definitive intent at The University of Texas M. D. Anderson Cancer Center³. All patients received concurrent fluorouracil- based chemotherapy and a median prescribed RT dose of 50.4 Gy. Of these 66 patients, 24 had local-regional failure (37%); notably, 18 of those failures (75%) were located within the gross tumor volume (GTV). This finding suggests that although current therapies can be quite effective in some cases, local disease control, specifically within the GTV, remains a problem. Logically, the demonstrated benefits of radiation dose escalation for tumors at other anatomic sites in terms of improved local control and survival⁴⁻⁶ could be expected to apply to esophageal cancer as well.

The effectiveness of dose-escalation for esophageal tumors was evaluated in the Intergroup (INT) 0123 / Radiation Therapy Oncology Group (RTOG) 94-05 study⁷; in that trial, escalating the dose to 64.8 Gy was unsuccessful in that it did not improve survival or local-regional control, and as such was stopped prematurely. The radiation technique used in that study, however, was two-dimensional conformal RT (2D-CRT) with a sequential boost for dose escalation. The margins for both the primary and high-dose volumes were significantly larger than those used in current clinical practice, resulting in higher doses to the normal esophagus, heart, and lungs, which would have increased the possibility of toxicity. Perhaps the outcome would have been different if more modern techniques had been applied.

Several groups have demonstrated that the implementation of intensity-modulated radiation therapy (IMRT) can provide additional flexibility to modify dose distributions and improve normal tissue sparing⁸. Although IMRT is clearly useful for reducing the dose to critical structures, it is also beneficial for increasing the dose to volumes at high risk. Moreover, the simultaneous integrated boost (SIB) technique offers the advantage of simultaneously delivering a higher dose to the primary tumor (at 2.2 Gy or 2.3 Gy per fraction) while conventional lower doses are used to treat subclinical disease or electively treated regions (at 1.8 Gy or 2.0 Gy per fraction). Because most local failures after radiation therapy for esophageal cancer seem to occur in the GTV, we hypothesized that an SIB-IMRT technique could be used to selectively escalate the RT dose to the area at highest risk of recurrence. In the current study, we sought to compare the dose-volume constraints to critical structures of a traditional 2D-CRT plan, a modern-day IMRT plan, and a dose-escalated SIB-IMRT plan.

Our goal was to evaluate if the dose could be escalated while still meeting dose-volume histogram (DVH) dose constraints to critical normal-tissue structures, specifically the heart, lung, liver, and spinal cord.

METHODS AND MATERIALS

We retrospectively identified 10 patients with biopsy-proven adenocarcinoma of the distal esophagus treated at M.D. Anderson Cancer Center whose staging evaluations included positron emission tomography (PET) /CT and endoscopic ultrasonography. This post-hoc analysis of these treatment plans was approved by the appropriate institutional review board of M. D. Anderson.

For treatment simulation and planning purposes, all patients had undergone 4D CT scanning to account for respiratory motion. The CT images were acquired first while the patient was free-breathing, with 4D images acquired immediately thereafter. During the 4D CT image acquisition, patient respiration was monitored with an external respiratory gating system (Real-Time Position Management Respiratory Gating System; Varian Medical Systems, Palo Alto, CA). Each 4D CT image set consisted of 10 CT data sets representing 10 equally divided breathing phases in a complete respiratory cycle. The 4D CT images provided quantitative time-dependent 3D information about internal organ motion, allowing quantitative description of internal organ motion for both treatment targets and normal organs.

The GTV was delineated by the attending physician using all available resources, including fused PET/CT data, endoscopic reports, and diagnostic CT images. The GTV was expanded to the clinical target volume (CTV) by extending coverage 3 cm superiorly, 1 cm laterally, 3 cm inferiorly, and 3 cm into the mucosa of the stomach, depending on the physician's preference. The planning target volume (PTV) was the CTV plus a uniform 0.5-cm expansion margin. Organs at risk were outlined. Calculations of the total lung volume (and mean lung dose) excluded portions of the lung included in the GTV. The heart was contoured from the apex to the base of the right pulmonary artery. For each of the 10 patients, we then developed a 2D-CRT plan and an IMRT plan, both to a total dose of 50.4 Gy, and then an SIB-IMRT plan in which the GTV was dose-escalated to 64.8 Gy. We then evaluated DVH parameters for each plan to estimate the dose to critical structures, specifically the lung, heart, liver, and spinal cord.

2D-CRT plans were generated by using techniques similar to that used for the RTOG 94-05 trial⁷. The Pinnacle planning system (Phillips Medical Systems, Andover, MA) was used to generate treatment plans by starting with anterior/posterior beams until the spinal cord maximum dose was reached and then the plan was changed to oblique beams. The dose of 50.4 Gy was prescribed in 28 fractions to the isodose line, which covered the volume at risk. Although RTOG 94-05 did not use lung heterogeneity corrections, we did use them in this study to improve the comparability of this technique to more modern IMRT techniques.

IMRT plans were generated by using the step-and-shoot technique and a Pinnacle planning system (Phillips Medical Systems). Beam arrangements were optimized for each of the 10

patients with the goal of reducing both cardiac and pulmonary dose. The prescribed dose was 50.4 Gy in 28 fractions of 1.8 Gy per fraction, with the requirement that 95% of the PTV receive the prescribed dose. Planning objectives placed the highest priority on achieving PTV coverage, with secondary objectives to avoid normal lung and heart. Mean doses to normal tissues and total volumes irradiated to given dose levels were recorded, and lung heterogeneity corrections were used.

SIB-IMRT plans were generated similarly to the IMRT plans above, except that the dose to the GTV was simultaneously escalated to 64.8 Gy (28 fractions at 2.3 Gy per fraction) and the CTV and PTV received the standard IMRT dose of 50.4 Gy (28 fractions at 1.8 Gy per fraction). All SIB-IMRT plans were generated with the same five beams, as the IMRT plan, with beams at 80, 110, 160, 210, and 240 degrees, using 6MV photons.

Data were analyzed by using Stata/MP 11.0 statistical software. The equality of means for continuous variables was assessed by using *t* tests. A *p* value of 0.05 or less was considered to indicate statistical significance. Statistical tests were based on a two-sided significance level.

RESULTS

Mean dose-volume parameters for all four plans (50.4-Gy 2D-CRT, 50.4-Gy IMRT, 64.8-Gy 2D-CRT, and 64.8-Gy SIB-IMRT) for 10 patients are listed in the Table. Specific comparisons among the plans are discussed in the following paragraphs *2D-CRT versus IMRT*. We first compared the mean dose-volume parameters from a traditional 2D-CRT plan with those from a modern IMRT plan, both to a total dose of 50.4 Gy, for all 10 patients (Table, columns 1 and 2). Both the mean lung dose and the lung V_{20} were significantly lower with IMRT, from 9.9 Gy to 7.4 Gy (a 25% reduction, $p = 0.003$) and from 19% to 13% ($p = 0.007$). Mean doses to cardiac and hepatic tissue were also reduced in the IMRT plan (heart from 32.4 Gy to 22.7 Gy [33%], $p = 0.0006$; and liver from 18.4 Gy to 14.9 Gy [20%], $p = 0.04$). The mean spinal cord maximum point dose was 6% lower in the IMRT plan 34 Gy vs. 37 Gy in the 2D-CRT plan) ($p =$ not significant), even though both plans met the predefined dose constraints. Representative dose distributions between the 2D-CRT and IMRT plans to 50.4 Gy are presented in Figure 1.

Next we compared the mean dose-volume parameters from a traditional 2D-CRT plan with those from a modern IMRT plan, both planned to 64.8 Gy (Table, columns 3 and 4). Again both the mean lung dose and the lung V_{20} were reduced in the IMRT plan, from 11.8 Gy to 7.7 Gy (a 35% reduction, $p = 0.0006$) and from 23% to 12% ($p = 0.0002$). Mean heart and liver doses were similarly reduced in the IMRT plan (heart from 37.9 Gy to 22.7 Gy [41%], $p=0.0001$; and liver from 23 Gy to 15.6 Gy [32%], $p=0.003$). The mean spinal cord maximum point dose was decreased by 15% (from 44 Gy to 38 Gy), but again, this apparent difference was not significant ($p = 0.1362$). Notably, the differences between the two techniques were more apparent at the higher dose of 64.8 Gy, yet most of the classical dose constraints were still met.

IMRT versus SIB-IMRT

To evaluate the influence of using an SIB for dose escalation, we next compared the mean dose-volume values for 10 patients with treatment planned with IMRT to 50.4 Gy versus those of a dose-escalation plan in which the SIB-IMRT technique was used to deliver 64.8 Gy to the GTV while the PTV was treated to 50.4 Gy (Table, columns 2 and 4). In the conventional IMRT plan, the mean GTV dose was 52 Gy, whereas the SIB plan resulted in a 28% increase to the GTV with a mean dose of 66.9 Gy. The mean lung dose was similar in the IMRT plan and the SIB plan (7.4 Gy SIB-IMRT vs. 7.7 Gy IMRT, $p = 0.06$), as was the lung V_{20} (13% SIB-IMRT vs. 12% IMRT, $p = 0.06$). Mean doses were also comparable to the heart (22 Gy IMRT and 22.7 Gy SIB-IMRT, 3%) and to the liver (14.9 Gy IMRT and 15.6 Gy SIB-IMRT (5%). Lastly, the maximum dose to the spinal cord met the constraints set for both plans at 34.9 Gy IMRT and 38 Gy SIB-IMRT (a 9% difference, $p = 0.0041$) (Fig. 2).

2D-CRT versus SIB-IMRT

To test our hypothesis that SIB-IMRT plan could selectively escalate the dose to the GTV while reducing the dose to critical normal structures, we compared dose-volume values from a traditional 2D-CRT plan at 50.4 Gy to those of an SIB-IMRT boost plan delivery 64.8 Gy to the GTV (Table, columns 1 and 4). In the traditional 2D-CRT plan, the mean GTV dose was 52 Gy, whereas in the SIB the mean dose was 66.9 Gy, a 28% increase ($p = 0.0001$). Despite this higher GTV dose, both the mean lung dose and V_{20} were significantly lower in the SIB plan (9.9 Gy 2D-CRT and 7.7 Gy SIB-IMRT [23%], $p = 0.007$ and 19% 2D-CRT and 12% SIB-IMRT [37%], $p = 0.004$). The mean heart dose was significantly reduced (32.4 Gy 2D-CRT vs. 22.7 Gy SIB-IMRT [30%], $p = 0.001$). The mean liver dose seemed to have been reduced (18.4 Gy to 15.6 Gy [15%]), but this apparent difference was not significant at $p = 0.1$. The V_{30} for the liver, however, was significantly reduced (23% 2D-CRT vs. 13% SIB-IMRT [44%], $p = 0.04$). The maximum dose to the spinal cord was no different for the 2D-CRT plan statistically (37 Gy) and the SIB-IMRT plan (38 Gy). Representative dose distributions between 2D-CRT and IMRT plans are presented in Figures 3 and 4.

No significant differences were found among plans with respect to target coverage of the PTV or GTV. All plans achieved excellent target coverage with 95% or more of the PTV receiving at least 100% of the prescription dose, as expected based on our standard in-house planning restrictions.

DISCUSSION

The treatment related outcomes for locally advanced esophageal cancer are poor with a median survival just over one year⁷, and outcomes in patients with unresectable disease are even worse. Our prior work demonstrated that in most cases, local failure after combined chemoradiation therapy with a radiation dose of 50.4 Gy for unresectable esophageal cancer develops in the GTV³. In the current study, we sought to evaluate if an SIB-IMRT technique could be used to escalate the dose to the area at highest risk of recurrence while still achieving safe DVH constraints. We found that an SIB-IMRT technique could significantly escalate the dose to the GTV by 28% (to 64.8 Gy), not only without violating the DVH

parameters for the lung, heart, and liver but also reducing the dose to those normal structures relative to doses from traditional 2D-CRT plans.

The radiation dose used currently for esophageal cancer, either as preoperative or definitive treatment, has largely remains unchanged over the past several decades. Yet during this same period profound improvements in tumor localization, radiation planning, and radiation delivery have allowed both improved tumor treatment and reduced toxicity to proximal critical structures. We have gone from relying on x-ray films to map the extent of disease to using 3D planning with CT and now PET/CT fusions scans plus bronchoscopy and endoscopy. Also vastly improved are treatment planning systems, which allow dramatic reductions in lung dose, for example, relative to older 3D techniques⁹. Another major advance in the past several years has come from the use of charged-particle radiation such as protons, which offers further benefits for sparing critical tissues beyond those offered by current IMRT planning systems¹⁰. Patient setup and delivery have also been greatly improved through the use of image-guided radiation therapy (IGRT), which uses the enhanced imaging provided by kV x-ray images as well as those from cone beam-CT scans. While the majority of these technologies are now being used for the treatment of esophageal cancer they have not resulted dose escalation.

Another shortcoming of older planning systems is their inability to account for the influence of different tissue densities, such as lung and bone, on photon delivery and the resulting isodose lines. Other groups have demonstrated that when heterogeneity corrections are applied to plans that had been generated without them, coverage of the volume of interest is reduced, as such we now know that the earlier plans from the 2D era where in reality delivering higher doses to both the treatment planning volume and the critical structures of interest¹¹. The exact amount that the delivered dose is reduced depends on patient variables such as lung volume and anatomy and has been shown to range from 0–3.0 Gy lower with an average equivalent uniform dose reduction of 1.4 Gy¹². Taking this difference into account, older 2D plans were actually delivering a higher dose to the tumor and more modern plans that account for tissue heterogeneity are better able to deliver the actual prescribed dose of 50.4 Gy and have unintentionally lead to a dose reduction. This again speaks to the irony of the dose used for treating this tumor, which has gradually become lower over time despite vast improvements in radiation planning and delivery. By comparison, many of these improvements have been quickly adopted for the treatment of lung cancer, resulting in a steady rise in dose from 60 Gy to 74 Gy, with at least two phase II trials^{6,13} showing that 74 Gy can be delivered safely and a phase III trial (RTOG 0617) now underway to investigate the effectiveness 60 Gy vs 74 Gy for lung cancer. Given that most patients with unresectable non-small cell lung cancer have N2 or N3 disease, some or all of the esophagus in such patients is now routinely treated to 74 Gy. Yet patients with unresectable esophageal cancer receive a lower esophageal dose of only 50.4 Gy.

Although dose escalation has been shown to improve local control and survival in patients with tumors at other anatomic sites¹⁴, caution is needed in applying this logic to esophageal cancer. Given the proximity of the esophagus to several critical structures, care must be taken in treating esophageal cancer to not exchange improvements in local control with increased morbidity. Excessive exposure of the esophagus during high-dose irradiation of

lung cancer can result in esophageal stricture, a potentially life-threatening complication¹⁵. Another consideration would be changes in tumor size over the course of treatment, which is likely to be a dose-limiting parameter that will need to be monitored. Lastly, tumors with extensive gastric penetration should be restricted, as gastric radiation tolerance is thought to be less than that of the esophagus^{16,17}.

In summary, over the past 2 decades, tremendous advances have been made in treatment planning and delivery. Yet despite these dramatic improvements we now routinely use a lower dose for treating esophageal cancer than was used several decades ago. Not only has the dose been reduced from 60 Gy to 50 Gy but the routine use of heterogeneity corrections may have inadvertently reduced the treatment dose still further. Not surprisingly, the GTV is at high risk of failure after chemoradiation therapy for unresectable esophageal cancer³. This planning series illustrates that, theoretically, using an SIB-IMRT technique can safely increase the dose to the GTV while also reducing toxicity to critical structures. We are currently evaluating this technique in a phase I clinical trial to establish the maximum tolerated dose to which the GTV can be both safely and effectively escalated.

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Fig. 1.
 (top row) Axial, sagittal, and coronal views of a 2D-CRT plan to deliver 50.4 Gy to a patient with esophageal cancer, similar to the plans used in Intergroup 0123. (bottom row) A modern plan for delivering 50.4 Gy as intensity-modulated radiation therapy to the same patient with esophageal cancer.

Figure 2.
 (top row) Axial, sagittal, and coronal views of an intensity-modulated radiation therapy (IMRT) plan with the planning target volume being treated to 50.4 Gy. (bottom row) Simultaneous integrated boost IMRT plan with the gross tumor volume being treated to 64.8 Gy and the planning target volume to 50.4 Gy.

Figure 3.
 (top row) Axial, sagittal, and coronal view of a 2D-CRT plan to deliver 50.4 Gy to a patient with esophageal cancer (similar to the plans used in Intergroup 0123). (bottom row) Simultaneous integrated boost IMRT plan with the gross tumor volume being treated to 64.8 Gy and the planning target volume to 50.4 Gy.

Figure 4.

Dose volume histogram of an individual patient comparing an a 2D-CRT plan (dashed line) to 50.4 Gy (similar to that used in Intergroup 0123) to a simultaneous integrated boost (SIB)-IMRT plan (solid line) in which the gross tumor volume is treated to 64.8 Gy and the planning target volume to 50.4 Gy. The SIB-IMRT plan increased the mean GTV dose by 28% ($p = 0.001$) and decreased the mean heart dose by 30% ($p = 0.001$), the mean total lung dose by 23% ($p = 0.007$), and the lung V_{20} by 37% ($p = 0.004$).