From the neck to the upper thoracic section, the distance between the esophagus and the epidermis varies dramatically. Routine radiation therapy for cervical-thoracic esophageal cancer usually employs projection at an oblique anterior angle, where the receptive doses for the esophagus and spinal cord are heterogeneous, in which the variation between the maximum and minimum doses may be 20% or more. Thus, the advantage of intensity modulation radiation therapy (IMRT) is the application of a physical method to optimize the dose distribution at the target site, where equivalent linear projections of high doses can be evenly distributed over the three-dimensional space of the target site. In addition, the dose exterior of the target mass drops rapidly, and thus, to regulate complications in the surrounding normal tissue, it is possible to increase the radiation dose for the target tumor and allow for better local control. However, IMRT usually relies on marginal line calculus index (MLC) to create multiple subfields for step-and-shoot radiation exposure. More subfields will lead to a smaller surface area and lengthen treatment time, where the motor function of internal organs will lead to more errors in dose distribution.

For each patient who undergoes IMRT, proper dosage must be checked, which requires more resources. To examine this problem in the context of actual clinical situations, we used the simplified IMRT (sIMRT) developed by the Tumor Hospital of Chinese Academy of Sciences. This study explored the feasibility of simplified IMRT (sIMRT) and concurrent chemotherapy for neck and upper thoracic esophageal carcinoma. Two target volumes were defined as PTV1, the target volume of the primary lesion, which received up to 64 Gy of radiation (2.13 Gy × 30 fractions) and PTV2, the prophylactic irradiation volume, which received up to 54 Gy of radiation (1.8 Gy × 30 fractions). The sIMRT plan included five equiangular coplanar beams. All patients received a DDP + 5-FU regimen concurrently with radiation therapy on days 1–5 and days 29–33. Chemotherapy was repeated for two more cycles 28 days after completing the radiation therapy. Results: Treatment was completed for all patients within 6 weeks, and only one patient had grade I–II acute bronchitis. The complete response (CR) rate was 90% (27/30) and the partial response (PR) rate was 10% (3/30). Overall response was 100% for esophageal lesions and the CR rate was 76.5% (13/17). The PR rate was 23.5% (4/17) in lymph-node lesions. The major toxicity observed was grade I–II leukocytopenia. Conclusions: sIMRT can generate the desirable dose distribution for neck and upper thoracic esophageal carcinoma, which is similar to robust IMRT but obviously better than 3D-CRT. The short-term efficacy of sIMRT is satisfactory and acute toxicities are tolerable.

Key words: esophageal neoplasm, simplified intensity-modulated radiotherapy, chemotherapy, combined modality, efficacy

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[Abstract] Background and Objective: For neck and upper thoracic esophageal carcinoma, three-dimensional conformal radiation therapy (3D-CRT) does not necessarily meet all clinical requirements while intensity modulated radiation therapy (IMRT) may take up a lot of manpower and material resources. This study explored the feasibility of simplified IMRT (sIMRT) and concurrent chemotherapy for neck and upper thoracic esophageal carcinoma, and investigated the acute toxicities and short-term efficacy of this modality. Methods: sIMRT plans were designed for 30 patients with neck and upper thoracic carcinoma. Two target volumes were defined as PTV1, the target volume of the primary lesion, which received up to 64 Gy of radiation (2.13 Gy × 30 fractions) and PTV2, the prophylactic irradiation volume, which received up to 54 Gy of radiation (1.8 Gy × 30 fractions). The sIMRT plan included five equiangular coplanar beams. All patients received a DDP + 5-FU regimen concurrently with radiation therapy on days 1–5 and days 29–33. Chemotherapy was repeated for two more cycles 28 days after completing the radiation therapy. Results: Treatment was completed for all patients within 6 weeks, and only one patient had grade I–II acute bronchitis. The complete response (CR) rate was 90% (27/30) and the partial response (PR) rate was 10% (3/30). Overall response was 100% for esophageal lesions and the CR rate was 76.5% (13/17). The PR rate was 23.5% (4/17) in lymph-node lesions. The major toxicity observed was grade I–II leukocytopenia. Conclusions: sIMRT can generate the desirable dose distribution for neck and upper thoracic esophageal carcinoma, which is similar to robust IMRT but obviously better than 3D-CRT. The short-term efficacy of sIMRT is satisfactory and acute toxicities are tolerable.

Key words: esophageal neoplasm, simplified intensity-modulated radiotherapy, chemotherapy, combined modality, efficacy
radiation therapy (3D-CRT).

Materials and methods

General information
A total of 30 patients with esophageal cancer at the neck and upper thoracic section underwent sIMRT at the First People's General Hospital in Huaian City from April 2008 to August 2008, of which 19 were men and 11 were women. Their ages ranged between 52 years and 75 years, with the median age of 57 years. A total of 14 patients had lesions localized in the neck and 16 had lesions in the upper thoracic section. As for lesion length, 10 patients had lesions less than or equal to 5.0 cm, 18 had lesions between 5.1 cm and 8.0 cm, and 2 had lesions greater than 8.0 cm. Under the esophagoscope, these lesions were confirmed to be squamous cell carcinoma. Nine patients had a total of 17 lymphatic metastases, with the largest lymph node at 3.5 cm × 3.7 cm. There were 11 lymph nodes with diameters less than 2 cm and 6 lymph nodes with diameters greater than 2 cm. Lymphatic metastasis was confirmed by a size greater than 1 cm. (The standard is different when circling out the target area for lymph node, with > 0.5 cm as the limit.)

Radiation therapy
An ONCOR linear accelerator (Siemens) was used for the radiation therapy. Patients lay in a supine position with a fixed head, where a complete mask was used to secure the head, neck, and shoulders. Under CT, the area was scanned continuously at a thickness of 5 mm. For dynamic scans, an intravenous injection of the contrast agent Iohexol was administered to all patients. During the scan, the patient was instructed to breathe normally. After the positioning image was obtained, the lesion site and the outlines of important functional organs were circled using the CMS system.

Delineation of gross tumor volume (GTV) of primary tumor (GTVnx)
The upper and lower boundaries of the tumor were confirmed from results of the esophageal radiography and the CT examination. If the thickness of the esophageal wall exceeded 5 mm, it was considered abnormal. According to Konski, multiple CT examinations could more accurately display the size of the lesion, so when both the esophageal radiography and the CT examination revealed an abnormality, the CT examination had a higher priority. The tumor was classified as GTV when the lymph node was larger than 5 mm (labeled as GTVnd).

Verification of clinical target volume (CTV)
Combining the research of Shi and Wan et al. and our own experiences, when labeling the primary tumor GTV, we expanded the vertical boundaries between 3 cm and 3.5 cm, the anterior boundary three-dimensionally to the right and left by 0.5 cm, and the posterior boundary between 0.3 cm and 0.5 cm, which this was considered CTV1. When we included the lymphatic drainage area between the clavicle and the cricothyroid membrane, and the lymphatic drainage areas 2, 4, 5, and 7 of the thorax, it was classified as CTV2. The partition of lymph nodes was based on standards of the American Thoracic Association.

Confirmation of planning target volume (PTV)
After taking into account the lowered influence of respiratory movement in the neck and upper thoracic section, the relatively fixed membranous body, and our own departmental conditions, PTV1 was defined as the outward expansion of CTV1 by 0.5 cm, and PTV2 was defined as the outward expansion of CTV2 by 0.5 cm.

The CMS 4.33 system was used for scheduling designs, including the 5 viewing angles of 0°, 72°, 144°, 216°, and 288°. The sIMRT technique was used. The average number of subfields for a single shot was less than or equal to 5. The area of a subfield was greater than or equal to 10 cm². The number of machine monitors for a subfield was no fewer than 10 MU.

The constraint criteria for PTV1 included that the dose for 98% of body volume was greater than or equal to 60.8 Gy (95% of the target dose) and allowed a dose for 5% of body volume greater than or equal to 67.2 Gy (105% of target dose). As for PTV2, the dose for 98% of body volume was greater than or equal to 51.3 Gy (95% of the target dose) and allowed a dose for 3% of body volume to be greater than or equal to 59.4 Gy (110% of the target dose).

Because the CMS system included PTV2 and PTV1, the assessment of maximum doses for PTV2 was performed on the screenshot of each layer image, where they were V20 Gy ≤ 25% and V30 Gy ≤ 20% for both lungs and 100% volume ≤ 45 Gy for the spinal cord. For the optimized weight of each constraint criteria, the orders were PTV1 > PTV2 > spinal cord > lungs. After satisfying the plan requirements, relocation was performed under a simulation machine. In sIMRT, because of the close parameters in the subfields and the number of machine monitors used for the 3D-CRT method, dose verification was done only during the trial period. The position was verified by an Electron Portal Imaging Device (EPID) during the initial treatment before the official therapy began.

Chemotherapy
Intravenous fusion of cisplatin (DDP, 75 mg/m²) was administered on day 1; 5-fluorouracil (5-FU, 500 mg/m²) was given on days 1–5. Chemotherapy was given twice during radiotherapy and it was repeated on day 29. On day 28 after the completion of radiotherapy, two treatment courses of the original proposal were repeated.

Assessment of the treatment proposal
The therapy was assessed from two aspects. The first was to understand its ability to satisfy the requirement for adequate dosing in clinical practice by interpreting the dose distribution from the screenshots and a dose-volume histogram (DVH). The statistical indices included 1) the minimum, maximum, and average absorbed doses for CTV and PTV, and 2) the maximum and average absorbed doses for each organ in a critical state.

The second aspect was to measure the actual duration for completing the three planned courses of treatment, which was the time from aligning the patient’s body position to completing exposure to the designated subfields. For 3D-CRT, this time included the time of exchanging wedge filters. For IMRT and sIMRT, this time included the time to realign the slides of MLC and to rotate the scaffold. Table 1 details doses in the target areas and organs at risk.
Observational indices

According to the Radiation Therapy Oncology Group (RTOG) in the United States, assessment was performed for any acute response to radiation. The chemical toxicity was assessed according to the Common Terminology Criteria for Adverse Events v.3.0 (CTCAE). After completing radiation therapy for esophageal carcinoma, the therapeutic effect was assessed using referenced standards. Lymph nodes, as solid tumors, would be assessed according to World Health Organization (WHO) standards. (There was difficulty assessing and distinguishing false positives when lymph nodes were less than 1.0 cm, and thus, this study only evaluated the therapeutic effect for lymph nodes greater than 1.0 cm).

Results

Follow-up

All patients had 6 months of follow-up, yielding a 100% follow-up rate.

The characteristics of dosing in the target areas and the status of dosing in organs at risk

We selected one patient and conducted a dosimetric comparison of the three treatments on the DVH. Figure 1 shows the dose distribution from the sIMRT screenshots. The DVH curve of the target region showed an overlap between the curves of the sIMRT and IMRT, with steep ends to the curves (Fig. 2), while the starting end of the 3D-CRT curve was located more in the low-dose region. PTV2 received high doses of radiation (Fig. 3), suggesting that the dose distributions in sIMRT and IMRT were significantly more homogeneous than those in 3D-CRT. Also, PTV2 of sIMRT and IMRT only received radiation at a preventive dose to effectively shield normal tissue. In comparison to 3D-CRT, sIMRT and IMRT could provide better protection to lungs and reduce the receptive amount of radiation in the spinal cord (Figs. 1–3). Table 1 lists the averages of statistical data of radiation dose of each target region and organs in critical states from 30 patients who received the three treatments. It could be seen that the minimum dose of PTV in 3D-CRT was significantly lower than those in sIMRT and IMRT. The high receptive doses in the lungs and the spinal cord rendered this plan less feasible for execution.

Figure 1 Cross-section dose distribution of simplified intensity modulated radiation therapy (sIMRT)

Figure 2 The dose-volume histogram (DVH) curves of target and organs at risk of sIMRT and IMRT
Dash line, sIMRT; solid line, IMRT.

Figure 3 The DVH curves of target and organs at risk of sIMRT and three dimensional conformal radiation therapy (3D-CRT)
Dash line, sIMRT; solid line, 3D-CRT.

Actual duration of treatment

The total monitor unit (MU) value of 3D-CRT was 270. The IMRT, which contained 76 subfields, had 662 as its total MU value. The sIMRT, which contained 25 subfields, had 360 as its total MU value. During treatment, the dose rate of 200 MU/min was employed. The execution times for these treatments were 5.2 min for 3D-CRT, 16.7 min for IMRT, and 7.8 min for sIMRT. The treatment time for sIMRT was slightly longer than 3D-CRT, which was approximately half of IMRT.

Acute response to treatment

The acute responses to radiotherapy for all patients included radioactive bronchitis and radioactive esophagitis. The primary manifestation of radioactive bronchitis was coughing: 7 patients (23.3%) had grades I and II and one had grade III. Acute radioactive esophagitis primarily showed up as ingesta pain, where 12 patients (40%) were classified as grades I and II if only pharyngeal pain was described. Hematological toxicity signified a grade 3–4 drop in white blood cell count. Patients did not withdraw from the study after being treated to elevate white blood cell count.
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Table 1  Average statistical data of three treatment plans of target and organs at risk in 30 patients

<table>
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<tr>
<th>Plan method</th>
<th>Max (Gy)</th>
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<th>Average (Gy)</th>
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<th>V20(%)</th>
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sIMRT, simplified intensity modulated radiotherapy; L, left; R, right; 3D-CRT, three dimensional conformal radiation therapy.

Short-term therapeutic effect

In the short-term, the rate of complete response (CR) for esophageal lesions reached 90% (27/30). The rate of partial response (PR) in the short-term was 10% (3/30). The overall response rate (CR + PR) was 100%. The CR rate for lymph nodes was 76.5% (13/17), in which the CR rate for those with diameters less than 2 cm was 90.9% (10/11). The PR rate was 23.5% (4/17). These yielded an overall effectiveness rate of 100%. However, only three patients with 6 lymph node diameters greater than 2 cm resulted in CR.

Discussion

Esophageal carcinoma is one of the most common malignant tumors in China. For esophageal carcinoma of the upper section (including the neck and the upper thoracic section), radiotherapy is the primary treatment. Over the last 10 years, radiotherapy for esophageal carcinoma has improved in several aspects of the radiation application technique, the fraction method, and the use of other sciences. Late-course accelerated hyperfractionation radiotherapy has promising therapeutic effects, even though the rate of local recurrence and the inability to control the disease still remain rather high. To increase the local control rate and to reduce the rate of remote metastasis, high doses of radiation (60~70 Gy) were usually applied to the tumor (that is, the primary lesion and metastatic lymph nodes), while related lymph nodes were exposed to 50 Gy of preventive radiation. However, in routine clinical practice, it usually starts with diffuse radiation over a large area before the exposure field shrinks as the treatment dose increases. As a result, high doses of radiation generally increase injury to the surrounding normal tissue, especially when there is a bigger difference in distance between the neck and the upper thoracic section, which eventually leads to an uneven exposure dose to the target site. Currently in China, research has been initiated to understand 3D-CRT for esophageal carcinoma, which is yielding promising results. However, the effect of IMRT for esophageal carcinoma remains to be studied.

Research has shown that IMRT, not only increased the actual dose in the target site, but also has more advantages in highly adapting to the target region, uniformity in dose, and greater protection for more sensitive organs than 3D-CRT. Fu et al. compared routine 3D-CRT and IMRT plans used in simultaneous integrated boost treatment for 5 patients with esophageal carcinoma of the upper section, and found that IMRT plan with 5~7 radiation fields was better than 3D-CRT plan in terms of homogeneous dose distribution at the target site, compatibility index, and the receptive dose for organs at risk. However, IMRT usually employs MLC to form multiple subfields for further step-and-shoot. As the number of subfields increases and the area becomes smaller, it will require longer treatment time, where slight organ motion will lead to errors in dose distribution. IMRT treatment will also require dose verification for each patient, and thus, more resources to do so.

Our hospital is located in the northern region of Jiangsu and this region has a high incidence of esophageal carcinoma, especially esophageal carcinoma of the neck and the upper thoracic section. 3D-CRT may not satisfy clinical needs, while the multiple subfields in IMRT cannot improve the dose distribution. To examine these questions, we employed the sIMRT technique developed by the Tumor Hospital of China Academy of Science to treat patients with esophageal carcinoma of the neck and the upper thoracic section. The sIMRT was defined as the average number of subfields for a single shot less than or equal to 5. The area of a subfield was greater than or equal to 10 cm. The number of machine monitors for each subfield is no fewer than 10. Because in sIMRT, the parameters such as the exposure area of the subfield and the number of machine monitors were similar to 3D-CRT, it was considered to perform dosimetric verification for each case during the trial period of sIMRT, while a similar verification based on the 3D-CRT technique would be used later on.

Esophageal carcinoma has higher rates of lymphatic metastasis. Mizowaki et al. by contrasting the surgical pathology of cases, believed that the diagnostic standard for lymphatic metastasis in the thorax should be defined as having diameters greater than 5 mm, where this would provide a sensitivity of 68% and an accuracy of 87%. In this study, 9 patients had 17 lymphatic metastatic sites. Considering the difficulty of assessment and that more false-positive results are reported at sizes between 0.5 cm and 1.0 cm, through simulated CT localization, we included all lymph nodes with diameters 5 mm or above into the exposure range. However, lymph nodes between 0.5 cm and 1.0 cm were not assessed and only the
lymph nodes greater than or equal to 1.0 cm were evaluated.

This study fully considered the difficulty in treating patients with esophageal carcinoma of the neck and the upper thoracic section, as well as the advantage of better dose distribution by IMRT. We selected one patient with esophageal carcinoma at the neck and the upper thoracic section for a dosimetric comparison of 3D-CRT, IMRT, and sIMRT. The dose distributions at the target sites of sIMRT and IMRT were significantly better than those of 3D-CRT, while the sIMRT was slightly worse than the dose distribution of IMRT. In the DVH images, the curves of the two were almost completely overlapped. As for the protection to the lungs and the spinal cord, sIMRT and IMRT were much better than 3D-CRT, too. Also, to protect the spinal cord, 3D-CRT, if not sacrificing partial PTV2, would also cause the lungs and the spinal cord to be exposed to higher radiation doses due to a larger oblique radiation angle, where the planned treatment would certainly fail. In addition, the 3D-CRTs of our 30 patients, because of avoiding the spinal cord and the more oblique angle, part of PTV2 was discarded, causing the average minimum doses of GTVnx, PTV1, and PTV2 to be much lower than those of sIMRT and IMRT. This demonstrated a problem in dose distribution for 3D-CRT.

As for execution time, the treatment time by sIMRT was slightly longer than that for 3D-CRT, which was approximately half of IMRT. sIMRT, when compared to IMRT, saved large amounts of resources. With respect to fractionalization, PTV1 fractioned the dosage at 2.13 Gy/fraction, with the goal of reaching 64 Gy in total, the entire plan would only require 6 weeks to complete. When compared to the traditional mode of fractionalization at 1.8 to 2.0 Gy/fraction, it saved a lot of treatment time. Biologically, this, no doubt, could improve the therapeutic effect.

Because the prevention area was regarded as a low-risk zone to administer 1.8 Gy/fraction, it would also reduce long-term radioactive injury and improve quality of life. However, in another trial of PTV1 and PTV2 in 3D-CRT, to increase the dose while minimizing the range of exposure, PTV2, as the preventive zone, could obtain the same dose as PTV1 for radical treatment. This would, no doubt, worsen injury to normal tissue in preventive zone.

This mode of fractionalization showed promising results in the short term, where the overall rate of effectiveness on esophageal lesions could reach 100%, while the rate of CR for lymphatic metastasis was 76.5% (13/17). For lymph nodes smaller than 2 cm in diameter, the rate of CR was 90.9% (10/11), and the rate of PR was 23.5% (4/17). Only 3 out of 6 lymph nodes with diameters larger than 2 cm achieved CR. As a result, treating lymphatic metastasis was difficult for sizes larger than 2 cm.

Because there were more advantages in protecting the surrounding normal tissue by sIMRT than by 3D-CRT and routine radiation therapy, we did not observe any increase in therapy-related toxicity with concurrent chemotherapy. During treatment, there were 7 patients (23.3%) with acute radioactive bronchitis of grades I and II and one with grade III. There were 12 patients (40%) with acute radioactive esophagitis of grades I and II, and there was no report of grade III. The decrease in white blood cell count was primarily of grades I and II, while no hematological toxicity of grade III or above was detected. This portion of patients did not stop treatment after the elevated white blood cell count. After surpassing a dosage of 2.13 Gy/fraction at the exposure site due to uneven dose distribution during the traditional method of using two anterior oblique fields, as well as having no reports of increased injury due to radiation therapy for esophageal carcinoma at the neck by routine treatment, we remain optimistic about the incidence of long-term radioactive injury in these patients.

IMRT for esophageal carcinoma is a new technique and many problems still need to be investigated. The procedures for outlining the target region and verifying dose still require standardization. Currently, around the world, there are many reports about using 3D-CRT for esophageal carcinoma. The application of IMRT on esophageal carcinoma has yet to mature and requires further exploration into its potential. The long-term therapeutic effect of this treatment will need larger scale clinical testing and long-term follow-up. As for quality comparisons, sIMRT is similar to IMRT and it is obviously better than 3D-CRT. As for treatment time, sIMRT is equivalent to half of IMRT and is only slightly longer than 3D-CRT. The technique of sIMRT provides a more efficient and convenient option for clinical practice. We are continuing the feasibility study on the applicability of sIMRT to other tumors.

References