·**Intensity-Modulated Radiotherapy Column**·

Dosimetric comparison between intensity-modulated radiotherapy and conformal radiotherapy for upper thoracic esophageal carcinoma

Wu-Zhe Zhang, Zhi-Jian Chen, De-Rui Li, Zhi-Xiong Lin, Dong-Sheng Li and Chuang-Zhen Chen

Department of Radiation Oncology, Cancer Hospital, Shantou University Medical College, Shantou, Guangdong, 515031, P. R. China

[**Abstract**] **Background and Objective:** Treatment planning for radiotherapy of upper thoracic esophageal carcinoma is challenging due to the anatomical features. The difficulty may be resolved by intensity-modulated radiotherapy (IMRT). This study was to compare the dosimetric advantages of IMRT to that of conformal radiotherapy (CRT) for upper thoracic esophageal carcinoma, and to explore the clinical application of IMRT. **Methods:** Eleven patients with upper thoracic esophageal carcinoma were enrolled. In addition to the actually used CRT plan, a five-field IMRT plan was generated for each case. The parameters of dose volume histogram for targets and organs at risk were compared between two techniques. **Results:** For the planning target volume (PTV) of tumor and para-tumor tissues, the mean dose, maximal dose, doses covering 99% and 95% volume were similar in IMRT and CRT plans ($P > 0.05$). However, IMRT plan had a higher conformity index than CRT plan (0.68 ± 0.04 vs. 0.46 ± 0.11, $P < 0.01$). For the PTV of supraclavicular region, IMRT plan showed a better dose heterogeneity index than CRT plan (1.17 ± 0.05 vs. 1.33 ± 0.15, $P = 0.01$). IMRT plan had lower maximal dose to the planning risk volume of the spinal cord (44.4 Gy vs. 52.5 Gy, $P < 0.05$) and lower lung volume received dose of 10 Gy or higher [$(32 \pm 6)\%$ vs. $(35 \pm 9)\%$, $P < 0.05$] than CRT plan. **Conclusion:** For the upper thoracic esophageal carcinoma, IMRT has more conformal distribution of dose and better spinal cord sparing than CRT, and can reduce the volume of lung that received dose of 10 Gy or higher.

Key words: esophageal neoplasm, radiotherapy, intensity-modulated radiation therapy, radiotherapy planning, computer-assisted

Radiotherapy is one of the important treatment modalities for upper thoracic esophageal carcinoma. As to radiotherapy, the treatment planning is challenging because of the anatomical structures involved. It is kind of tricky to incorporate the tumor coverage and the sparing of critical structures, such as the spinal cord and lungs. This is mainly due to the close proximity of the upper thoracic esophagus to the spinal cord and the drastic changes of anatomic contour and diameter. The intensity-modulated radiotherapy (IMRT), with high dose conformity, seems to be a reasonable technique to deal with the difficulty. The only literature presenting clinical application of IMRT for esophageal cancer was recently reported by Wang et al.[1] They treated seven patients with locally advanced cervical or upper thoracic esophageal cancer using IMRT with concurrent chemotherapy. Severe complications were found in this small cohort. Among 4 survivors, 2 patients developed esophageal stricture requiring frequent dilation and 1 developed tracheal-esophageal fistula. In two dosimetric studies on upper thoracic esophageal carcinoma, both Fu et al.[2] and Wang et al.[3] found IMRT superior to conformal radiotherapy (CRT) in terms of dose distribution. In these two studies, the schemes of dose fractionation were higher than 2 Gy/fraction, which referred the scheme currently used for head and neck cancer.

Because the application of IMRT for esophageal cancer is still immature, we conducted this preclinical study to compare IMRT with CRT in terms of dosimetric features in 11 executive patients with upper thoracic esophageal carcinoma, in order to have a thorough preparation for the coming clinical trial.

Materials and Methods

Patient characteristics

Eleven patients with upper thoracic esophageal carcinoma, who underwent initial CRT between June, 2008 and September, 2008, were selected. Eight were men and three were women. The lower lesion margins were at the levels of the 7th thoracic vertebra (two cases), 6th thoracic vertebra (five cases), 5th

thoracic vertebra (one case), 4th thoracic vertebra (two cases), and 3rd thoracic vertebra (one case). The length of tumor lesion ranged from 4.5 to 10.5 cm, with a median of 6.0 cm and a mean of 6.3 cm. The volume of esophageal tumor was 5.9–51.0 cm^3, with a median of 21.0 cm^3 and a mean of 25.1 cm^3.

Simulation

All patients were immobilized with head and upper thoracic thermoplastic mask in supine position with arms by their sides. The CT images were taken at a 5 mm thickness throughout the entire thorax and neck extending 10 cm beyond tumor lesion. All CT image acquisition was carried out at a helical CT scanner (Picker, PQ5000). The data were transferred to the Pinnacle 8.0m treatment planning system with DICOM 3.0 protocol.

Delineation of targets and critical organs

Gross tumor volume (GTV) was defined as the tumor extent shown by imaging and endoscope, and this included primary esophageal and involved regional lymph nodes. Clinical tumor volume (CTV) was defined as GTV plus a margin for potential microscopic spread. Two CTVs were contoured. CTV1 included GTV and its surrounding tissue in high risk involved region, which was defined as GTV plus a margin of 5-10 mm transversely and 20 mm longitudinally. CTV2 was defined as CTV1 plus lymph node draining area in upper mediastinum and bilateral supraclavicular region. Uninvolved bony structure and lung tissue were kept outside CTV. Planning target volume (PTV) was defined as an additional 5 mm expansion beyond CTV. A 5 mm margin was also added to the spinal cord for the planning organ-at-risk volume (PRV).

The contract CRT plans in this study were the actual plans used in previous treatment. In our daily practice, PTV was not contoured. Instead, 5 mm margin beyond CTV for PTV and 5 mm margin for penumbra were built in the treatment field. In this study, PTV was made up to CTV with 5 mm expansion aim to process the IMRT plan and to compare between IMRT and CRT plans.

CRT planning

All CRT plans were the actual plans used in previous treatment. Three or four beams with individual wedge compensation were used depending on location and size of tumors. An anterior vertical beam plus two anterior oblique beams were used in 7 plans; a posterior vertical beam plus two anterior oblique beams were used in 2 plans; a pair of contra-anterior-posterior beam plus a pair of contra-oblique beam were used in 2 plans. The plan was composed of the phase 1 irradiation which covered CTV2 and the phase 2 irradiation which shrank to CTV1. The goals were to prescribe 64 Gy by 32 fractions to CTV1 and 50 Gy by 25 fractions to CTV2, which were normalized to the center of CTV1. The spinal cord was constrained to a maximal dose (D_{max}) of 50 Gy. The volume received more than 20 Gy (V_{20}) of total lungs was limited to 25%. As to incorporate the tumor coverage and sparing of critical structures in case of large tumor with a close proximity to the spinal cord, the goals and limitations were compromised as follows: D_{max} of 50 Gy to the spinal cord; length of <5 cm for the segment of spinal cord received 45 Gy irradiation; V_{20} of < 35%

for total lungs; minimal dose (D_{min}) of 60 Gy to GTV; the 64 Gy and 50 Gy isodose lines covered CTV1 and CTV2 as more as possible.

IMRT planning

All plans were consisted of 5 beams in equal interval. The beam's gantry angles were 0°, 72°, 144°, 216° and 288°, respectively. The plans were generated in Pinnacle 8.0m treatment planning system with inverse direct machine parameter optimization (DMPO). The goals were to ensure that PTV1 and PTV2 received mean dose (D_{mean}) of 64 Gy and 54 Gy by 32 fractions, D_{min} of 60 Gy and D_{max} of 70 Gy were given to PTV1, and the volume of PTV1 received 105% prescribe dose (67.2 Gy) was less than 5%. The following dose limitations to critical structures were used for planning optimization: D_{max} of < 40 Gy to the spinal cord; D_{max} of <45 Gy to the PRV of the spinal cord (PRV$_{sc}$); V_{20} of $\leqslant 25$ % and V_{30} of $\leqslant 20$% for total lungs. The machine parameters were set as follows: total segment number of $\geqslant 50$; segment size of $\geqslant 4$ cm^2; minimal unit dose of $\geqslant 5$ MU.

Dosimetric assessment

Dosimetric parameters of tumor targets and the definitions D_{mean} and D_{max} were the mean dose and maximal dose. D_{99} and D_{95} stood for the absolute dose to 99% and 5% volume of targets. V_{105} was the percentage volume of targets received dose higher than 105% of prescribed dose. The conformity index (CI) of PTV1 was defined as CI = $(V_{T,ref}/V_T) \times (V_{T,ref}/V_{ref})$, in which V_T referred to the total volume of PTV1, $V_{T,ref}$ referred to the volume of PTV1 covered by 64 Gy isodose line, V_{ref} referred to the total volume of 64 Gy coverage. The heterogeneity index (HI) was defined as HI = D_5/D_{95}; in which D_5 and D_{95} corresponded to the dose delivered to 5% and 95% of the target volume.

Dosimetric parameters of organs at risk and the definitions the D_{max} to spinal cord and PRV of spinal cord; D_{mean} to total lung; the V_5, V_{10}, V_{20} and V_{30} of total lung, that corresponded to the volume received 5Gy, 10Gy, 20Gy and 30Gy or more respectively.

Statistical analysis

All data were analyzed by paired t test using Microsoft Office Excel 2007. The significant different level was set as 0.05.

2 Results

Target coverage and dose distribution

The mean results of CRT and IMRT are listed in Tables 1 and 2. Dose volume histograms (DVH) of two plans are shown in Figures 1 and 2. As to GTV, the Dmean and Dmax were not significantly different between CRT and IMRT plans ($P= 0.84$, $P=0.28$), but the D_{99} and D_{95} of IMRT plan were higher than those of CRT plan ($P<0.01$, $P=0.02$). As to PTV1, the D_{mean}, D_{99}, D_{95} and D_{max} were not significantly different between two techniques (all $P>0.05$); IMRT plan had a higher CI than CRT plan ($P<0.01$) and also had a lower V_{105} ($P=0.02$). As to PTV2, CRT plan had a higher HI than IMRT plan ($P=0.01$); more region of PTV2 in CRT plan received over dose.

Table 1   Parameters of dose distribution for tumor and its planning target volume

Item	D_{mean}(cGy)	D_{99}(cGy)	D_{95}(cGy)	D_{max}(cGy)	V_{105}(%)	HI	CI
GTV							
CRT	6512±84	6290±105	6334±101	6767±129	8.4±10.5	1.1±0.0	
IMRT	6517±45	6429±40	6450±43	6709±112	0.7±1.9	1.0±0.0	
t	−0.20	−3.84	−3.23	1.15	2.71	2.95	
P	0.84	0.00	0.01	0.28	0.02	0.01	
PTV1							
CRT	6421±41	5839±87	6063±73	6866±144	6.3±5.9	1.1±0.0	0.5±0.1
IMRT	6412±22	5832±139	6065±58	6853±74	1.0±0.8	1.1±0.0	0.7±0.0
t	0.60	0.12	−0.07	0.24	2.86	1.85	−6.05
P	0.56	0.91	0.95	0.82	0.02	0.09	0.00

GTV, gross tumor volume；CRT, conformal radiotherapy；IMRT, intensity-modulated radiotherapy；PTV1, planning target volume of GTV and the adjacent high risk infiltrated region；D_{mean}, mean dose；D_n, dose covering n percent of volume；D_{max}, absolute maximal dose；V_{105}, volume received dose excessing 105% of prescription dose；HI, heterogeneity index；CI, conformity index.
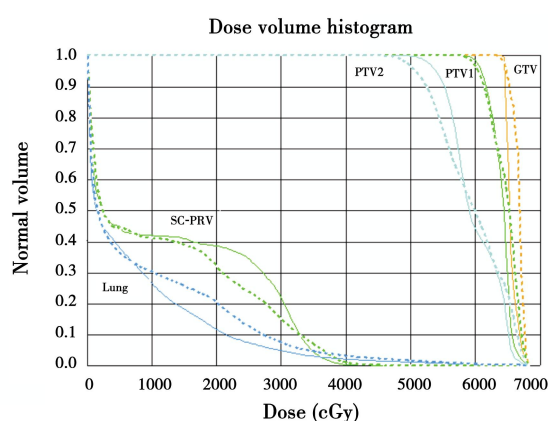

Figure 1   Dose volume histogram of targets and organs at risk of a patient with small tumor
Gross tumor volume （GTV）=5.9 cm³. Solid lines are drawn by intensity-modulated radiotherapy （IMRT） plan；dash lines are drawn by conformal radiotherapy （CRT） plan.

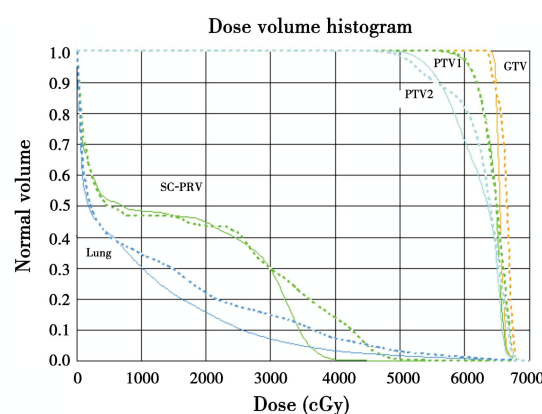Figure 2   Dose volume histogram of targets and organs at risk of a patient with large tumor
GTV = 22.1 cm³. Solid lines are drawn by IMRT plan；dash lines are drawn by CRT plan.

Table 2   Parameters of dose distribution for planning target volume of the supraclavical region

Item	D_{mean}^a	D_{99}^a	D_{95}^a	D_{max}^a	V_{105}(%)	HI
CRT	1.2±0.1	1.0±0.1	1.0±0.1	1.4±0.2	84.9±13.4	1.3±0.2
IMRT	1.1±0.0	0.9±0.1	1.0±0.0	1.2±0.0	65.3±11.6	1.2±0.1
t	3.96	1.38	2.31	5.35	3.91	3.32
P	0.00	0.09	0.07	0.00	0.00	0.01

ªThe goal doses of PTV2 are different between IMRT and CRT plans （54 Gy vs. 50 Gy）. These values represent the ratio of the absolute doses to their goal doses. Abbreviations as in Table 1.

Table 3   Irradiation dosage and volume of organs at risk

Item	PRVsc D_{max}(cGy)	SC D_{max}(cGy)	D_{mean}(cGy)	Lung			
				V_5(%)	V_{10}(%)	V_{20}(%)	V_{30}(%)
CRT	5254±456	4369±368	1084±246	42±10	35±9	23±6	12±3
IMRT	4442±56	3741±133	879±168	45±11	32±6	15±3	7±1
t	6.44	5.24	6.32	−1.95	2.44	5.86	6.34
P	0.00	0.00	0.00	0.08	0.03	0.00	0.00

PRV_{SC}, planning risk volume of the spinal cord；SC, spinal cord；D_{mean}, mean dose；V_n, volume received dose excessing n percent of prescription dose.

Dosimetric results for organs at risk

The dosimetric results are listed in Table 3. The DVH characters of OARs are shown in Figures 1 and 2. The D_{max} to the spinal cord and its PRV were significantly higher in CRT plan than in IMRT plan （P<0.01）. The goal of dose limitation to the spinal cord and the PRV was obtained in all IMRT plans.

However, it was obtained only in 45.5% （5/11） of CRT plans. IMRT significantly reduced D_{mean}, V_{10}, V_{20} and V_{30} of total lungs when compared with CRT （P<0.01, P<0.03, P<0.01 and P<0.01）. IMRT resulted in higher lung V_5 than CRT, but the difference was insignificant （P>0.05）.

2.3   Treatment related characters

The fractionation monitor unit was higher in IMRT plan than

in CRT, but without significant difference [(487±110) MU *vs.* (412±102) MU, *P*=0.14].

Discussion

Radiotherapy is a major treatment for upper thoracic esophageal carcinoma. As to radiotherapy, the treatment planning is challenging because of the anatomical structures involved. It is hardly to balance the tumor coverage and the spinal cord sparing when the esophagus is close to the spinal cord as well as the drastic change of anatomical contour and diameter occurred. CRT can overcome such difficulty partly.[4,5] However, an ideal dose distribution will hardly be obtained by CRT when there are extensive primary tumors or spread regional lymph nodes. With IMRT technique, a highly conformal dose distribution can be easily accomplished, and the critical organs around tumor can be spared efficiently. A simultaneous integrated boost approach can be applied by IMRT, with which different doses can be delivered to specific PTVs within a single fraction. These characters of IMRT make it an ideal radiotherapeutic technique for upper thoracic esophageal cancer.

Both Hu et al.[2] and Wang et al.[3] proved that IMRT was better than CRT in dosimetric content; in addition, adding beams did not further improve the dosimetric results of 5-beam IMRT plan. The dose fractionation schemas were 67.2 Gy at 2.4 Gy/fraction adopted by Hu et al. and 66.0 Gy at 2.2 Gy/fraction adopted by Wang et al. Either the total dose or single fractionation dose are higher than ours. Wang et al.[1] reported a preliminary result of clinical application of IMRT in MD Anderson Cancer Center. Seven patients were treated by IMRT with or without chemotherapy. The prescribed doses were 59.4–66.0 Gy at 1.8–2.3 Gy/fraction. Consequently, severe late complications occurred in three of four patients who survived at the time of report, with esophageal stricture in 2 and tracheal-esophageal fistula in 1. Sykes et al.[6] found that the radiation-induced esophageal stricture was associated with high irradiation dose. In a word, the total prescribed dose as well as single fractionation dose in IMRT of esophageal cancer should be carefully concerned and not be higher than that in CRT. The schema with high fractionation dose used in IMRT for head and neck tumors is not appropriate for esophageal cancer that settles at a hollow viscus. Therefore, the total prescribed dose was kept at 64 Gy or lower and hot spot at the esophagus was carefully avoided in our IMRT plans.

Our study showed that IMRT has a little advantage in target coverage. The coverage of PTV1 was compatible between IMRT and CRT plans. The D_{mean} and D_{max} of GTV were also similar in the two plans. IMRT slightly improved dose homogeneity of targets. It showed that IMRT had a lower V_{105} to PTV1 and GTV, a higher V_{99} to GTV, but the HI of PTV1 was not significantly different between the two techniques. As contrast to CRT, IMRT presents definite benefit in improving conformity of dose distribution, and it ensures the full coverage of targets as well as the efficient reduction of dose to the surrounding tissues. Keeping with the consensus of radiotherapy for upper thoracic esophageal carcinoma in China, all patients in our study received prophylactic irradiation to the supraclavicular areas. As previously mentioned, IMRT can deliver different doses to specific targets within a single fraction by simultaneous integrated boost approach. Therefore, the dosimetric results to PTV2 achieved by IMRT matched the goal prescription more closely than by CRT.

For radiotherapy of esophageal carcinoma, the most valuable merit of IMRT is the spinal cord sparing. Our study showed that the D_{max} received by the spinal cord and its PRV were lower than 40 Gy and 45 Gy in all IMRT plans. However, the D_{max} of the spinal cord was (4 369±368) cGy, ranged from 3 769 to 4 720 cGy; the D_{max} of PRV-spinal cord was (5 254±456) cGy, ranged from 4 609 to 5 861 cGy in CRT plans. This benefit of IMRT is more significant when the target volume is large.

The other side of coin is that high dose conformality of IMRT necessarily accompanies by low dose irradiation to normal tissues more extensively. It is the drawback of IMRT that should be concerned, particularly in radiotherapy for thoracic cancers. Gopal et al.[7] found that dose as low as 13 Gy will lead to damage to pulmonary function. In this study, we found that IMRT led to a higher V_5 of total lungs than CRT, but it was insignificant. However, IMRT significantly decrease the volume of lungs received dose of 10 Gy or higher. The D_{mean}, V_{10}, V_{20} and V_{30} of total lungs in IMRT plan were significant lower than those in CRT plan. The previous study conducted by Wang et al.[3] also demonstrated that IMRT can reduce the lung volume received over 20 Gy. As to evaluate if the predominance of IMRT in lung sparing be weakened with increase of PTV volumes, we extended all CTVs and their PTV inferior for 1 cm and generated another pair of IMRT and CRT plans. Consequently, we found that IMRT is still superior to CRT in lung sparing, particularly for the V_{20} and V_{30}. Chandra et al.[8] also proved that IMRT do decrease V_{10}, V_{20} and V_{30} of total lungs comparing with CRT for lower thoracic esophageal cancer.

For simplifying the planning and treatment, 5 beams were chose for the IMRT plans in this study; DMPO was used with the total segment number set at 50 and the minimal segment monitor unit set at 5 MU. As results, the total monitor units in IMRT plan were not remarkably increased than in CRT plan. The result demonstrates that it will not be an extra burden to a busy department when using IMRT instead of CRT for upper thoracic esophageal cancer.

In conclusion, IMRT has significant advantage in spinal cord sparing than CRT for radiotherapy of upper thoracic esophageal cancer, and it has better coverage and dose distribution for tumor targets as well as prophylactic areas. IMRT also decreases the volume of total lungs received over 10 Gy irradiation. IMRT is a reasonable radiotherapeutic technique for upper thoracic esophageal cancer and it is ready for clinical trial.

References

[1] Wang SL, Liao Z, Liu H, et al. Intensity-modulated radiation therapy with concurrent chemotherapy for locally advanced cervical and upper thoracic esophageal cancer [J]. World J Gastroenterol，2006，12(34)：5501－5508.

[2] Fu WH, Wang LH, Zhou ZM, et al. Comparison of SIB-IMRT treatment

plans for upper esophageal carcinoma ［J］. Acta Academiae Medicinae Sinicae, 2003,25(3):337－342.［in Chinese］

［3］ Wang J, Zhu SC, Han C, et al. Comparison of dose distribufions between conformal and intensity-modulated radiotherapy for the upper esophageal carcinoma ［J］. Chin J Radiat Oncol, 2008,17 (4):275－279. ［in Chinese］

［4］ Liu H, Zeng ZF, Cui LJ, et al. Trial study on design of irradiated fields of radiotherapy in cervical and upper thoracic esophageal ［J］. Chin J Radiat Oncol, 2006,15(4):286－289.［in Chinese］

［5］ Wang L, Han C, Zhu SC, et al. Dosimetric study on conventional and three dimensional conformal radiotherapy for esophageal cancer [J]. Chin J Radiat Oncol, 2006,15(3):176－180.

［6］ Sykes AJ，Burt PA，Slevin NJ，et al. Radical radiotherapy for carcinoma of the esophagus：an effective alternative to surgery ［J］. Radiother Oncol，1998,48(1)：15－21.

［7］ Gopal R，Tucker SL，Komaki R，et al. The relationship between local dose and loss of function for irradiated lung ［J］. Int J Radiat Oncol Biol Phys，2003,56(1)：106－113.

［8］ 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 ［J］. Radiother Oncol，2005,77(3)：247－253.