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ORIGINAL ARTICLE

Patterns of failure after involved field radiotherapy for locally advanced esophageal squamous cell carcinoma

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Summary

Purpose: *To retrospectively analyze the patterns of failure and the treatment effects of involved-field irradiation (IFI) on patients treated with locally advanced esophageal squamous cell carcinoma (ESCC) and to determine whether IFI is practicable in these patients.*

Methods: *A total of 79 patients with locally advanced ESCC underwent three dimensional conformal (3D-CRT) or intensity modulated radiotherapy (IMRT) using IFI or elective nodal irradiation (ENI) according to the target volume. The patterns of failure were defined as local/regional, in-field, out-of-field regional lymph node (LN) and distant failure. With a median follow-up of 2.0 months, failures were observed in 66 (83.6%) patients.*

Results: *The cumulative incidence of local/regional failure (55.8 vs 52.8%) and in-field regional lymph node failure (25.6 vs 19.4%) showed no statistically significant difference between the IFI and the ENI group (p=0.526 and 0.215, respectively). Out-of-field nodal relapse rate of only 7.0% was seen in the IFI group. Three-year survival rates for the ENI and IFI group were 22.2 and 18.6%, respectively (p=0.240), and 3-year distant metastasis rates were 27.8 and 32.6%, respectively (p=0.180). The lung V_{10} , V_{20} , V_{30} and mean lung dose of the ENI group were greater than those of the IFI group, while the mean lung dose and V_{10} had statistically significant difference.*

Conclusions: *The patterns of failure and survival rates in the IFI group were similar as in the ENI group; the regional recurrence and distant metastasis are the main cause of treatment failure. IFI is feasible for locally advanced ESCC. Further investigation is needed to increase local control and decrease distant metastasis in these patients.*

Key words: *esophageal squamous carcinoma, irradiation, patterns of failure*

Introduction

Esophageal cancer (EC) is the fifth most common cancer and the fourth leading cause of cancer-related deaths in China. Different from the Western countries, ESCC accounts for 95% of all Chinese EC patients [1]. Due to no typical symptoms in early stage, many patients are diagnosed at advanced stages in China. For these patients, the results of RTOG 85-01 study have made definitive chemoradiotherapy (CRT) the first standard treatment option [2].

The clinical tumor volume is a very important factor in definite radiotherapy [3]. ESCC is a malignancy with an extensive and not clearly defined range of LN metastases [4]. The radiation fields of many trials involve larger ranges and have included ENI, i.e., nodal target volume that covers both metastatic LNs and regional LNs in consideration of microscopic spread. The choice of ENI may seem logically feasible when considering the benefit from 3-field lymphadenectomy of EC [5] and it theoretically provides a better local tumor control. But some published reports indicated that serious toxicities would occur in at least 50% of patients with EC receiving concurrent CCRT if ENI was adopted [6].

Theoretically, treatment-related toxicities would decline if the irradiation volume was diminished.

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IFI, i.e., nodal target volume that includes only the metastatic nodes, is a selective way of decreasing the irradiation volume. Some recent studies showed that IFI may be feasible for locally advanced patients with ESCC in China [7,8], but the optimal radiation field remains globally controversial [9]. The present study sought to retrospectively document the failure patterns and survival of these patients, and evaluate the feasibility of IFI for locally advanced ESCC.

Methods

Patients

Between January 2008 and December 2013, 79 patients with histologically or cytologically proven ESCC entered into this clinical trial. The study was approved by the ethics committee of the First Affiliated Hospital of Bengbu Medical College, and all patients gave written informed consent. All patients underwent the following examinations: ultrasound examination of the LNs of the neck; chest radiography; chest computed tomography (CT) scan; esophageal barium tomography; ultrasound examination of the abdomen, and liver and renal function tests; electrocardiography; and blood cell counts. All tumors were staged according to the TNM staging system of the 2002 International Union Against Cancer, on the basis of physical examination and radiographic images. Eligibility criteria were age 90 years or less, Karnofsky performance status 70 or higher, esophageal lumen not completely obstructed, and primary tumor length 10 cm or less without distant metastasis. Baseline patient characteristics by treatment group are shown in Table 1.

Table 1. The characteristics of the two groups

Patient characteristics	*IFI*	*ENI*	*P value*
Sex			0.16
Male	33	29	
Female	10	7	
Age(y)			0.35
Median	65.6	56.8	
Range	42-90	43-75	
Location			0.25
Upper	14	10	
Middle	23	18	
Lower	6	8	
Tumor length (cm)			0.32
Median	5.8	5.3	
Range	3-10	2-9	
Clinical stage			0.11
II	3	2	
III	32	25	
IVa	8	9	
Radiotherapy			0.42
3D-CRT	4	6	
IMRT	39	30	
Chemotherapy			0.36
Yes	19	10	
No	24	26	

Radiotherapy

CT images were obtained from the angulus mandibulae level to the lower border of the second lumbar vertebra; 5 mm slice thickness images were required. The images were then transferred to a 3-D planning system (Pinnacle 7.6c Philips Medical Systems, USA). The delineation of clinical target volume (CTV) was based on CT, barium esophagogram, and endoscopic examination. Esophageal wall thickness of more than 0.5cm and positive LNs were included in the gross tumor volume (GTV) [10]. LNs that were well vascularized, measured more than 8 mm in the short axes, and showed central necrosis or extracapsular extension in CT examination were considered malignant [11]. As tracheoesophageal groove nodes are usually less than 5 mm, any medial tracheoesophageal groove node measuring more than 5 mm in the short axes detected on CT was regarded highly suspicious of metastatic involvement [12]. The total dose of GTV was 58-66 Gy/29-33F. At the same time, the volume of CTV was appropriately adjusted on the basis of the human anatomic structure so that the maximum dosage in the spinal cord did not exceed 45 Gy.

In the ENI group, the first clinical target volumes (CTV1) encompassed the primary tumor, the malignant LNs, and 3 cm proximal and distal margins; a 0.5-0.8 cm radial margin was added to the GTV. The first planning target volumes (PTV1) encompassed 1 cm proximal and distal margins, 0.5 cm radial margin on the basis of CTV1, with a total dose of 54-60 Gy/29-33F. The second CTV (CTV2) encompassed only 3-cm proximal and distal margins; a 0.5 cm radial margin was added to the GTV, and uninvolved regional LNs were encompassed in the CTV2 (Figure 1 A). The second PTV (PTV2) encompassed 1-cm proximal and distal margins, 0.5 cm radial margin on the basis of CTV2, with a total dose of 50-54 Gy/29-33F.

In the IFI group, CTV only encompassed 3 cm proximal and distal margins and 0.5-0.8 cm radial margin on the basis of GTV. Uninvolved regional LNs were not encompassed in the CTV (Figure 1 B). At the same time, the volume of CTV was appropriately adjusted on the basis of the human anatomic structure so that the maximum dosage in the spinal cord did not exceed 45 Gy. PTV encompassed 1 cm proximal and distal margins, 0.5 cm radial margin on the basis of CTV, with a total dose of 50-56Gy/29-33F.

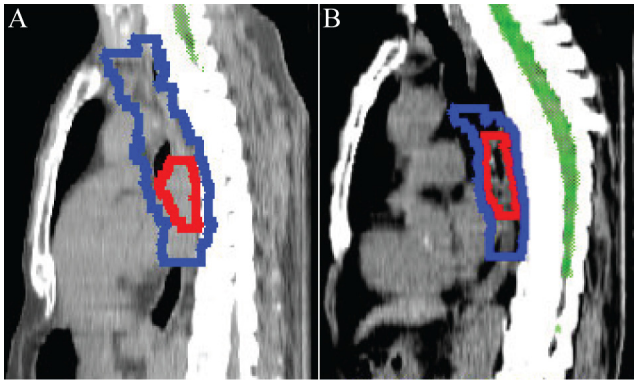

Figure 1. Comparison of target volumes delineation in ENI **(A)** and IFI **(B)** group.

Chemotherapy

Chemotherapy began on day 1, concurrent with the beginning of radiation. The chemotherapeutic regimen consisted of two cycles of cisplatin (20 mg/m^2/day on day 1 to day 4) and 5-fluorouracil (5-FU) (500 mg/m^2/day as a continuous infusion from day 1 to day 4) every 28 days; an additional 1-3 (median 2) cycles of chemotherapy with the same regimen were administered only to 29 patients.

Follow-up evaluation

After radiation, patients were evaluated at 3-month intervals for 1 year and at 6-month intervals thereafter until disease progression. Examination items included medical history, physical examination, toxicity assessment, complete blood cell count, serum biochemistry profile, chest X-ray, barium swallow and upper gastrointestinal, abdominal, and chest CT scan or PET-CT, and quality of life assessment. Biopsy of the primary tumor site or regional LNs was used in patients if there was any imaging evidence of local or regional recurrence. Overall survival (OS) and patterns of failure were calculated from the first day of irradiation.

Patterns of failure

Treatment failure analysis was based on local esophageal recurrence, such as out-of-field regional LN spread or in-field recurrence, and distant metastasis. Local failure was defined as any recurrence of the primary tumor, including persistent disease after initial treatment. In-field recurrence included primary lesion and involved regional LN failure. Out-of-field regional LN spread was defined as the failure of initially uninvolved LN within the regional LN. The LN metastases outside the regional level were considered as distant failures.

Statistics

Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized by descriptive statistics such as means, standard deviations, medians, and ranges. Categorical variables were tabulated by frequencies and percentages. The time to each outcome was calculated from the date of treatment. Analysis of patterns of failure was performed using crude calculations. Local/regional or distant failure rates were compared for statistical difference using Fisher's exact test. OS was calculated by the Kaplan-Meier method, and survival curves were compared using the log-rank test. Median OS time was obtained from the time corresponding to 50% survival based on the Kaplan-Meier survival curve. A p value <0.05 was considered as statistically significant.

Results

Patient characteristics

A total of 79 locally advanced ESCC patients (62 men, 17 women) were enrolled into this trial (median age 62 years, range 42-90). Staging was as follows: stage II in 5 patients, stage III in 57, stage IVa in 17, with N0 in 53 patients and N1 in 26 patients. There was no statistically significant difference between the 2 groups regarding patient characteristics. The follow-up period ranged from 18 to 53 months for all patients, with a median of 32 months. Two of the patients were lost to follow-up.

Patterns of failure

The patterns of cumulative failure are seen in Table 2. The cumulative incidence of local/regional failure (52.8 vs 55.8%) and distant failure (27.8 vs 32.6%) was lower in the ENI compared with the IFI group in 3 years, with no statistical significance (p=0.526 and 0.180, respectively). The cumulative incidence of regional LN failure was 25.6% for the IFI group compared with 19.4% for the ENI group (p=0.215). Out-of-field nodal failure rate of only 7.0% (3/43) was observed in the IFI group vs 2.0% (1/36) in the ENI group (p=0.285).

Overall survival rate

OS curves for the ENI and IFI groups are shown in Figure 2. The 1-, 2-, and 3-year OS rates

Table 2. The patterns of failure in the two groups

Group	*Patterns of failure*			*Location of regional failure*	
	Local failure	*Regional failure*	*Metastases*	*In-field*	*Out-of-field*
IFI (n)	24	14	14	11	3
ENI (n)	19	8	10	7	1
X^2		1.58		0.164	
P		0.34		0.51	

Table 3. The doses used in different groups

Group	*V_{10} (%)*	*V_{20} (%)*	*V_{30} (%)*	*Mean lung dose (cGy)*
IFI	42.56±4.62	23.56±4.85	18.69±4.62	1284.53±288.69
ENI	57.88±5.98	28.63±5.56	21.28±5.37	1726.31±345.21
t	4.26	1.64	1.24	3.44
P	0.003	0.06	0.10	0.01

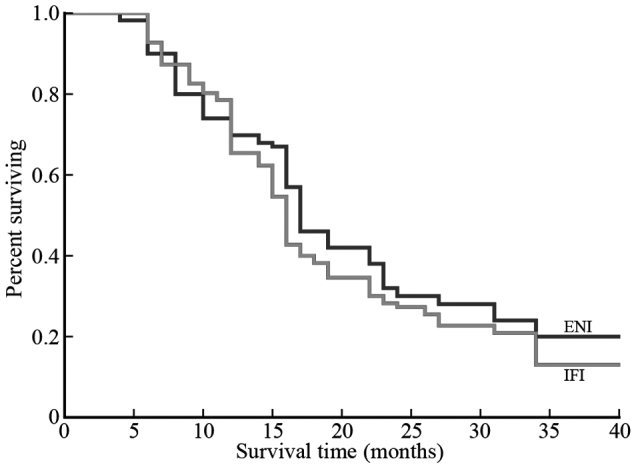

Figure 2. Actuarial statistics showing overall survival rates of patients with involved-field irradiation (IFI) compared to elective nodal irradiation (ENI). The difference between the 2 groups was not statistically significant (p=0.240).

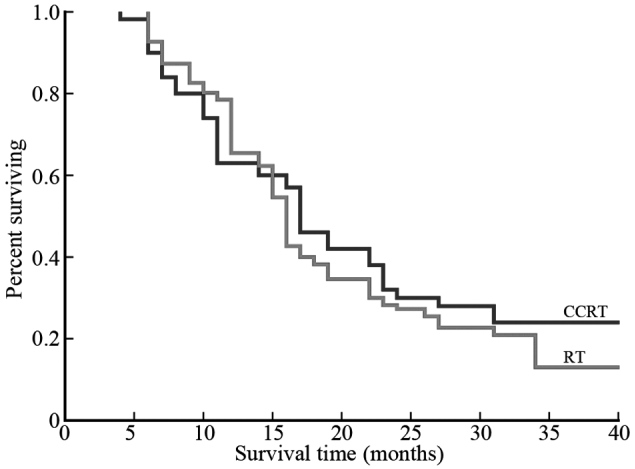

Figure 3. Actuarial statistics showing overall survival rates of patients with concurrent chemoradiation (CCRT) compared to radiotherapy alone (RT). The difference between the 2 groups was not statistically significant (p=0.356).

were 74.4, 36.1, and 22.2% for the ENI group, and 88.4, 23.3, and 18.6% for the IFI, without statistically significant difference between the 2 groups (p=0.240). The median OS time was 21.2 months (95% confidence interval (CI) 13.6, 32.8) in the IFI group versus 22.9 months (95% CI 15.7, 30.3) in the ENI group (p=0.285).

OS for the CCRT and radiotherapy (RT) groups is shown in Figure 3. The 1-, 2-, and 3-year OS rates were 61.2, 38.4, and 24.6% for the CCRT group, and 78.8, 22.8, and 16.8% for the RT group, without statistically significant difference between the 2 groups (p=0.356). The median OS time was 21.6 months (95% CI 10.8, 38.4) in the CCRT group versus 19.6 months (95% CI 11.7, 36.3) in the RT group.

Treatment toxicity

The lung V_{10}, V_{20}, V_{30} and mean lung dose of extended field group were greater compared with the involved field group, while the mean lung dose and V_{10} had statistical difference (Table 3).

Discussion

EC is notorious for its LN metastases, and LN involvement is an early process. Skip metastases are also common. Nodal spread of esophageal tumors may be extensive at initial clinical presentation. More than 50% of EC cases in China are diagnosed at locally advanced stage with obvious LN enlargement, long lesion and/or serious esophageal invasion. RT is the most important treatment for locally advanced ESCC. But in practice, the optimal radiation field for EC has not reached global consensus till now.

ESCC is epidemic in Asian countries. Recent studies from Japan [13,14] have confirmed ENI was effective in preventing regional and distant nodal failure in patients with EC undergoing CCRT. But the benefit of ENI for ESCC remains controversial in Japan. Kawaguchi et al. even found that IFI did not result in significant incidence of regional LN failure in clinical stage I thoracic EC patients [15]. In China, many recent studies showed that IFI may be feasible for locally advanced patients with ESCC [7,8].

In this study, we investigated treatment results and patterns of first site failure after IFI for locally advanced ESCC. We found that in-field failure and distant metastasis remained the predominant failure patterns in these cases. Among the 63 patients with failure, the rate of out-of-field regional LN failure alone in the IFI group was 7.5%. Zhao et al. have evaluated the results of IFI for EC patients with 3D-CRT. The rate of in-field recurrence was 44%, but only 8% of the cases were isolated out-of-field nodal recurrences [16]. Uno et al. reported that a radiotherapy PTV including only clinically involved lesion for patients with EC aged 75 and older, resulted in no isolated LN recurrence [17]. Ji et al. performed a dosimetric analysis to show that LN stations near ESCC receive considerable incidental irradiation doses with IFI that may contribute to the elimination of subclinical lesions [18]. Van de Voorde and colleagues reported that regional LN failure rates ranged from 5 to 15% for ENI in EC patients receiving RT [19]. In conclusion, for ENI or IFI, the regional LN failure was not the main pattern of recurrence in these advanced stage ESCC patients.

Radiation injury of the lung is a major limiting factor of ESCC radiotherapy. Some patients with severe radiation-induced injury have significantly increased risk of death. In this study, we noted one death in the ENI group combined with chemotherapy caused by radiation pneumonitis. Thus limitation of the lung volume dose is the main factor to reduce radiation injury of the lung in clinical practice. So we compared the lung V_{10}, V_{20}, V_{30} and mean lung dose of the ENI group and that of the IFI group, while the mean lung dose and V_{10} had statistical difference.

From another point of view, considering the high incidence of nodal failure and distant failure in the combined modality therapy in locally advanced ESCC, chemotherapy seems to play a limited role in preventing local/regional or distant failure. The concern was that the persistence of disease was the greatest cause of treatment failure (despite therapy), and many patients receiving combined therapy experienced local failure. In our study, we compared the 3-year OS in the RT andCCRT groups, but found the OS rate had no significant difference associated with combined regimens. Maybe this study cohort consisted of a high proportion of patients with stage IVa disease. Furthermore, only 36.7% of the patients received chemotherapy in this study, but no significant difference in survival was found between patients with or without chemotherapy (p=0.356). However, due to the limitations of this retrospective study, it is difficult to define the precise role of chemotherapy in locally advanced ESCC.

In the present study, the failure rate of more than 75% in the whole patient group and the OS (20.3% for 3 years) appeared worse than preceding reports. Some factors may have contributed, in part, to the high failure rate and worse OS in this study. First, all of the patients included in our study were in locally advanced stage with wide local tumor extension and/or clinically obvious nodal metastases, which was the most important cause for bad prognosis. Second, EUS, PET scans and other functional images were not available for all of the cases in the trial, which might lead to diagnostic underestimation, and might have impacted the target volume of IFI. The microscopic disease in normal-sized nodes and LN enlargement caused by benign conditions, limit the diagnostic accuracy of CT for nodal enlargement caused by EC. In future studies, if IFI is to be used, the more accurate diagnostic technique should be performed to avoid missing involved LNs. Third, ENI should be really effective for providing regional control of LN micrometastases, especially for responding cases which have a relatively long survival.

Although all of the patients included in this study were in locally advanced stage, a few patients achieved long-term survival, which indicated a good response to RT or CCRT. Previous studies have demonstrated that only patients with histological complete response can acquire survival benefits [20,21]. Unfortunately, most EC patients are resistant to chemoradiation, with only 20-40% pathologic CR rate after definitive CCRT in advanced stage patients [22]. In our opinion, for patients with complete response ENI may be appropriate to eliminate micrometastases in regional LNs, which might lead to longer survival. And for non-responders or non-complete responders, ENI seems unnecessary if the primary lesions could not be well controlled. So additional evaluations may be warranted to assess the sensitivity of patients to CCRT and then individualize treatments, thereby sparing patients unnecessary toxicity from ineffective therapy.

In summary, this study found that local and distant failure remained the major failure patterns in patients with locally advanced ESCC treated with IFI and impacted OS more significantly. Omission of ENI did not sacrifice OS, suggesting the usefulness of IFI for the locally advanced cases. However, this study cohort consisted of a high proportion of patients with stage IVa who had, anyhow, worse prognosis. Its retrospective nature with a relatively small sample size limits the generalization of our findings. Further observations with large-scale, multi-center, prospective, randomized clinical trials are needed to verify the feasibility of IFI in locally advanced ESCC patients.

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Conflict of interests

The authors declare no confict of interests.

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