HELICAL TOMOTHERAPY FOR ADVANCED ESOPHAGEAL CANCER IMPROVES TARGET CONFORMITY AND HOMOGENEITY: A COMPARISON WITH FIXED-FIELD INTENSITY-MODULATED RADIOTHERAPY

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Abstract

Purpose: To evaluate the usefulness of helical tomotherapy (HT) in the treatment of advanced esophageal cancer (EC) and compare target homogeneity, conformity and normal tissue doses between HT and fixed-field intensity-modulated radiotherapy (ff-IMRT).

Methods: In all, 23 patients with cT3-4N0-1M0-1a thoracic EC (upper esophagus, 9 patients; middle esophagus, 6; distal esophagus, 6 and esophagogastric junction, 2) who were treated with ff-IMRT (60 Gy in 30 fractions)were re-planned for HT and ff-IMRT with the same clinical requirements. Comparisons were performed using the Wilcoxon matched-pair signed-rank test.

Results: Compared with ff-IMRT, HT significantly reduced the homogeneity index for thoracic, upper, middle and distal ECs by 38%, 31%, 36% and 33%, respectively (P < 0.05). The conformity index was increased by HT for thoracic, upper and middle ECs by 9%, 9% and 18%, respectively (P < 0.05). Target coverage was improved by 1% with HT (P < 0.05). The mean lung dose was significantly reduced by HT for thoracic and upper ECs (P < 0.05). The V20 (volume receiving at least 20 Gy) and higher dose volumes of the lungs were decreased by HT in all cases, but the differences were significant for thoracic, upper and distal ECs (P < 0.05), with reductions of 2.1%, 3.1% and 2.2%, respectively. HT resulted in a larger lung V5 for thoracic, upper, middle and distal ECs, with increases of 3.5%, 1.5%, 7.2% and 3.2%, respectively. Heart sparing was significantly better with HT than with ff-IMRT in terms of the V30 and V40 for thoracic, upper, middle and distal ECs (P < 0.05).

Conclusions: Compared to ff-IMRT, HT provides superior target coverage, conformity and homogeneity, with reduced the volume of high doses to the lungs and heart for advanced EC. HT may be a treatment option for advanced EC, especially upper EC.

Keywords

helical tomotherapy, esophageal cancer, dosimetric comparison, IMRT

Introduction

Esophageal cancer (EC) is the eighth most common cancer worldwide.[1]Approximately 70% of all EC cases in the world occur in China, with squamous cell carcinoma accounting for more than 90% of Chinese EC cases.[2, 3]Radiotherapy plays a key role in the treatment of localized EC, and is usually combined with concurrent chemotherapy. However, radiotherapy has the potential to cause substantial toxicity in the form of radiation pneumonitis (RP) and lung fibrosis as well as pericardial effusion, pericarditis, myocardial ischemia and heart failure.

Compared to three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT) enables the modification of radiation-dose distributions and improves conformal and homogeneous target coverage while potentially decreasing radiation dose to the normal tissues.[4-8] Therefore, IMRT may improve clinical outcomes and reduce radiation-related toxicity,[7]and itis emerging as a standard of care for EC. However, even with the use of IMRT, the incidence of radiation-induced toxicity remains high,[9, 10] and definitive dose must still be limited in the case of bulky, long and complex targets in order to limit the dose delivered to the lungs, heart and spinal cord.

Helical tomotherapy (HT) is a rotational radiotherapy modality that when combined with image-guided IMRT, allows adaptive and dose-guided radiotherapy. HT has been widely used in clinical radiation oncology, since it is associated with sharper dose gradients, greater target coverage, better homogeneity and conformity, and significantly reduced doses to organs at risk (OARs).[11-13]Although several reports have compared HT with IMRT, few of these studies focused on EC patients; moreover, these studies generally had small sample sizes, assessed tumors located at certain primary sites and involved plans using simultaneous integrated boost techniques.[14-16]Large-scale studies on definitive radiotherapy in EC are very scarce. Thus, the aim of the present study was to determine the usefulness of HT in the treatment of advanced-stage EC and compare target homogeneity, conformity and normal-tissue doses between HT and fixed-field IMRT (ff-IMRT).

Patients and Methods

We enrolled 23 consecutive patients who had cT3-4N0-1M0-1a thoracic EC (upper esophagus, 9 patients; middle esophagus, 6; distal, 6 and esophagogastric junction [EGJ], 2), according to the American Joint Committee on Cancer staging system (2002 and 2010), and were treated with ff-IMRT. Each patient underwent re-planning using HT and ff-IMRT by one physicist. For analysis, the patients were divided into the upper EC, middle EC and distal EC subgroups according to the location of the primary tumor, and the entire study population was termed the thoracic EC group. EGJ cancer was included in the distal EC subgroup.

Computed tomography (CT) was performed with a 5-mm slice thickness, and the CT data was imported to a treatment-planning system. The gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), nodes and OARs (lungs, heart, spinal cord, liver and kidneys) were contoured by the treating physician as per the Radiation Therapy Oncology Group 0436 protocol.[17] The CTV was defined as the GTV with 3–5 cm superior–inferior margins and 1 cm lateral and anterior–posterior margins, positive nodes with 1-cm uniform margins and the involved lymph node drainage area. The PTV was delineated with additional 0.5-cm margins around the CTV. All PTVs and OARs were contoured using the Pinnacle planning system, and the contoured volumes were transferred to the HT planning system.

All patients received 60 Gy to the PTV in 30 fractions. The dose uniformity requirement was Dmin(PTV) > 95% and Dmax(PTV) < 110% of prescription dose. The doses to the OARs were as follows: the V20 for both lungs (volume of both lungs receiving a dose of at least 20 Gy) was ≤30%; the mean lung dose (MLD) was ≤18 Gy; the V30 and V40 for the heart were ≤40% and ≤30%, respectively; and the maximum dose (Dmax) delivered to the spinal cord was ≤45 Gy. The treatment-planning software used in this study was HiART TomoPlan 4.1.2. The process of HT planning was similar to that previously described.[18, 19] We used a field width of 2.5 cm, a pitch value of 0.287 and a mean modulation factor of 2.0. A normal dose-calculation grid (256 × 256 pixels) with a convolution–superposition algorithm was used for dose calculation.[20] The Philips Pinnacle Planning System 9.0 was used for ff-IMRT planning. The direct machine parameter optimization module, which was adopted for the planning, used 5–7 angles to evenly separate coplanar fields. The minimum segment area was set to 10 cm^2, and the minimum segment MU was 10 MUs. A collapsed-cone convolution algorithm was used to calculate dosage, with a dose grid resolution of 4 mm.

Based on the International Commission on Radiation Units report no. 83,[21] dosimetric parameters were evaluated quantitatively. For the PTV, the parameters were D98% (near-minimum dose), D2% (near-maximum dose), mean dose, dose standard deviation, conformity index (CI), homogeneity index (HI) and target coverage (TC). The CI was defined as

$$(TVPV/VPTV)/(VTV/TVPV), \qquad (1)$$

where VPTV is the volume of the PTV, TVPV is the volume of the PTV covered by the prescribed isodose line, and VTV is the treated volume of the prescribed isodose line.[22] The 95% isodose was selected as the prescribed isodose line. Possible CI values ranged from 0 to 1, with values closer to 1 indicating better conformity. The HI was defined as

$$(D2 - D98)/DP, \qquad (2)$$

where D2 and D98 are the doses at 2% and 98% of the PTV, and DP is the prescribed dose.[23] Theoretically, a lower HI value represents a plan that provides a more homogenous dose distribution. TC was defined as

$$TVPD/TV, \qquad (3)$$

where TVPD and TV are the target volume receiving the prescribed dose and the PTV, respectively. A value closer to unity represents better TC.[24] For each patient, analyses were performed to determine the MLD, the V5, V10, V15, V20, V25 and V30 of the lungs, the mean heart dose (MHD), the V20, V30 and V40 of the heart, Dmax to the spinal cord, maximum dose delivered to 1 cm^3 of the spinal cord (D1cc), V5 and V10 of normal tissue (NT; body excluding the PTV), V25 and V35 of the liver, V10 and V15 of each kidney and the mean dose to each kidney. Delivery time was calculated from beam-on to beam-off; it included the time required for radiation delivery and gantry rotation but not the time required for patient setup and image comparison.

Statistical analysis was performed using the Wilcoxon matched-pair signed-rank test and IBM SPSS Statistics (version 19.0.0). P values <0.05 were defined as statistically significant.

Results

The axial, coronal and sagittal views of the dose distributions in the HT and ff-IMRT plans for upper, middle and distal ECs are shown in Figure 1that showed the sharper dose gradient in HT. The HT plans were better than the ff-IMRT plans in terms of PTV coverage, conformity and homogeneity, but the 5-Gy isodose line of the HT plans showed slightly larger lung and NT volumes. Figure 2 presents the average dose–volume histograms (DVHs) for the PTV and OARs in the entire study population (thoracic EC group) and the three subgroups. The PTV line in the DVHs showed that HT was associated with better TC and homogeneity. The curves showed that in the low-dose regions (e.g., V5) of the lungs, HT was worse than ff-IMRT; however, in the relatively high-dose regions (e.g., V20), HT was significantly superior to ff-IMRT, especially for upper ECs. In terms of the V30 and V40 of the heart, HT was superior to ff-IMRT. The dose distribution in the PTV and OARs, and the delivery time for the entire study group and the three subgroups are listed in Tables 1 and 2, respectively. The data is presented as the averages over all patients and the errors at the standard deviation level.

The data for the PTV showed that compared with ff-IMRT, HT significantly improved homogeneity for thoracic, upper, middle and distal ECs (P < 0.05), with reductions of 38%, 31%, 36% and 33%, respectively, in HI. In addition, HT significantly improved conformity for thoracic, upper and middle ECs (P < 0.05), with increases of 9%, 9% and 18%, respectively in CI. However, in the case of distal ECs, similar conformity was achieved with HT and ff-IMRT (P = 0.125). The use of HT improved TC by 1% in the entire study group and the three subgroups (P < 0.05).

The lungs were better spared by HT. The MLD was significantly lower with HT than with ff-IMRT in the case of thoracic (10.9 Gy vs. 11.6 Gy) and upper ECs (11.6 Gy vs. 12 Gy; P < 0.05 for both). The V20 and higher dose volumes of the lungs were decreased by HT in all groups, but the differences were significant for thoracic, upper and distal ECs (P < 0.05), with reductions of 2.1%, 3.1% and 2.2%, respectively. The V20 and V25 of the lungs in the case of middle ECs did not significantly differ between HT and ff-IMRT, though they were better with HT. In the low-dose regions however, HT resulted in a larger V5, with increases of 3.5%, 1.5%, 7.2% and 3.2% for thoracic, upper, middle and distal ECs, respectively. The difference was statistically significant for thoracic ECs (P = 0.017; 56.6% vs. 53.1%), but not for the three subgroups (P > 0.05). In addition, V10 and V15 for both the entire group and the three subgroups did not significantly differ between HT and ff-IMRT (P > 0.05), except that V15 for upper ECs was better with HT (P < 0.05).

The sparing of the heart was also significantly better with HT than with ff-IMRT in terms of the V30 and V40 for the thoracic, upper, middle and distal ECs (P < 0.05), except in the case of V30 for middle ECs. The MHD for thoracic ECs was significantly lower with HT than with ff-IMRT (P < 0.05); this dose was also lower with HT in the three subgroups, but

the difference was not significant (P > 0.05).

In the case of the spinal cord, the dose constraints were always met with both HT and ff-IMRT. However, HT resulted in greater values of Dmax and D1cc of the spinal cord for thoracic, upper, middle and distal ECs.

For distal ECs, the mean dose to the left and right kidneys and the V10 and V15 of the kidneys were lower with HT, but the differences were not significant. The V25 of the liver was similar in both HT and ff-IMRT, but the V35 was significantly reduced by HT (P < 0.05).

The delivery time was slightly lengthened by HT for thoracic, middle and distal ECs (P < 0.05), but was similar for both HT and ff-IMRT in the case of upper ECs.

Discussion

In our study, both HT and ff-IMRT produced good plans and dose distributions, however, HT achieved superior HI, CI and TC for the PTV, indicating better target homogeneity, conformity and coverage than ff-IMRT, which may result in better clinical outcomes, and HT may be particularly beneficial in those patients who have target volumes in close proximity to the spinal cord because of its sharper dose gradient.Although it is generally agreed that in radiotherapy planning, improvement in conformity often occurs at the cost of worsening homogeneity, we have demonstrated that HT can provide not only better conformal TC but also more homogeneous dose distributions.

In our study, the order of priority in organ sparing was lungs, heart, and spinal cord for both IMRT and HT. We found that HT could reduce the volume of high doses of the lungs (MLD and V20 or higher), which may reduce the risk of radiation-induced lung toxicity, although HT may result in slightly larger low-dose volume of lungs, whereas, it is still very controversial whether larger low-dose lung volume could increase the risk of radiation pneumonitis. In a dosimetric study comparing IMRT with HT for ECs, Chen et al. demonstrated superior lung sparing in terms of V20 and MLD by HT.[15] Similarly, in the present study, HT significantly improved lung sparing in terms of the MLD, and V20 and higher dose volumes. Because lung V20 and MLD is generally considered the threshold dose for the lungs,[25-30] in theory, HT could reduce pulmonary complications. However, HT might result in a larger low-dose volume when rotational therapies are applied.[15] In the current study, HT resulted in a higher V5 of the lungs than did ff-IMRT, especially for thoracic ECs (P = 0.017); the difference was not significant for the three subgroups (P > 0.05). The larger low-dose volume of the lungs might result in radiation-induced lung toxicity; however, no long-term data exist on using HT for EC. Whether or not the low lung dose increasesthe risk of RP remains controversial, and this topic warrants further investigation. Wang et al.[31] reported that several DVH parameters (lung V5–V65 and MLD) were highly correlated with RP; however, V5 was the only factor significantly associated with RP. The 1-year actuarial incidences of RP of grade ≥3 in the groups with V5 ≤42% and V5 >42% were 3% and 38%, respectively (P= 0.001).[31]Lee et al. demonstrated that pulmonary complications were noted more often (35% vs. 8%, P = 0.014) when V10 was ≥40% vs. <40% and when V15 was ≥30% vs. <30% (33% vs. 10%, P= 0.036).[32] However, a later update of the study reported V5 ≥ 47% as a significant risk factor instead of V10 and V15.[33]

A few studies have reported that reduction in the high-dose region is more important than a counterbalanced increase in the low-dose region.[10, 30, 34-36]Ahmed et al.[35] reported that 12 of 52 patients with locally advanced lung tumors treated with volumetric modulated arc therapy (VMAT) had demonstrable fibrosis on CT. The mean MLD and V20 in the patients with fibrosis were 12.3 Gy and 20%, respectively. Moreover, in 83% of all patients with evidence of lung fibrosis, the entire fibrotic region was encompassed by the ≥36 Gy isodose line. This suggests a characteristic pattern of fibrosis after VMAT.[35]

However, few DVH parameters that are consistently related to RP have been reported, such as V5, V10, V15, V20 and MLD.[10, 25-36]Wang et al. reported that multiple dosimetric factors that define the shape of the DVH, rather than a single factor might affect the incidence of RP.[31]It is promising that in the current study, HT resulted in reduced V20 and higher dose volumes and MLD, comparable V10 and V15, and slightly increased V5. Considering all these factors, we think that compared to IMRT, HT for ECs might reduce the risk of RPor allow dose escalation to the tumor with acceptable lung toxicity.

The analysis of the data regarding the dose delivered to the lungs stratified according to the target location showed that compared with ff-IMRT, HT showed the best lung sparing for upper ECs, even with similar low-dose volumes, followed by thoracic and distal ECs. Patients with upper EC might benefit the most from HT, whereas those with middle EC might benefit less from HT. However, the true benefit of HT still awaits clinical results.

The effect of RT on the heart has been reported in many studies on EC.[37-39]It is reported that cardiac complications in this case are related to heart V30, V40 and higher dose volumes, and MHD.[40, 41] HT might spare the heart better than does IMRT because of its sharper dose gradient, and might thus reduce the risk of heart diseases related to radiation. A study including 101 patients with inoperable ECs treated with chemoradiotherapy found that the risk of pericardial effusion increased significantly with a mean pericardial dose of >26.1 Gy (73% vs. 13%, P = 0.002) and a pericardium V30 of >46% (73% vs. 13%, P = 0.001).[41] Gayed et al.[40] reported a 54% rate of cardiac ischemia 3 months following chemoradiotherapy for EC; they found that most perfusion defects were located in the region of the heart receiving ≥45 Gy. The INT 0123 study reported a total of 11 (10%) treatment-related deaths in the group of patients receiving 64.8 Gy combined with chemotherapy, and 3 of these 11 deaths were cardiac related.[42]Thus, lowering the radiation dose to the heart may be potentially life-saving. In the present study, HT spared the heart better than IMRT in terms of the volume of high doses (V30, V40 and MHD), which could potentially decrease radiation-related cardiac diseases in long-term survivors.

Axial views pointed out how to apply the dose in the area of the spinal cord (Fig. 1). In the current study, the Dmax for the spinal cord was ≤45 Gy, with a 3- to 5-mm safety margin for setup uncertainty in all HT and ff-IMRT plans. However, HT resulted in slightly higher values of Dmax and D1cc of the spinal cord because of the lower priority than lungs. Better sparing of the spinal cord may result in a loss of sparing of the lungs. Therefore, Dmax and D1cc of the spinal cord were accepted as no more than 45 Gy in order to spare the lungs as much as possible.

Compared to IMRT, HT results in larger low-dose volume of the NT after whole pelvic radiotherapy in postoperative endometrial cancer patients.[43] In the current study, the HT technique also resulted in larger volumes of NT receiving low doses (e.g., V5, V10) as compared to ff-IMRT, which may cause radiation-induced secondary malignancy. Because most EC patients are elderly with poor prognosis, the secondary malignancy from radiation is generally not considered a significant clinical problem because such malignancies invariably develop long after radiotherapy.[44]

We compared dosimetric parameters according to tumor location, and found HT could result in much better target conformity and normal tissue sparing for upper esophageal cancer.However, dosimetry plan comparison studies are very hard to perform adequately due to the many variables needing to be controlled.Some bias might exist because of the use of different calculation algorithms in the planning software systems[14, 45, 46], and the order of priorityin organs sparing also greatly affects the resulting doses.

Conclusion

This study demonstrates that compared to ff-IMRT, HT can provide superior plans with improved target conformity, homogeneity, and coverage, and significantly reduce the irradiated volume of high doses of most critical structures (lungs and heart) in patients with advanced EC, which may improve survival and reduce radiation-induced toxicities. HT may be a treatment option for advanced ECs, especially upper ECs, tumors that are bulky, long and have a complex shape, and tumors in close proximity to the spinal cord. The potential role of HT in improving the clinical outcomes of patients with advanced EC must be confirmed using early and long-term clinical results.

Acknowledgments

Referrence

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127: 2893–917.

2. Yaping Xu, Xinmin Yu, Qixun Chen, et al. Neoadjuvant versus adjuvant treatment: which one is better for resectable esophageal squamous cell carcinoma? World J SurgOncol 2012;10: 173.

3. Siwei Zhang, Min Zhang, Guanglin Li, et al. An analysis of incidence and mortality of esophageal cancer in China, 2003–2007. China Cancer 2012;21: 241–247.

4. Chandra A, Guerrero TM, Liu HH, et al. Feasibility of using intensity-modulated radiotherapy to improve lung sparing in treatment planning for distal esophageal cancer. Radiother Oncol 2005;77: 247–253.

5. Nutting CM, Bedford JL, Cosgrove VP, et al. A comparison of conformal and intensity-modulated techniques for esophageal radiotherapy. Radiother Oncol 2001;61: 157–163.

6. Kole TP, Aghayere O, Kwah J, et al. Comparison of heart and coronary artery doses associated with intensity-modulated radiotherapy versus three dimensional conformal radiotherapy for distal esophageal cancer. Int J Radiat Oncol Biol Phys 2011;83: 1580–1586.

7. Steven H. Lin, Lu Wang, Bevan Myles, et al. Propensity score-based comparison of long-term outcomes with 3-Dimensional Conformal Radiotherapy vs Intensity-Modulated Radiotherapy for esophageal cancer. Int J Radiation Oncol Biol Phys 2012;84(5):1078-1085.

8. Weihua Fu, Luhua Wang, Zongmei Zhou, et al. Comparison of conformal and intensity-modulated techniques for simultaneous integrated boost radiotherapy of upper esophageal carcinoma. World J Gastroenterol 2004;15;10(8):1098-1102.

9. Lawrence B. Marks,Soren M. Bentzen,Joseph O. Deasy, et al. Radiation dose volume effects in the lung. Int J Radiat Oncol Biol Phys. 2010;76: S70–S76.

10. Palma D, Senan S, Haasbeek C, et al. Radiological and clinical pneumonitis after stereotactic lung radiotherapy: A matched analysis of three-dimensional conformal and volumetric modulated arc therapy techniques. Int J Radiat Oncol Biol Phys 2011;80: 506-513.

11. Cozzarini C, Fiorino C, Di Muzio N, et al. Significant reduction of acute toxicity following pelvic irradiation with helical tomotherapy in patients with localized prostate cancer. Radiother Oncol 2007;84: 164–70.

12. Welsh J, Lock M, Harari P, et al. Clinical implementation of adaptive helical tomotherapy: A unique approach to image-guided intensity modulated radiotherapy. Technol Cancer Res Treat 2006;5: 465–479.

13. Welsh JS. Helical tomotherapy in the community setting: A personal account. Commun Oncol 2009;6: 463–467.

14. Spencer Martin, Jeff Z. Chen, A. Rashid Dar, et al. Dosimetric comparison of helical tomotherapy, RapidArc, and a novel IMRT & Arc technique for esophageal carcinoma. Radiotherapy and Oncology 2011;101: 431–437.

15. Yijen Chen, An Liu, Chunhui Han, 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: 166–171.

16. Yaoching Wang, Shangwen Chen, Chunru Chien, 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. *Technology in Cancer Research & Treatment 2013;12: 485-491.*

17. A phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer who are treated without surgery. RTOG 0436.

18. Saibishkumar EP, Jha N, Scrimger RA, et al. Sparing the parotid glands and surgically transferred submandibular gland with helical tomotherapy in postoperative

radiation of head and neck cancer: a planning study. Radiother Oncol 2007;85: 98–104.

19. Fiorino C, Dell'Oca I, Pierelli A, et al. Significant improvement in normal tissue

sparing and target coverage for head and neck cancer by means of helical tomotherapy. Radiother Oncol 2006;78: 276–82.

20. Mackie TR. History of tomotherapy. Phys Med Biol 2006;51: R427–53.

21. International Commission on Radiation Units and Measurements Report 83. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT). J ICRU 2010; 10.

22. Feuvret L, Noel G, Mazeron J J, et al. Conformity index: a review. Int J Radiat Oncol Biol Phys 2006;64: 333-342.

23. Wu Q, Mohan R, Morris M, et al. Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas. I: dosimetric results. Int J Radiat Oncol Biol Phys 2003;56: 573-585.

24. Danita Kannarunimit, Martina Descovich, Aaron Garcia, et al. Analysis of dose distribution and risk of pneumonitis in stereotactic body radiation therapy for centrally located lung tumors: A comparison of robotic radiosurgery, helical tomotherapy and volumetric modulated arc therapy. Technology in Cancer Research and Treatment 2015;14(1): 49-60.

25. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45: 323–329.

26. Hernando M, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: A dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51: 650–659.

27. Kwa SL, Lebesque JV, Theuws, et al. Radiation pneumonitis as a function of mean dose: An analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 1998;42: 1–9.

28. Seppenwoolde Y, Lebesque JV, de Jaeger K, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Int J Radiat Oncol Biol Phys 2003;55: 724–735.

29. Semenenko VA, Molthen RC, et al. Irradiation of varying volumes of rat lung to same mean lung dose: a little to a lot or a lot to a little? Int J Radiat Oncol Biol Phys 2008;71: 838-847.

30. Lujun Zhao, Wei Ji, Guangfei Ou, et al. Risk factors for radiation-induced lung toxicity in patients with non-small cell lung cancer who received postoperative radiation therapy. Lung Cancer 2012;77: 326– 330.

31. Shulian Wang, Zhongxing Liao, Xiong Wei, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys 2006;66: 1399-1407.

32. Lee HK, Vaporciyan AA, Cox JD, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. Int J Radiat Oncol Biol Phys 2003;57: 1317–1322.

33. Shulian Wang, Zhongxing Liao, Vaporciyan AA, et al. Investigation of clinical and dosimetric factors associated with postoperative pulmonary complications in esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006;64: 692–9.

34. Willner J, Jost A, Baier K, et al. A little to a lot or a lot to a little? An analysis of pneumonitis risk from dosevolume histogram parameters of the lung in patients with lung cancer treated with 3-D conformal radiotherapy. StrahlentherOnkol 2003;179: 548-556.

35. M. Ahmed, A. Dunlop, C. Johnson, et al. Patterns Of lung fibrosis following Volumetric Modulated Arc Radiation Therapy (VMAT) for locally advanced lung cancer –Is there a dosimetric relationship? Int J Radiat Oncol Biol Phys2014. S8.

36. Indira Madani, Kim De Ruyck, Hannelore Goeminne, et al. Predicting risk of radiation-induced lung injury. J Thorac Oncol 2007;2: 864–874.

37. Kumekawa Y, Kanedo K, Ito H, et al. Late toxicity in complete responses cases after definitive chemoradiotherapy for esophageal squamous cell carcinoma. J Gastroenterol 2006;41: 425–432.

38. Morota M, Gomi K, Kozuka T, et al. Late toxicity after definitive concurrent chemoradiotherapy for thoracic esophageal carcinoma. Int J Radiat Oncol Biol Phys 2009;75: 122–128.

39. Ishikura S, Nihei K, Ohtsu A, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21: 2697–702.

40. Gayed IW, Liu HH, Yusuf SW, et al. The prevalence of myocardial ischemia after concurrent chemoradiation as detected by gated myocardial perfusion imaging in patients with esophageal cancer. J Nucl Med 2006;47: 1756–62.

41. Xiong Wei, Liu HH, Tucker SL, et al. Risk factors for pericardial effusion in inoperable esophageal cancer patients treated with definitive chemoradiation therapy. Int J Radiat Oncol Biol Phys 2008;70: 707–14.

42. Minsky B.D., Pajak T.F., Ginsberg R.J., 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 2002;20: 1167–74.

43. R. Yang, S. Xu, W. Jiang, et al. Integral dose in three-dimensional conformal radiotherapy, intensity-modulated radiotherapy and helical tomotherapy. Clinical Oncology 2009;21: 706-712.

44. Hall EJ, and Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys 2003;56(1): 83–88.

45. Davidson M. T., Blake S. J., Batchelar D. L., et al. Assessing the role of volumetric modulated arc therapy (VMAT) relative to IMRT and helical tomotherapy in the management of localized, locally advanced, and post-operative prostate cancer. Int J Radiat Oncol Biol Phys 2011;80: 1550-1558.

46. Florian Sterzing, Gabriele Sroka-Perez, Kai Schubert, et al. Evaluating target coverage and normal tissue sparing in the adjuvant radiotherapy of malignant pleural mesothelioma: Helical tomotherapy compared with step-and-shoot IMRT. Radiotherapy and Oncology 2008;86: 251–257.

Table 1. Summary of numeric analysis of dose–volume histograms and delivery times for the target volumes and organs at risk for thoracic esophageal cancers

	Parameters	HT	IMRT	P
PTV	Mean dose (Gy)	62.4±0.4	63.2±0.5	0.000
	HI	0.08±0.01	0.13±0.02	0.000
	CI	0.88±0.02	0.81±0.07	0.000
	TC	0.96	0.95	0.000
Total lungs	MLD (Gy)	10.9±1.4	11.6±1.9	0.001
	V5 (%)	56.6±7.0	53.1±10.3	0.017
	V10 (%)	36.9±5.4	36.0±7.5	0.187
	V15 (%)	26.0±4.3	25.7±5.3	0.806
	V20 (%)	16.8±3.3	18.9±3.8	0.000
	V25 (%)	11.1±2.6	14.5±3.4	0.000
	V30 (%)	8.0±2.3	11.3±3.1	0.000
Heart	MHD (Gy)	19.0±9.7	19.8±10.0	0.038
	V20 (%)	46.5±30.8	46.3±28.8	0.905
	V30 (%)	20.9±14.5	25.5±15.1	0.001
	V40 (%)	9.3±6.9	14.6±8.9	0.000
Spinal cord	Dmax (Gy)	39.7±0.9	38.6±1.7	0.002
	D1cc (Gy)	38.6±1.0	36.3±1.6	0.000
NT	V5 (%)	71.5±14.2	62.9±12.5	0.000
	V10 (%)	52.7±12.1	46.4±9.3	0.000
Liver	V25 (%)	18.0±7.6	15.3±6.6	0.078
	V35 (%)	8.1±3.2	10.2±5.1	0.008
Kidney L	Mean dose (Gy)	5.1±3.9	6.6±5.2	0.219
	V10 (%)	17.2±20.1	21.0±27.3	0.219
	V15 (%)	7.8±10.7	14.1±15.7	0.156
Kidney R	Mean dose (Gy)	4.6±3.4	5.0±4.8	0.906
	V10 (%)	16.1±18.2	15.1±22.8	0.844
	V15 (%)	4.9±7.0	8.4±13.1	0.438
Delivery time	(m)	5.9±1.2	5.3±1.1	0.026

Abbreviations: HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; HI, homogeneity index; CI, conformity index; TC, target coverage; MLD, mean lung dose; MHD, mean heart dose; Dmax, maximum dose; D1cc, maximum dose delivered to 1 cm^3 of the spinal cord; NT, normal tissue; Vx, volume receiving at least x Gy.

Table 2. Summary of numeric analysis of dose–volume histograms and delivery times for target volumes and organs at risk for upper, middle and distal esophageal cancers

Parameters		Upper			Middle			Distal & EGJ		
		HT	IMRT	P	HT	IMRT	p	HT	IMRT	P
PTV	MD (Gy)	62.5±0.4	63.1±0.4	0.109	62.4±0.3	63.5±0.7	0.063	62.2±0.4	63.0±0.5	0.016
	HI	0.09±0.01	0.13±0.02	0.004	0.09±0.01	0.14±0.03	0.031	0.08±0.01	0.12±0.02	0.016
	CI	0.87±0.02	0.80±0.04	0.016	0.90±0.02	0.76±0.10	0.031	0.88±0.02	0.86±0.04	0.125
	TC	0.96	0.95	0.016	0.96	0.95	0.031	0.96	0.95	0.031
Total lungs	MLD (Gy)	11.6±1.3	12.8±1.7	0.008	10.4±1.6	10.5±2.0	0.750	10.6±1.2	11.0±1.4	0.086
	V5 (%)	57.1±7.6	55.6±8.3	0.164	57.7±5.7	50.5±13.3	0.219	55.3±7.9	52.1±10.6	0.117
	V10 (%)	38.8±5.2	40.0±6.6	0.820	33.8±6.2	32.2±8.3	0.438	37.1±4.3	34.5±6.5	0.250
	V15 (%)	27.3±3.8	29.4±4.5	0.039	23.7±5.8	22.4±5.6	0.250	26.4±3.1	24.2±3.7	0.148
	V20 (%)	18.4±2.9	21.5±2.7	0.004	15.6±4.4	16.1±4.9	0.438	16.0±2.1	18.2±2.0	0.016
	V25 (%)	12.9±2.1	16.9±2.3	0.004	9.6±3.1	12.2±4.5	0.094	10.3±1.4	13.4±1.5	0.008
	V30 (%)	9.8±1.8	13.6±2.4	0.004	6.1±2.2	9.4±3.9	0.031	7.3±1.4	10.2±1.5	0.008
Heart	MD (Gy)	8.7±4.0	9.1±4.5	0.406	22.0±6.4	22.9±5.5	0.219	28.3±3.0	29.4±2.9	0.250
	V20 (%)	15.0±9.8	16.6±10.1	0.195	54.6±21.0	52.7±16.4	0.563	75.5±15.9	74.7±14.6	0.742
	V30 (%)	5.9±4.3	9.9±6.9	0.008	25.8±10.2	31.4±9.9	0.094	34.1±7.5	38.6±7.2	0.109
	V40 (%)	2.3±1.9	5.7±4.4	0.008	11.8±5.6	19.1±6.9	0.031	15.3±3.5	21.3±4.7	0.016
Spinal cord	Dmax Gy)	40.0±0.9	38.0±1.1	0.012	40.1±0.6	39.1±0.7	0.063	39.0±0.7	38.8±2.5	0.547
	D1cc (Gy)	39.1±1.0	35.8±1.0	0.004	39.2±0.4	36.6±0.7	0.031	37.7±0.8	36.6±2.5	0.188
NT	V5 (%)	71.9±10.5	65.4±8.8	0.008	60.6±12.7	51.8±10.2	0.156	79.1±15.1	68.6±13.3	0.008
	V10 (%)	52.1±8.3	48.5±6.8	0.020	42.6±9.3	38.1±8.0	0.063	60.9±12.6	50.3±9.6	0.008
Delivery time (m)		5.6±1.0	6.0±1.2	0.289	5.3±0.3	4.3±0.5	0.031	6.7±1.6	5.3±0.8	0.016

Abbreviations: HT, helical tomotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; HI, homogeneity index; CI, conformity index; TC, target coverage; MLD, mean lung dose; MHD, mean heart dose; Dmax, maximum dose; D1cc, maximum dose delivered to 1 cm^3 of the spinal cord; NT, normal tissue; Vx, volume receiving at least x Gy; EGJ, esophagogastric junction; MD, mean dose.

Fig. 1: Isodose distributions in the helical tomography (HT) and fixed-field intensity-modulated radiation therapy (ff-IMRT) plans for three typical cases of upper (a), middle (b) and distal (c) esophageal cancer shown on the same axial, coronal and sagittal computed tomography slices.
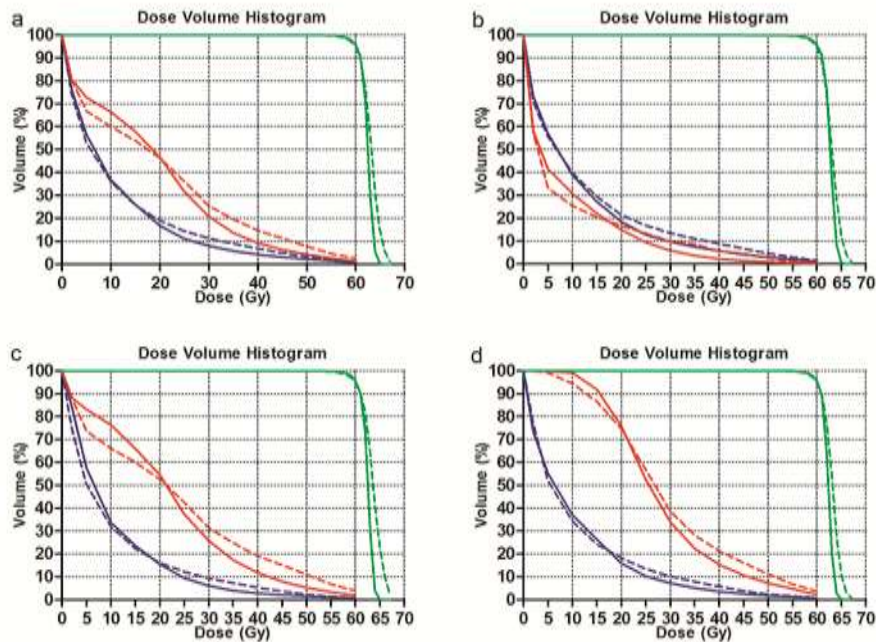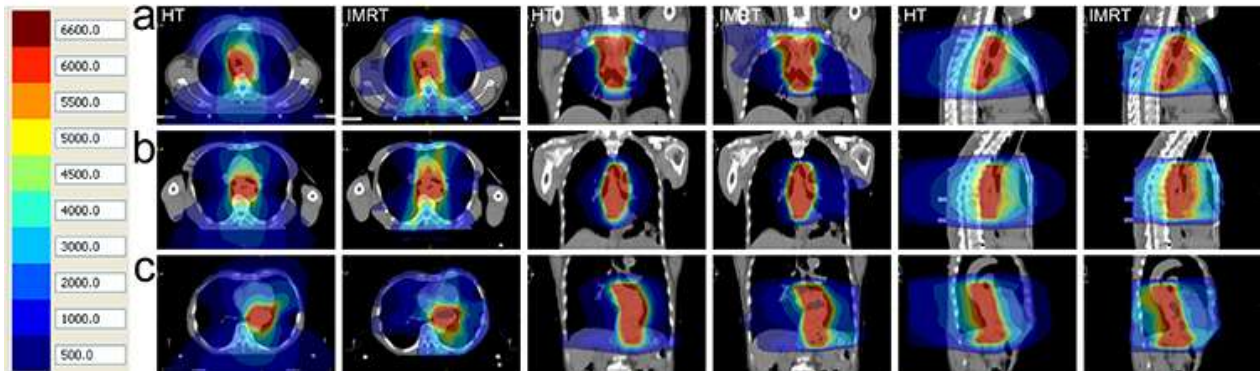
Fig. 2: Average dose–volume histograms for the planning target volume (green), lungs (blue) and heart (red) obtained with the helical tomography plans (solid line) and the fixed-field intensity-modulated radiation therapy plans (dashed line) for thoracic (a), upper (b), middle (c) and distal & EGJ (d) esophageal cancers.