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Oesophagus IMRT

Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer

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Abstract

***Background and purpose*: To evaluate the feasibility whether intensity-modulated radiotherapy (IMRT) can be used to reduce doses to normal lung than three-dimensional conformal radiotherapy (3DCRT) in treating distal esophageal malignancies.**

***Patients and methods*: Ten patient cases with cancer of the distal esophagus were selected for a retrospective treatment-planning study. IMRT plans using four, seven, and nine beams (4B, 7B, and 9B) were developed for each patient and compared with the 3DCRT plan used clinically. IMRT and 3DCRT plans were evaluated with respect to PTV coverage and dose-volumes to irradiated normal structures, with statistical comparison made between the two types of plans using the Wilcoxon matched-pair signed-rank test.**

***Results*: IMRT plans (4B, 7B, 9B) reduced total lung volume treated above 10 Gy (V_{10}), 20 Gy (V_{20}), mean lung dose (MLD), biological effective volume (V_{eff}), and lung integral dose ($P<0.05$). The median absolute improvement with IMRT over 3DCRT was approximately 10% for V_{10}, 5% for V_{20}, and 2.5 Gy for MLD. IMRT improved the PTV heterogeneity ($P<0.05$), yet conformity was better with 7B-9B IMRT plans. No clinically meaningful differences were observed with respect to the irradiated volumes of spinal cord, heart, liver, or total body integral doses.**

***Conclusions*: Dose-volume of exposed normal lung can be reduced with IMRT, though clinical investigations are warranted to assess IMRT treatment outcome of esophagus cancers.**
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Keywords: Esophageal cancer; Intensity-modulated radiotherapy; Three-dimensional conformal radiotherapy; Treatment planning

Treatment of esophageal cancer, which has a 5-year overall survival rate of 20–25% [1–3], traditionally involves chemoradiation for inoperable or unresectable disease or preoperative chemoradiation for operable disease [1–3]. Because the locoregional persistence or failure rate after chemoradiation is approximately 50% [1,3], better local treatment through radiotherapy may be needed to improve the overall treatment outcome. The goal of radiotherapy for esophageal cancer is to ensure appropriate coverage of the targeted structures while minimizing irradiation of normal tissues. One study found higher rates of postoperative pulmonary complications, such as pneumonia and acute respiratory distress syndrome, when higher lung volumes received low doses of lung radiation preoperatively: the pulmonary complication rate was 35% when the volume of lung receiving $\geq$10 Gy (V_{10}) was $\geq$40 and 8% when V_{10} was $<$40% ($P=0.014$) [4]. In that study, the treatment plan used conventional radiotherapy techniques, usually two-dimensional techniques using simulation films. Three-dimensional conformal radiotherapy (3DCRT) techniques have been shown to improve tumor targeting and to reduce irradiation of surrounding normal tissues, especially the lung [5].

Further improvement on dose conformity and normal tissue sparing can be accomplished by using intensity-modulated radiotherapy (IMRT) [6]. With IMRT, the possible gains over 3DCRT could come from reduced toxicity and delivery of a higher dose to target volumes. Use of IMRT for specific disease sites, including the prostate and the head and neck, has been investigated extensively and has become part of standard practice at many institutions [6]. However, very few studies have assessed whether IMRT is suitable or effective for treating esophageal cancer, partly because of

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the concern that IMRT may spread radiation at low doses to large volumes of normal lung tissue, which could be detrimental to radiosensitive structures. Only three reports have been published so far on the use of IMRT for esophageal cancer [7–9]. In two earlier studies [7,8], Nutting et al. showed 9B-IMRT plans were equivalent compared with 3DCRT plans regarding planning target volume (PTV), dose homogeneity and mean lung dose (MLD). However, 4B-IMRT plans with the same beam orientation as the 3DCRT plans increased PTV dose homogeneity and reduced the mean lung dose. A more recent report from Wu et al. [9] found that IMRT could be an effective tool to reduce volume of lung irradiated above 25 Gy for mid-thoracic esophageal cancers. Apparently, more extensive studies are needed to explore the potential gains of IMRT with respect to dosimetric improvements, before embarking on a clinical trial.

In this work, we completed a pilot study investigating the feasibility of using IMRT for cases of distal esophageal cancers, which typically involves higher lung volume being irradiated than cervical esophageal cancers. We determined whether IMRT could reduce dose delivered to normal lung than 3DCRT. Three types of IMRT beam arrangements were also made to assess optimal beam angles. Through this study, we intended to establish IMRT treatment strategies for esophagus cancers, and obtain preliminary results for designing future clinical trials.

Patients and methods

Ten patients who underwent treatment for esophageal cancer were selected from our existing patient population. Because the anatomy of distal esophageal cancers only varies slightly from patient to patient, these 10 cases were sufficient to represent typical anatomies for this group of patients. The patient identifiers were removed in accordance with an Institutional Review Board-approved retrospective study protocol. All of the patients had tumors involving the distal esophagus and gastroesophageal junction. Eight patients had stage III disease, one had stage IIB disease, and one had stage IVA disease. Through treatment simulation session, CT images of the entire thorax and upper abdomen were obtained using 3-mm slice spacing, including the entire liver and both kidneys. Images were obtained with the patient in the supine position. Gross tumor volume (GTV) was determined and reviewed by the attending radiation oncologist. Clinical target volume (CTV) was expanded with a 2-cm radial expansion and a 5-cm superior–inferior expansion, which followed our clinical guideline. PTV was defined as an additional 0.5-cm expansion beyond CTV. The median PTV was 899 cc (range, 585–1264 cc). Pinnacle treatment-planning system (version 6.0i; Philips Medical Systems North America, Andover, MA, USA) with collapsed cone convolution algorithm and heterogeneity correction was used for dose calculations.

Four types of treatment plans were generated for each patient case: 3DCRT, 4B-IMRT, 7B-IMRT, and 9B-IMRT. Most of the 3DCRT plans had the traditional four- beam arrangement with anteroposterior (AP), posteroanterior (PA), and two posterior oblique fields, but some used two parallel opposed oblique fields or an anterior and posterior oblique field to avoid the spinal cord. Typical oblique angles were 150 or 210° from the posterior side. The 3DCRT plans used clinically to treat the patients served as the comparison group; these plans were further renormalized to have the same PTV prescription as that of the IMRT plan and were approved to be clinically acceptable by the attending physician. The target dose was 50.4 Gy delivered in 28 fractions prescribed to 95% coverage of the PTV with concurrent chemotherapy. Mean PTV dose was 51.8 Gy in average for the 10 cases.

The 4B-IMRT plan used the same beam orientations as the four-beam 3DCRT plan. The intention of using the identical beam angles as the 3DCRT plans was to assess the effect of intensity modulation alone for the treatment. The 9B-IMRT plan was generated using equispaced (every 40°) beams, whereas the 7B-IMRT plan was generated using an equispaced nine-beam arrangement but without the two lateral beams (80 and 280°). These two laterally oriented beam angles may cause more lung exposure along the beam paths and thus may not be ideal for treatment of esophageal cancer. All IMRT plans were generated with 6MV photon beams with the above beam-angle template to minimize confounding factors such as manipulation of the beam orientation or beam energy. Because traditional issues of target localization, such as setup error and motion, are of concern in treatment planning, the *same PTV* that was considered adequate to address these issues in 3DCRT was used in IMRT. Using the same PTV allowed direct comparison of results from 3DCRT and IMRT plans without bias due to differences in planning margins.

The goals for inverse planning with IMRT were to ensure 95% coverage of the PTV to the prescribed dose (50.4 Gy at 1.8 Gy per fraction) while keeping the dose delivered to other normal structures, such as the lung, spinal cord, heart, and liver, within normally accepted tolerances. The treatment-planning parameters used to ensure coverage of the PTV were as follows: minimum dose of 48 Gy to 100% volume; maximum dose of 65 Gy to 5% of volume. Occasionally, a fictitious structure called 'expanded PTV' (i.e. PTV uniformly expanded by 1 cm) was created and prescribed $\geq$45 Gy to ensure adequate coverage of the PTV if necessary.

For the total lung, the planning objectives of V_{10} and V_{20} were generally assigned a level 10–20% lower than the median value of the 3DCRT plans (in absolute percentage of the lung volume at 10 and 20 Gy). More explicitly, with the 3DCRT plans, the DVHs for total lung were computed from which, V_{10} and V_{20} were deducted by 10–20% and were used as the planning goal for the corresponding IMRT plans. The maximum spinal cord dose used in the inverse planning was 45 Gy. Another fictitious structure named 'expanded spinal cord' (i.e. uniform expansion of the spinal cord by 1 cm) was created and prescribed a maximum of 40 Gy to ensure acceptable spinal cord doses and an additional geometric margin for the cord. For the heart, the planning goals were set to reduce V_{40} and V_{50} by 10–20% (in absolute percentage of the heart volume) than the median values of the 3DCRT plans. In general, V_{40} and V_{50} were kept to $<$50 and 30%, respectively, for the heart. For the liver, V_{30} was kept to $<$30% and no more than absolute 10% greater than the median value of the 3DCRT plans. To minimize hot spots

outside the PTV, a structure called 'normal tissue' was created to include all of the tissues enclosed by the external skin minus the expanded PTV. A maximum dose of 40 Gy was assigned to this structure, which represented normal tissue. The planning objectives for this structure were generally prioritized in the following order: PTV, lung, spinal cord, heart, liver, and normal tissue.

The full inverse planning process of the IMRT plans were carried over three to four iterations, during which the priority of various objectives was adjusted to obtain plans with results congruent with the planning goals. The treatment-planning software uses a gradient search-based inverse planning algorithm to generate optimal beam modulation satisfying the planner specified dose objectives and constraints. The goal of optimization was to minimize the overall cost of objective function (i.e. the function of the difference between the desired and calculated doses for the target and all specified critical organs).

After the inverse planning, the leaf motion required for the accelerator (Varian 2100EX with a 120-leaf Millennium multileaf collimator; Varian Oncology Systems, Palo Alto, CA, USA) was generated for each IMRT plan by using the sliding-window technique [10]. This was achieved using an in-house leaf conversion software program that has been tested for clinical implementation at our institution. We used the actual beam fluence delivered by the leaf motion to compute the deliverable dose distribution by using the convolution algorithm with the Pinnacle treatment-planning system. The accuracy of the dose-calculation algorithm for the IMRT dynamic multileaf collimator delivery system has been verified by separate phantom measurements at our institution. The final dose distribution in each plan was normalized to 95% coverage of the PTV receiving the prescribed dose (50.4 Gy in 28 fractions). Each plan was evaluated with respect to dose distribution, dose–volume histograms (DVHs), and additional dosimetric endpoints described below.

To assess the plan quality with respect to the dose delivered to the tumor, the conformity index (CI) and heterogeneity index (HI) were computed using the dose-volume histograms of the PTVs. CI was defined as $CI = V_{Dp}/PTV$, in which V_{Dp} is the volume enclosed by the 50.4-Gy prescription isodose cloud. CI was usually >1. Larger values indicate greater volumes of the prescription dose delivered outside the PTV (i.e. less dose conformity in the PTV). HI was defined as $HI = D_{5\%}/D_{95\%}$, in which $D_{5\%}$ and $D_{95\%}$ correspond to the dose delivered to 5 and 95% of the PTV, respectively. Greater HI values indicate doses exceeding the prescription dose and, thus, a greater degree of dose heterogeneity in the PTV.

To assess the effect of IMRT on normal lung irradiation, we computed several different dosimetric indices, including V_5–V_{20} for the normal lung, mean dose delivered to the normal lung (MLD), and biologically effective volume (V_{eff}). The rationale behind using V_5–V_{20} for the normal lung evaluation in comparing the different plans was based on

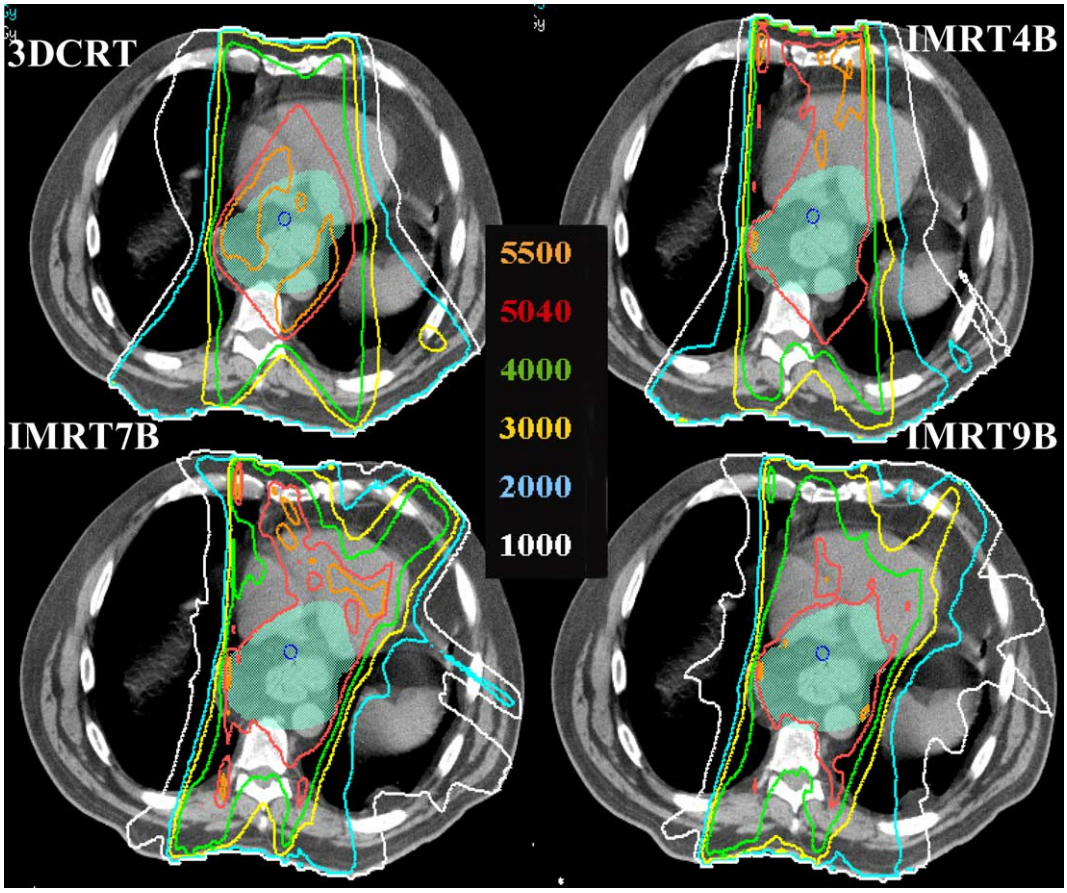

Fig. 1. Sample transverse CT images showing the isodose distributions in the middle of PTV for one of the cases studied.

observations that lung tissue tends to have a low dose tolerance [11–13], particularly for preoperative concurrent chemoradiation of esophagus cancers [4]. The rationale behind computing MLD was based on studies that suggested it may correlate strongly with lung toxicity [11]. V_{eff} was defined according to the power-law relationship using the Lyman–Kutcher dose–volume histogram reduction technique [14,15]:

$$V_{\text{eff}} = \sum_i V_i \times (D_i/D_0)^{1/n},$$

in which n is the 'volume parameter,' estimated by Burman et al. [16] to be 0.87 for the lung, and D_0 is the reference dose with which V_{eff} is computed; i.e. V_{eff} corresponds to the biologically effective lung volume if the lung is irradiated with a uniform dose (D_0). We chose D_0 using the TD_{50} of the lung, which has been estimated to be 20–40 Gy [11–13,16]. However, because normal tissue complication probability models for lung radiation injury are not well established, rather different results have emerged from studies conducted by different researchers. We selected 30 Gy as the reference dose on the basis of data reported by Kwa et al. [11], whose study used the largest patient population.

To evaluate the overall IMRT dose distributions, we computed the integral dose of the total tissue volume (including the tumors and lungs) enclosed by certain isodose surfaces of the entire thorax. The integral dose was defined as follows:

$$\text{ID} = \sum_i D_i \times V_i \times \rho_i,$$

in which V_i is the volume of the tissue irradiated at a dose of D_i, and ρ_i is the local density of the tissue based on the CT number. Thus, the integral dose was essentially the product of the mean dose and mean density of the tissue, reflecting the entire energy imparted by all the beams.

For each endpoint, differences between 3DCRT plans and the corresponding 4B-, 7B-, 9B-IMRT plans were analyzed using the Wilcoxon matched-pair signed-rank test. Statistical significance was set at $P<0.05$. The median difference and range of differences between the corresponding 3DCRT and IMRT plans were analyzed using box and whisker plots. Although the three types of IMRT plans appeared to be similar, we did not assess the specific differences among them in this pilot study, which was designed primarily to compare IMRT with 3DCRT for planning esophageal cancer treatment.

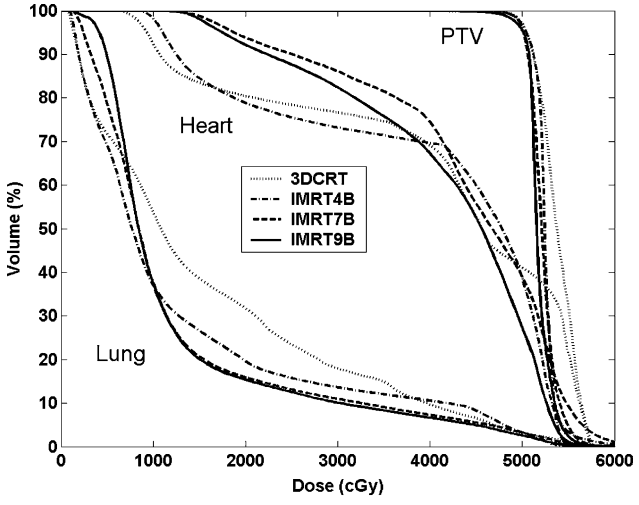

Fig. 2. DVHs from the 3DCRT and three IMRT plans for the case shown in Fig. 1.

Results

Isodose distributions of 3DCRT plan and three IMRT plans for one of the typical esophagus cases studied in this work are presented in Fig. 1. In the 3DCRT plan, two AP–PA parallel opposed beams and two posterior oblique beams were used to create the dose distribution. In the 4B-IMRT plan, even though identical beam angles were used, intensity modulation has helped to push the 10 and 20 Gy isodose lines away from the normal lung and reduced the corresponding lung volumes treated as a result. In the 7B- and 9B-IMRT plans, the 10–20 Gy isodose lines were further removed from the normal lung by adding more beam angles. Meanwhile, there was a slightly more spread of the 10 Gy isodose to the left side of the body because of these beam angles added. For the PTV, 9B-IMRT plan seemed to achieve the highest conformity for the 50.4 Gy isodose line because of a greater number of beams were involved, though this isodose line was spread further to the heart in the 4B- and 7B-IMRT plans.

DVHs for the four different plans are further illustrated in Fig. 2. Consistent with the finding from the isodose distribution, V_{20} was reduced 15–18% for the normal lung using the three IMRT plans. The degree of lung sparing between 7B- and 9B-IMRT plans is nearly the same. At low dose levels below 7 Gy, there was a tendency of increasing the volume with more beams for IMRT plans. Overall, there was a significant reduction of the V_{20} and mean lung dose for this case using the IMRT plans compared to the 3DCRT plan, illustrating the potential benefit of introducing intensity modulation to the beams, even if they had identical beam angles with the 3DCRT plan. For the PTV, a significant improvement on the dose homogeneity using the IMRT plans was also achieved without sacrificing dose to the heart. In fact, volume above 50 Gy to the heart was reduced with the 9B-IMRT plan, though V_{20}–V_{30} were elevated due to increased beam angles used. DVHs for other normal structures such as liver and spinal cord are not included because they are fairly comparable among the 3DCRT plan and IMRT plans.

More detailed comparisons of the 3DCRT and IMRT plans are presented in Table 1 and subsequent figures for all the cases studied. Figs. 3 and 4 show the lung irradiation at V_{20} and lung mean dose, respectively. In Fig. 5, comparison of the total body integral dose was made among the four types of treatment plans. Compared with the V_5 values in the 3DCRT plans, V_5 was reduced in the 4B-IMRT plans for 9 of the 10 patients, in the 7B-IMRT plans for seven patients, and in the 9B-IMRT plans for two patients. Among the 10 cases, the median V_5 for the 3DCRT plans was 63.9%. Compared with this value, the 4B-IMRT plans had a median reduction of 5.3% ($P=0.01$), the 7B-IMRT plans had a median reduction of 2.7%

Table 1
Median and range of endpoint values in the 3D CRT and the differences from the corresponding IMRT plans of the esophagus cases studies

Endpoint	Differences between 3D and IMRT plans[a]			
	3D-CRT (Median (min, max))	IMRT 4B (Median (min, max) [*P* value])	IMRT 7B (Median (min, max) [*P* value])	IMRT 9B (Median (min, max) [*P* value])
Heterogeneity index	1.1 (1.1, 1.2)	0.0 (−0.0, 0.0) [0.01]	0.0 (−0.0, 0.0) [0.02]	0.0 (−0.0, 0.0) [0.01]
Conformality index	1.9 (1.2, 2.2)	0.1 (−0.5, 0.5) [0.05]	0.2 (−0.1, 0.5) [0.05]	0.1 (−0.1, 0.7) [0.01]
Lung V5 (%)	63.9 (37.6, 83.8)	5.3 (−1.1, 18.1) [0.01]	2.7 (−10.3, 17.7) [0.20]	−4.4 (−23.0, 10.9) [0.14]
Lung V10 (%)	40.4 (24.3, 54.6)	9.4 (1.4, 16.5) [0.01]	11.2 (3.6, 17.9) [0.01]	10.2 (6.2, 19.8) [0.01]
Lung V20 (%)	19.3 (7.7, 37.6)	4.4 (1.6, 19.7) [0.01]	5.8 (1.1, 15.8) [0.01]	6.1 (1.1, 18.9) [0.01]
Lung Veff at 30 Gy (%)	44.0 (22.7, 51.6)	8.8 (3.4, 10.4) [0.01]	9.7 (4.1, 12.3) [0.01]	9.5 (2.3, 12.4) [0.01]
Lung mean does (Gy)	14.8 (8.6, 17.7)	2.3 (1.1, 3.1) [0.01]	3.0 (1.1, 3.4) [0.01]	2.6 (0.7, 3.6) [0.01]
Lung integral dose (J)	13.7 (7.5, 22.9)	2.1 (0.9, 3.7) [0.01]	3.1 (1.2, 4.3) [0.01]	2.0 (0.9, 4.4) [0.01]
Max dose to cord (Gy)	45.4 (36.8, 48.8)	0.145 (−6.9, 5.4) [0.88]	−2.7 (−10.2, 4.8) [0.08]	−0.15 (−8.9, 4.4) [0.96]
Heart V45 (%)	48.7 (24.2, 77.6)	0.2 (−16.4, 44) [0.65]	2.6 (−10.9, 39.6) [0.33]	6.6 (−11.3, 34.5) [0.14]
Liver V30 (%)	16.3 (6.9, 23.8)	−0.3 (−5.3, 2.2) [0.39]	−0.5 (−2.8, 3.3) [0.65]	−0.2 (−6.3, 5.4) [0.45]
Total body integral dose (J)	298.0 (152.0, 384.0)	−4.0 (−25, 19) [0.65]	−10.5 (−34.0, 26.0) [0.28]	−1.0 (−46.0, 22.0 [0.48]

[a] Differences are defined as values from the 3D plans subtracted by those from the IMRT plans.

($P=0.20$), and the 9B-IMRT plans had a median increase of 4.4% ($P=0.14$).

The results of the Wilcoxon matched-pair signed-rank test showed that all three IMRT plans significantly reduced V_{10}, V_{20}, V_{eff} at 30 Gy, mean dose, and integral dose for the lung (Table 1). The degree of reduction on irradiated lung volume varied from patient to patient, but it was generally greater for those patients whose 3DCRT plans had greater amount of lung treated (e.g. patients 2, 3, 7, and 10). The median V_{10} in the 3DCRT plans was 40.4%. The absolute median reduction in V_{10} was 9.4, 11.2, and 10.2% in the 4B-, 7B-, and 9B-IMRT plans, respectively ($P<0.05$ for all comparisons), and the reduction ranged up to nearly 20%.

For each patient, the IMRT plans reduced V_{20} (Fig. 3) to a less extent compared with the degree of reduction for V_{10}. As we expected, the median V_{20} (19.3%) was lower than the median V_{10} (40.4%) in the 3DCRT plan; thus, the absolute reduction in V_{20} using the IMRT plans was also lower, although patients 2 and 10 had reductions in V_{20} of $>10\%$. The absolute median reduction in V_{20} was 4.4, 5.8, and 6.1% in the 4B-, 7B-, and 9B-IMRT plans, respectively ($P<0.05$ for all comparisons), and the reduction ranged up to almost 20%.

For each patient, the IMRT plans reduced the MLD (Fig. 4). The median MLD in the 3DCRT plans was 14.8 Gy. The absolute median reduction in the MLD was 2.3, 3.0, and 2.6 Gy in the 4B-, 7B-, and 9B-IMRT plans, respectively ($P<0.05$ for all comparisons), and the reduction ranged up to 3.6 Gy. Correspondingly, the lung integral dose was also reduced using the IMRT plans. The median reduction was 2.1, 3.1, and 2.0 J using the 4B-, 7B-, and 9B-IMRT plans, respectively, with *P* value of 0.01.

For target coverage, the HI of PTVs decreased in 8 of the 10 patients with all three types of IMRT plans. The median HI in the 3DCRT plans was 1.12, and HI was equivalent or reduced with the 4B-, 7B-, and 9B- IMRT plans. Although the improvements in HI were statistically significant, the magnitudes of the differences were small and would likely have little clinical impact. As we have expected, the high-dose conformity of the target volumes in IMRT plans was generally improved, which resulted in a reduction in the CI of the PTVs. The 4B-IMRT plans produced the widest range of CI values because of using fewer beams in IMRT. The 7B-IMRT plans reduced CI in 6 of the 10 patients and resulted in similar CI values in three patients, and the 9B-IMRT plans

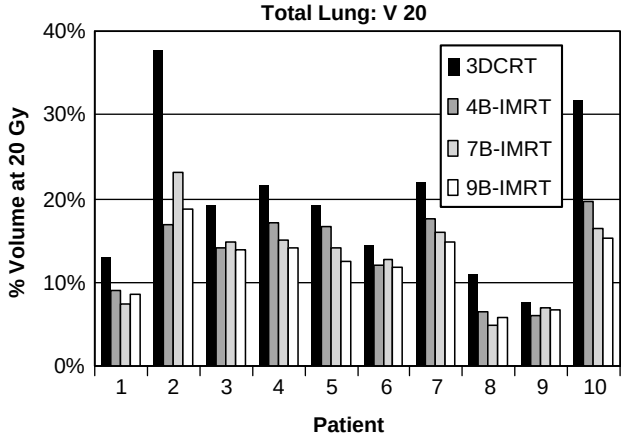

Fig. 3. Case-by-case comparison of lung V_{20} among the four types of treatment plans.

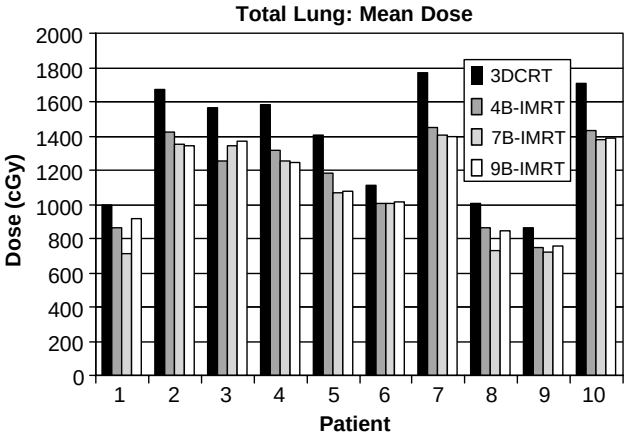

Fig. 4. Case-by-case comparison of mean lung dose (MLD) among the four types of treatment plans.

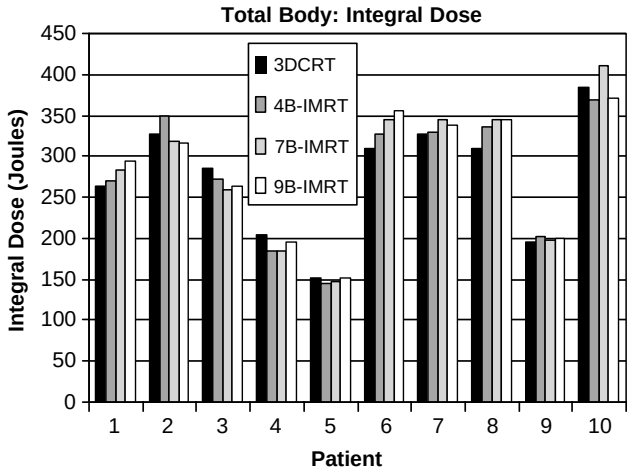

Fig. 5. Case-by-case comparison of total body integral dose among the four types of treatment plans.

reduced CI in nine patients. The mean CI in the 3DCRT plans was 1.9, and the CI was reduced for all patients with the 4B-, 7B-, and 9B-IMRT plans, respectively. Although the improvements in CI with the 7B- and 9B-IMRT plans were statistically significant, the magnitudes of the differences were small and their clinical significance is uncertain.

No clinically meaningful differences between the 3DCRT and IMRT plans were observed with respect to dose given to spinal cord, heart, liver, and total body integral doses. All four types of plans satisfied clinical constraints for normal tissue irradiation that traditionally have been considered acceptable. All of the plans had a maximum spinal cord dose of <50 Gy except for one 7B-IMRT plan, which had a maximum dose of 50.4 Gy. In all of the IMRT plans, the heart volume receiving ≥ 45 Gy was $<60\%$, and the liver V_{30} was $<30\%$. The median difference and range of differences in these parameters are listed in Table 1. For each patient, the IMRT plans had total body integral doses very similar to those of the corresponding 3DCRT plans (Fig. 5). The median 3DCRT total body integral dose was 298 J. The absolute median increase in the body integral dose were 4 ($P=0.65$), 10.5 ($P=0.28$), and 1.0 ($P=0.48$) with the 4B-, 7B-, and 9B-IMRT plans, respectively.

Discussion

Clinical studies have shown that chemoradiation used alone or preoperatively to treat esophageal cancer can result in severe complications [1–3]. Besides good clinical rationale, evidence exists that suggests that minimization of the volume of lung irradiated to low doses could results in fewer pulmonary complications [4]. Our study addressed whether IMRT for esophageal cancer can be used to reduce the volume of lung irradiated even at low doses of 10–20 Gy. This goal was achieved with all three types of IMRT plans, which also reduced V_{eff} at 30 Gy, MLD, and integral dose.

In comparing our data with those from other studies of IMRT versus 3DCRT, we generally found that IMRT provided greater benefit. For example, Nutting et al. [7,8] observed no benefit of 9B-IMRT over 3DCRT, whereas in our study, 9B-IMRT reduced lung irradiation, improved conformity, and slightly reduced heterogeneity. Nutting and co-workers [7,8] also found that the dose homogeneity with the 4B-IMRT plan was comparable to that with the 3DCRT plans ($11.8\pm3.3\%$ versus $12.4\pm3.9\%$; $P=0.6$) and that the MLD was reduced (9.5 ± 2.3 Gy versus 11.0 ± 2.9 Gy; $P=0.001$), whereas our data showed that PTV heterogeneity decreased with all three IMRT plans with an even lower MLD. The median improvement in MLD was 2.3–3.0 Gy in our study, whereas the average improvement was 1.5 Gy in the study by Nutting et al. [7,8]. A second study by Nutting et al. [7,8] showed lower heterogeneity with the use of 4B-IMRT than with 3DCRT (11.8 ± 3.3 Gy versus 16.0 ± 4.9 Gy; $P=0.03$) and an average reduction of 4.7% in the volume receiving ≥ 18 Gy ($14.1\pm10.1\%$ versus $18.8\pm11.9\%$; $P=0.001$), which is comparable to the median reduction in V_{20} of 4.4% ($P=0.005$) seen with 4B-IMRT in our study. On the other hand, a more recent study [9] on mid-thoracic esophageal cancers showed consistent results with our findings, that the lung volume can be reduced with IMRT compared with 3DCRT.

The reasons that we obtained different results from those of Nutting and co-workers may come from variation in the inverse planning algorithms, treatment-planning procedures, and patient selection. We limited our study to more commonly seen distal esophageal tumors involving the gastroesophageal junction. Because the principles and rationales of why IMRT plans improves dose sparing over 3DCRT plans will not change with the tumor location, we expect the conclusions from this study are readily applicable for mid to upper esophagus cases as well, as partially confirmed by the study from Wu et al. [9]. In fact, till now, we have already treated middle to upper esophagus cases with IMRT clinically and observed similar degree of improvement on normal tissue sparing from these cases.

In the inverse planning process for the IMRT plans, we gave PTV coverage and lung sparing higher priority than the other planning objectives. The IMRT plans and dose distributions will depend on how all of the planning objectives are specified during inverse planning and how the priorities for different objectives are balanced if they compete with each other. In essence, the degree of dose sculpting and normal tissue sparing achievable from using IMRT strongly depends on the planer's interaction with the treatment-planning system during the inverse planning process, which can be subjective and planer dependent, unfortunately. Our experience showed that if the planning objectives were not set aggressively or appropriately considering completing goals, the treatment-planning system will not honor various dose–volume constraints automatically by default.

In addition, we used only IMRT plans with deliverable (rather than ideal) dose distributions in the comparison. We found that dose distributions from ideal IMRT plans without considering delivery options can differ substantially from those of deliverable plans because the degradation of the fluence modulation in converting MLC sequences and MLC leakage and transmission. On the other hand, our results may be more specific for the sliding-window dMLC technique and could be different from those with nondeliverable plans or plans with other types of leaf sequence-conversion algorithms.

Our study was more extensive than those of Nutting et al. [7,8]: we also explored the effects of IMRT versus 3DCRT on the heart, liver, and total body doses. We found no significant statistical differences between the IMRT and 3DCRT plans on evaluation of the assigned endpoints for these structures. For certain cases, we observed that if the dose–volume constraints being set properly for these structures, it was also possible to reduce liver and heart doses using the IMRT plans. The IMRT plans did not significantly increase the total body integral dose in our study. Occasionally, IMRT produced areas of increased dose (i.e. hot spots) outside the PTV. The 9B- and 7B-IMRT plans had areas of increased dose in the paravertebral soft tissue areas posterior as well as anterior to the sternum (Fig. 1). These hot spots were seen occasionally in some of the patients in a few axial slices of the CT scans. The hot spots could be removed by further specifying a small region of interest and their dose constraints in the inverse planning process.

In comparison of the three IMRT plans, the 7B- and 9B-IMRT plans slightly improved CI, whereas CI with the 4B-IMRT plans was not significantly different from the 3DCRT plans. As we expected, IMRT plans with more beams have a greater potential for dose sculpting than do those with fewer beams. However, because beams have to enter patients through more directions to crossfire at the tumor, the volume of normal tissue exposed to low doses may be increased. We believe that the volume of normal tissue exposed to low doses may also be affected by leakage of the dynamic multileaf collimator, which increases with the number of beams and thus the amount of normal tissue exposed along the beam path. Although irradiation of the lung at all dose levels should be minimized, the clinical importance of V_5 has not been established in the literature except our most recent study [17]. Another advantage of using fewer beams is potentially shorter overall treatment times and higher delivery efficiency.

Currently, clinical procedure of using IMRT for treating distal esophagus is being established at our institution based on the results from this study. In general, 5–6 beams are being used for clinical IMRT treatment of distal esophagus cases. In a separate study on optimizing beam angles for the IMRT plans, we have found that equi-spaced beams as used in the previous studies [7,8] are not good options for treating the esophagus cases because lateral beams irradiated a greater lung volume and should be avoided. We also have to address issues related to respiratory motion, accuracy of IMRT dosimetry and patient setup in implementation of the IMRT procedure. Initial clinical results from the IMRT treatments are promising and are being used to develop clinical trials for esophageal cancers. Whether IMRT can be used to effectively reduce patient toxicity and improve local control await further clinical investigation.

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