Abstract

Background and Objective: Intensity-modulated radiotherapy (IMRT) for esophageal carcinoma has seldom been reported; its clinical efficacy and toxicity are still uncertain. This study was to evaluate the short-term efficacy of IMRT on esophageal carcinoma, and to observe adverse events. Methods: From June 2006 to March 2008, 37 patients with cervical and thoracic esophageal carcinoma were treated with IMRT. The treatment response, local control and survival were evaluated and the adverse events were observed. Results: The minimal prescription dose of 100% of gross tumor volume (GTV D_{95}) 95% of clinical target volume (CTV D_{95}), and 95% of planning target volume (PTV D_{95}) were (6.45\pm1.72) Gy, (6.29\pm1.45) Gy, and (5.98\pm0.53) Gy, respectively. The volumes of lung receiving irradiation of \geq 5 Gy, \geq 10 Gy, \geq 20 Gy and \geq 30 Gy were (59.8\pm12.8)%, (39.5\pm8.7)%, (22.0\pm5.4)%, and (12.0\pm4.3)%, respectively. The mean lung dose (MLD) was (1.178\pm0.248) Gy. The overall response rate was 97.3% (36/37). The patients were followed-up for 8–29 months (median, 13 months). The occurrence rates of grades 3–4 acute and late esophagitis, grades 2–4 acute and late pneumonitis were 16.2% and 7.2%, 10.8% and 8.1%, The 1- and 2-year local control rates were 72.9% and 72.9%. The 1- and 2-year overall survival rates were 80.9% and 67.4%. The 1- and 2-year disease-free survival rates were 73.5% and 51.4%. Local recurrence (69.2%) was the main reason of treatment failure. Conclusion: IMRT is an effective treatment for esophageal carcinoma with low occurrence of acute and late radiation-related pneumonitis, but local failure is still a main problem for treatment of esophageal carcinoma.

Keywords: esophageal neoplasm, intensity-modulated radiotherapy, prognosis, therapeutic effect

Esophageal carcinoma is often caught at later stages, when radiotherapy becomes an important treatment strategy. However, the main reasons for treatment failure are locally recurrent tumor and uncontrolled tumor. Most scientists believe that, in addition to controlling distant metastasis, improving the local control rate through radiotherapy for esophageal carcinoma will improve the survival rate. Therefore, determining how to improve the local control rate and to decrease the recurrence rate has become critical in improving treatment for esophageal carcinoma.

Intensity-modulated radiotherapy (IMRT) is an effective radiation technique. Numerous studies have suggested that, besides ensuring high conformity and radiation dosage in a target volume, IMRT protects normal tissue to the extent possible. In addition, IMRT is preferred to conventional radiotherapy and conformal radiotherapy because of its ability to give different radiation dosages in different radiation fields in one radiotherapy attempt. Currently, IMRT is widely used in treating head-and-neck cancers and prostatic cancer, but clinical studies on IMRT for treating esophageal carcinoma are rare, and its clinical efficacy is still uncertain. Whether the technique causes marked and extensive low-dosage radiation-related lung injury is also unclear. Since June 2006, our department has used IMRT to treat 37 patients with cervical and thoracic esophageal carcinoma. Here, we present our analysis of the short-term efficacy, toxicity, and side effects of IMRT in these patients.

Material and methods

Inclusion criteria

Inclusion criteria were as follows: the presence of treatment-naive cervical or thoracic esophageal carcinoma; pathologically confirmed squamous cell carcinoma; age up to 78 years old; a Karnofsky score of 70 or higher; and a lesion no longer than 10 cm as measured on an esophageal radiograph. Patients must also have had no contraindications for a semi-liquid or liquid diet and a clinical or adjuvant examination suggesting thoracic esophageal carcinoma without metastasis in supraclavicular and abdominal lymph nodes or cervical esophageal carcinoma without metastasis in abdominal lymph nodes and distant dissemination. Patients had no major heart or
lungs diseases and were able to tolerate radiotherapy.

Case data

Between June 2006 and March 2008, we enrolled 37 patients with cervical or thoracic esophageal carcinoma. Of these, 22 were men and median age was 66 years (range, 37 to 78 years). Included were 4 patients with cervical esophageal carcinoma, 7 with upper thoracic esophageal carcinoma, 23 with middle thoracic esophageal carcinoma, 2 with lower thoracic carcinoma, and I with multiple carcinomas in the upper and middle thoracic esophagus. Esophageal barium radiographs showed that lesions ranged from 1.0 to 10.0 cm, with a mean length of 4.9 cm. Also as revealed by barium radiography, the carcinoma was classified as medullary in 25 patients, ulcerative in 10, and intraluminal in 2. These non-surgically treated esophageal carcinomas were staged on the basis of thoracic computed tomography (CT) scans, barium radiography, and other adjuvant examinations. Of these patients, 3 were stage I, 12 were stage II, and 22 were stage III.

Treatment

Target volume was delineated by applying a thermoplastic sheet to the head and neck or the body of the patient to maintain immobility, then CT scans with an intravenously administered contrast agent were acquired in 3-mm-thick slices for simulation. The CT images were submitted to the Pinnacle 7.6c or 8.0h (Phillips) treatment planning systems to determine tumor target volume and organs at risk. Gross tumor volume for tumor (GTV-T) was delineated on the basis of the esophageal wall being at least 5 mm thick and local or circular thickening of the esophagus, together with the results of esophageal barium radiography and esophagoscoppy. The clinical target volume for tumor (CTV-T) was obtained by extending the longitudinal upper boundary of the GTV-T by 2.0 to 3.0 cm and the longitudinal lower boundary by 2.0 to 3.5 cm and by extending the axial boundary by 0.5 cm. The planning target volume for tumor (PTV-T) was obtained by evenly extending the boundary of the CTV-T by 0.5 to 1.0 cm.

Preventive radiation in the lymphatic drainage area was given only to patients with enlarged mediastinal lymph nodes. The GTV-N was determined on a minor diameter of 1.0 cm or more for an individual enlarged lymph node, 0.3 cm or more for positive images in para-tracheal and para-esophageal lymph nodes, and 0.5 cm or more for multiple enlarged lymph nodes in the same location. The clinical target volume for lymph nodes (CTV-N) was obtained by evenly extending the gross tumor volume for lymph nodes (GTV-N) by 0.5 cm, and the planning target volume for lymph nodes (PTV-N) was obtained by evenly extending the CTV-N by 0.5 to 1.0 cm. The PTV was modified if spinal cord tissue was involved.

Reverse plan designing was conducted using a 5-field, 7-field, or simple IMRT (s-IMRT) technique, and inhomogeneity was corrected along the radiation path. The simultaneous integrated boost technique was used in 31 patients, with a prescribed GTV (including the GTV-T and GTV-N) dosage of 220 cGy/time, a total dosage of 6 600 cGy/30 times, and a required GTV $D_{95}$ of 6 600 cGy or more. The prescribed CTV (including the CTV-T and CTV-N) dosage was 210 cGy/time, the total dosage was 6 300 cGy/30 times, and the required CTV $D_{95}$ was 6 300 cGy or more. The prescribed PTV (including the PTV-T and PTV-N) dosage was 200 cGy/time, the total dosage was 6 000 cGy/30 times, and the required PTV $D_{95}$ was 6 000 cGy or more. The remaining 6 patients were given the prescribed PTV dosage; no dosage limitation was placed on GTV and CTV. Requirements for the prescribed dosage were as mentioned above.

The dosage limitations for the organs at risk (OARs) were as follows: in the lungs, $V_{5}$ was less than or equal to 50% to 65%, $V_{10}$ less than or equal to 40%, $V_{20}$ less than or equal to 25% to 30%, $V_{30}$ less than or equal to 15% to 18%, and the minimum lethal dose (MLD) was less than or equal to 1 500 cGy (the requirements of $V_{5}$ and MLD should be meet if not all requirements could be fulfilled simultaneously; in the heart, $D_{mean}$ was less than or equal to 3 000 cGy; and in the spinal cord, $D_{mean}$ was less than or equal to 4 500 cGy.

Efficacy evaluation

Primary outcomes were short-term efficacy, local tumor control rate, total survival rate, and disease-free survival rate. At the end of radiotherapy and 1 month after radiotherapy, esophageal barium radiography was performed to evaluate short-term efficacy. According to the efficacy evaluation criteria proposed by Wan, tumor response was classified as complete response (CR), partial response (PR), or no response (NR). Locally uncontrolled tumor was defined as a lesion detected in the primary site within 6 months after radiotherapy, and a lesion detected after 6 months was regarded as a locally recurrent tumor. Local tumor control time, total survival time, and duration of disease-free survival were recorded from the date of hospitalization.

Evaluation of adverse events

Acute and late adverse events in the esophagus and lungs were mainly observed and evaluated with the RTOG/EORTC radiation-related damage evaluating system proposed by Cox.

Follow-up

The patients were followed by regular clinic visits and telephone calls till November 20, 2008. Follow-up time ranged from 8 to 29 months, with a median of 13 months and a follow-up rate of 100%.

1.7 Statistical methods

The SPSS Version 13.0 statistical software was used; the Kaplan-Meier method was used to calculated tumor local control, total survival rate and disease-free survival rate. Alpha was set at 0.05.

Results

Radiation dosages in tumor target volume and affected organs

Median treatment time for all patients was 42 days. Mean ± SD dosages in GTV, CTV and PTV were (6 712±264) cGy, (6 545±195) cGy and (6 396±109) cGy, respectively; GTV $D_{95}$ CTV $D_{95}$ and PTV $D_{95}$ were (6 456±172) cGy, (6 293±145) cGy and (5 988±53) cGy, respectively. $V_{10}$, $V_{20}$, $V_{30}$, $V_{5}$ and MLD in both lungs were...
The incidence of late radiation-related lung injury was 7.2%, and the incidence of late radiation-related lung injury of grade 2 or above was 8.1%.

Local control rate and survival rate
In all patients, the 1- and 2-year local control rates were 72.9% and 72.9%, respectively. The 1- and 2-year total survival rates were 80.9% and 67.4%, respectively, with a mean survival of 23 months. The 1- and 2-year disease-free survival rates were 73.5% and 51.4%, respectively, and mean disease-free survival was 21 months (Figs. 1–3).

Analysis of the reasons for treatment failure
As of the follow-up cut-off date, treatment was ineffective in 13 patients. Of these, 9 experienced local failure in the esophagus; 7 of the 9 had locally controlled tumor, and 2 had local recurrence. All these lesions were seen within the radiation field, accounting for 69.2% (9/13) of all treatment failures. Distant metastasis developed in 5 patients, of whom 1 had bone metastasis, 1 had liver metastasis, 1 had metastasis in the supraclavicular lymph nodes (and also had locally uncontrolled tumor), 1 had metastasis in the abdominal lymph nodes, and 1 had lung metastasis. Of these 13 patients, 4 survived with tumor and 9 died. Cause of death was liver metastasis in 1, locally uncontrolled tumor in 6 (major hematemesis in 5 and prostration in 1), gastric hemorrhage in 1, and death after blood transfusion in 1.

Table 1 Acute radiation-related complications of esophageal carcinoma patients after intensity-modulated radiotherapy (IMRT) [number(%)]

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>2(5.4)</td>
<td>14(37.8)</td>
<td>15(40.5)</td>
<td>5(13.5)</td>
<td>1(2.7)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>29(78.4)</td>
<td>4(10.8)</td>
<td>3(8.1)</td>
<td>0</td>
<td>1(2.7)</td>
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</tbody>
</table>

Table 2 Late radiation-related complications of esophageal carcinoma patients after IMRT [number(%)]

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagitis</td>
<td>20(71.4)</td>
<td>4(14.3)</td>
<td>2(7.1)</td>
<td>1(3.6)</td>
<td>1(3.6)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>11(29.7)</td>
<td>23(62.2)</td>
<td>1(2.7)</td>
<td>2(5.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

(59.6±12.8)%, (39.5±8.7)%, (22.0±5.4)%, (12.0±4.3)% and (178±248) cGy, respectively. \(D_{\text{max}}\) in the heart was (2 380 ±1 365) cGy, and \(D_{\text{max}}\) in the spinal cord was (4 415±124) cGy.

Short-term efficacy
Of the 37 patients, 36 completed the treatment as scheduled. In one patient, radiotherapy was discontinued for 1 week because of a grade 3 acute esophageal injury. Short-term efficacy showed a complete response rate of 81.1% (30/37), a partial response rate of 16.2% (6/37), a non-response rate of 2.7% (1/37), and a total response rate (CR+PR) of 97.3%.

Adverse events
Acute radiation-related injury was defined as a radiation-related injury that occurred between the first day and the 90th day of radiotherapy, and was graded 0 to 4. Late radiation-related injury was defined as a radiation-related injury that occurred after the 90th day of radiotherapy and was graded 0 to 5 (Tables 1 and 2). Nine patients who had local treatment failure as confirmed by esophageal radiography and endoscopic examination were excluded from the evaluation of late radiation-related esophageal injury. The incidence of acute radiation-related esophageal injury of grade 3 or above, which had a substantial effect on the patient’s quality of life, was 16.2%, whereas the incidence of acute radiation-related lung injury of grade 2 or above was 10.8%. The incidence of late radiation-related esophageal injury of grade 3 or above was 7.2%, and the incidence of late radiation-related lung injury of grade 2 or above was 8.1%.

Local control rate and survival rate
In all patients, the 1- and 2-year local control rates were 72.9% and 72.9%, respectively. The 1- and 2-year total survival rates were 80.9% and 67.4%, respectively, with a mean survival of 23 months. The 1- and 2-year disease-free survival rates were 73.5% and 51.4%, respectively, and mean disease-free survival was 21 months (Figs. 1–3).

Analysis of the reasons for treatment failure
As of the follow-up cut-off date, treatment was ineffective in 13 patients. Of these, 9 experienced local failure in the esophagus; 7 of the 9 had locally controlled tumor, and 2 had local recurrence. All these lesions were seen within the radiation field, accounting for 69.2% (9/13) of all treatment failures. Distant metastasis developed in 5 patients, of whom 1 had bone metastasis, 1 had liver metastasis, 1 had metastasis in the supraclavicular lymph nodes (and also had locally uncontrolled tumor), 1 had metastasis in the abdominal lymph nodes, and 1 had lung metastasis. Of these 13 patients, 4 survived with tumor and 9 died. Cause of death was liver metastasis in 1, locally uncontrolled tumor in 6 (major hematemesis in 5 and prostration in 1), gastric hemorrhage in 1, and death after blood transfusion in 1.
Discussion

With radiotherapy, the 5-year survival rate of patients with esophageal carcinoma is only 10% to 15%, and 70% to 80% of treatment failures result from a locally uncontrolled or recurrent lesion. Short-term efficacy and radiotherapy dosage are the main factors that affect local control and recurrence of esophageal carcinoma. Therefore, for more than 10 years, oncologic radiotherapists have been trying to optimize the radiotherapy schemes for esophageal carcinoma on radio-biological and radio-physical levels. Late-course accelerated hyperfractionation radiotherapy had the best efficacy in treating esophageal carcinoma among all non-regular fraction methods. Han et al. in a randomized trial in 100 patients with esophageal carcinoma, found that late-course accelerated hyperfractionation radiotherapy increased 1-, 3-, and 5-year survival rates from 62%, 22%, and 14% in a conventional radiotherapy group to 84%, 48% and 32% (P < 0.01), respectively.

Accurate radiotherapy is an important development in the realm of radiotherapy. Not only does it protect normal tissue, it also optimizes the dosage distribution in the target volume through a physical approach. Conventional conformal radiotherapy, late-course accelerated hyperfractionation conformal radiotherapy, or conformal therapy in combination with chemotherapy have been used to treat esophageal carcinoma; 1-, 3-, and 5-year local control rates were 73.5% to 87.9%, 31.0% to 63.0%, and 27.0% to 61.0%, respectively, and 1-, 3-, and 5-year survival rates were 53.0% to 83.2%, 20.0% to 51.5%, and 17.0% to 32.0%, respectively, which are better than those achieved with conventional radiotherapy.

As suggested by Fu et al., a 5-to 7-field intensity-modulated radiation method, as an advanced radiation technique in conformal radiotherapy, could achieve a desirable dosage distribution in upper thoracic esophageal carcinoma through a simultaneous integrated boost technique. Nutting et al. suggested that IMRT could improve the radiation dosage in the target volume with acceptable radiation-related lung injury. Chandra et al. treated 10 patients with lower thoracic esophageal carcinoma and cardiac carcinoma and found that 4-field, 7-field, and 9-field IMRT schemes decreased V20 by 10% and V50 by 5%, when compared with a conformal radiotherapy scheme; mean lung dosage was decreased by 2.5 Gy as well. Wang et al. reported that, for upper thoracic esophageal carcinoma, 5-field, 7-field, and 8-IMRT techniques were better than 4-field conformal radiotherapy in terms of the conformity and dosage distribution of the target volume and the protection of lung tissue. However, currently most studies of IMRT in esophageal carcinoma have focused on dosage; clinical reports and clinical experience are rare.

In our study of 37 patients with esophageal carcinoma treated by intensity-modulated radiotherapy, 1- and 2- local control rates were up to 72.9% and 72.9%, respectively. Local treatment failure mostly occurred within 1 year after treatment. In addition, 1-and 2-year total survival rates were 80.9% and 67.4%, respectively, and 1- and 2-year tumor-free survival rates were 73.5% and 51.4%. These findings suggested substantial short-term efficacy for IMRT in treating esophageal carcinoma. This treatment has a 1-year total survival rate similar to that for late-course accelerated hyperfractionation radiotherapy at our institution, but with gentler toxicity and side effects. Compared with results in 100 patients with esophageal carcinoma treated by conformal radiotherapy in our hospital. IMRT tended to improve 1-year and 2-year total survival rates.

Because IMRT uses a reverse design to treat esophageal carcinoma, it substantially limited radiation dosage in lung tissue. In our study, the incidence of acute radiation-related lung injury of grade 2 or above was markedly lower than with that conformal radiotherapy. No acute hypersensitive lung injury, which was related to low-dosage radiation in extensive lung tissue, was seen. However, because of the complexity of radiation-related lung injury and the limitation of sample size, it is hard to state that the low incidence of radiation-related lung injury is benefited from IMRT. In our study, 3 patients had late radiation-related lung injury of grade 2 or above (2 with grade 3 late lung injury), mostly in elderly patients and those with chronic obstructive lung diseases. In 1 patient, a sputum culture suggested a secondary dual infection with bacteria and fungus; in another patient, secondary pulmonary tuberculosis had a large effect on the patient's quality of life. Tolerance observation and aggressive treatment should be used to improve patients' nutritional and immune status.

In our study, the incidence of acute radiation-related esophageal injury of grade 3 or above was 16.2%, which was greater than that seen with conformal radiotherapy. This finding might be related to the fact that most patients were treated with a simultaneous integrated boost technique (a single dose in esophageal GTV was 220 Gy). Late radiation-related esophageal injury of grade 3 or above was seen in 2 patients, 1 of whom experienced severe esophageal stricture; another stage-T4 patient had an esophagus-tracheal fistula, which was secondary to grade 4 acute esophageal injury and was seen at the site of primary esophageal carcinoma.

Wang et al. reported the clinical efficacy of IMRT in 7 patients with cervical and upper thoracic esophageal carcinoma (median dose, 64.8 Gy): with concomitant chemotherapy, the median follow-up time was 15 months. Local recurrence was found in 2 patients, distant metastasis was found in 2 patients, and another 3 patients enjoyed tumor-free survival. Toxicity of the treatment was mainly myelosuppression, radiation-related dermatitis and radiation-related esophagitis. Asymptomatic radiation-related pneumonitis (imaging changes were seen in the lung radiation field in 2 patients) might be related to the fact that our patients had cervical and upper thoracic esophageal carcinoma, and thus the radiation dosage for lung tissue involved in the radiation field was minimal. The studies by Wang et al. also showed that, after IMRT, 1 stage-T4 patient experienced grade 4 acute radiation-related esophagitis accompanied by an esophagus-tracheal fistula; 2 other patients experienced grade 3 late radiation-related esophagitis accompanied by benign esophageal stricture that necessitated dilation treatment. Finally, 1 patient experienced grade 4 late radiation-related esophagitis...
that necessitated esophageal stenting. Also in our study, 1 patient had grade 4 acute radiation-related esophagitis accompanied by esophagus-tracheal fistula 2 weeks after the end of treatment.

Our study showed that IMRT had considerable short-term efficacy and that the incidence of late radiation-related lung injury of grade 2 or above, which has a substantial effect on the patients’ quality of life, was low, suggesting the treatment was well-tolerated by the patients. However, our sample size was small and the follow-up time was short. Therefore, these results are not definitive. Whether the treatment can improve long-term survival is unknown. Local failure still occurred in 69.2% of all patients with treatment failure, and those patients who died of massive hemorrhage tended to have a concomitantly locally uncontrolled lesion or recurrence, indicating that locally uncontrolled or recurrent tumor remains a major challenge in radiotherapy treatment for esophageal carcinoma. Clinical studies that employ IMRT in treating esophageal carcinoma are far from sufficient; also, whether combined concomitant chemotherapy can further improve efficacy must be explored further by expanding sample size and accumulating clinical experience.

References