# Comparison between late-course accelerated hyperfractionation radiotherapy and concurrent chemoradiotherapy in patients with esophageal carcinoma

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**Abstract.** This study aimed to compare the efficacy of late-course accelerated hyperfractionation radiotherapy (LAFR) and concurrent chemoradiotherapy (CRT) in patients with esophageal carcinoma and to evaluate the side effects of the two treatments. A total of 22 patients with primary esophageal squamous cell carcinoma were prospectively treated with LAFR, while 25 patients, during the same period, served as the control group and received CRT. The 22 patients in the LAFR group received conventional fractionated radiotherapy of 30 Gy over a 3-week period (5 daily fractions of 2.0 Gy per week), followed by accelerated hyperfractionated radiotherapy of 30 Gy for 2 weeks (twice daily, 1.5 Gy per fraction, with a minimal interval of 6 h between fractions, 10 fractions per week). The 25 patients in the CRT group received conventional fractionated radiotherapy of 50 Gy for 5 weeks, with 5 daily fractions of 2.0 Gy per week. Chemotherapy was started on the first day of irradiation (cisplatin 52.5 mg/m$^2$ on Day 1 and 5-fluorouracil 700 mg/m$^2$ on Days 1-5, repeated four times every 28 days). The median survival time in the LAFR and CRT groups were noted to be 17 and 21 months, respectively. The 1- and 2-year overall survival rates were 63.6 and 31.6% in the LAFR group and 76 and 57.4% in the CRT group ($\chi^2$=1.670; P=0.196). The median local control in the LAFR group was 17 months, while that in the CRT group was not determined. The 1- and 2-year local control rates were 54.5 and 39% in the LAFR group while those in the CRT group were 82.2 and 66.1% ($\chi^2$=3.527; P=0.060). The overall survival and local control rates of the LAFR group were lower than those of the CRT group, although the difference was not significant. The metastasis rates of the two groups were also not significantly different ($\chi^2$=0.030; P=0.862). Both acute and late adverse events in the two groups were tolerated. The side effects, including hematological toxicities, severe nausea and vomiting, and severe anorexia were significantly less in the LAFR group than those in the CRT group (P<0.05). In this small-sample exploratory study, the overall survival and local control rates were lower with LAFR than with CRT, but the difference was not significant. Moreover, LAFR was found to have fewer side effects and be more cost-effective compared to CRT. The long-term effects on LAFR survival should be evaluated in a phase III clinical trial.

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## Introduction

Various treatment strategies for esophageal carcinoma have been adopted in China and other countries. Concurrent chemoradiotherapy (CRT) is considered to be one of the standard regimens for esophageal carcinoma in the US (1,2) and Japan (3), although it is generally reported that the side effects of CRT are much more severe than those of radiotherapy (RT) alone. This observation was confirmed in the Radiation Therapy Oncology Group (RTOG) 85-01 trial (1). RT as a monotherapy is now widely preferred in China (4-7). Late-course accelerated hyperfractionation radiotherapy (LAFR) has achieved a 5-year overall survival rate of 33% in Chinese patients with esophageal carcinoma (4). In their study, Zhao e*t al* (7) found that LAFR offers similar survival and local control rates compared to standard chemotherapy plus RT, as in that delivered in the RTOG 85-01 (1,2) and 94-05 studies (8). Moreover, LAFR is more cost-effective in China. If LAFR provides successful treatment results comparable to those obtained with CRT and with fewer side effects, LAFR is likely to become a more feasible treatment regime for patients with esophageal carcinoma and one of the standard treatments used for Chinese individuals. However,

to the best of our knowledge, no studies have focused on a direct comparison of the efficacy of LAFR and CRT thus far. Before a multi-center phase III trial is conducted to confirm the role of LAFR, this small-sample, preliminary, prospective exploratory study was performed to compare the efficacy of LAFR and CRT. The maximal tolerated dose (MTD) of CRT for Chinese patients with esophageal carcinoma was used as the CRT regimen (9).

## Patients and materials

*Eligibility*. Patients (age range 18-70 years) for whom primary esophageal squamous cell carcinoma was proven by histology (T1-4N0-1M0) and staged by thoracoabdominal helical computed tomography (CT) were eligible for this study. All 47 patients provided written informed consent. Due to endoscopic ultrasound not being available in our center when the study commenced, clinical staging was evaluated based on CT scans, using the same standard as described in our previously published article (9). The T stage was defined by the maximal transverse diameter of the esophageal tumor: T1 ≤2 cm, T2 >2 cm and ≤4 cm, and T3 >4 cm. Tumors indicating an invasion of any adjacent structures were classified as T4. If the minimal transverse diameter of lymph nodes in mediastinal and celiac were >1 cm, the lymph nodes were classified as N1; otherwise, they were classified as N0. Inclusion criteria involved patients not receiving any prior RT or chemotherapy. Patients were required to have a Karnofsky performance status of ≥60. The required laboratory test results included a neutrophil count of $\geq 2.0 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l, a hemoglobin count of ≥100 g/l, and serum creatinine, aspartate aminotransferase, alanine aminotransferase and total serum bilirubin ≤ upper limits of normal. The exclusion criteria included any of the following: pregnancy, lactation, tracheoesophageal fistula, a history of other malignancies, with the exception of carcinoma *in situ* of the cervix, non-melanomatous skin cancer or cancer from which the patient had not been disease-free for 5 years, a general medical condition preventing combined modality therapy and a known hypersensitivity to cisplatin (CDDP) or 5-fluorouracil (5-FU), as well as use of any other concurrent antineoplastic therapy.

*Pre-treatment evaluation*. The pre-treatment evaluation included a medical history, a complete physical examination, barium esophagography, a chest and abdominal helical CT scan, upper gastroesophageal endoscopy, electrocardiography, bronchoscopy, a bone marrow scan (if clinically indicated), complete blood count and a biochemical profile. The pre-treatment tests were performed during the 2 weeks prior to treatment initiation. Patients received physical examinations and blood counts were obtained once a week or more often as required. A biochemical profile and electrocardiography was performed prior to each chemotherapy cycle.

*Recruitment and treatment plan*. A total of 22 patients were prospectively recruited and treated with LAFR. A further set of 25 patients, who were treated with CRT during the same time period, were selected as the control group. The treatment scheme is shown in Table I. In the LAFR group, patients received RT as a monotherapy. In the CRT group, RT began on Day 1, concurrently with the first cycle of chemotherapy.

Table I. Treatment plan.

A, LAFR group

| Week | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| RT | IIIII | IIIII | IIIII | II II II II | II II II II |

RT regimen: 30 Gy in weeks 1-3: 2 Gy/f, 1 f/d, 5 f/w; 30 Gy in weeks 4 and 5: 1.5 Gy/f, 2 f/d, 10 f/w; total dose: 60 Gy

B, CRT group

| Week | 1 | 2 | 3 | 4 | 5 | 9 | 13 |
|---|---|---|---|---|---|---|---|
| RT | IIIII | IIIII | IIIII | IIIII | IIIII | | |

RT regimen: Week 1-5: 2 Gy/f, 1 f/d, 5 f/w; total dose: 50 Gy. Chemotherapy: CDDP (52.5 mg/m$^2$) x1x4; 5-FU (700 mg/m$^2$) x5x4. Total dose: CDDP 210.0 mg/m$^2$, 5-FU 14,000 mg/m$^2$.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CDDP | ◆ | | | | ◆ | ◆ | ◆ |
| 5-FU | □ | | | | □ | □ | □ |

*Radiotherapy*. Multifield, external-beam megavoltage radiation was delivered using 6-MeV linear accelerators. All fields were treated each day. Treatment was administered with a combination of anterior-posterior, oblique or lateral fields, in a manner that the dose-to-target volume did not differ from the dose specified at the isocenter by >10%. The administered dose was prescribed to the isodose line covering the volume at risk. Port films were taken of 2 fields once weekly or more often if clinically indicated. The prescription dose was calculated without tissue heterogeneity correction. The bounds of the gross target volume (GTV) were delineated by esophagography, CT scan and esophagoscopy. The upper and lower bounds of clinical target volume (CTV) were defined as an extension of 3 cm outside the upper and lower bounds of GTV, respectively, while the lateral bounds of CTV were defined as an extension of 1 cm outside the lateral bounds of GTV. The planning target volume (PTV) was obtained by expanding CTV by 1 cm in all directions.

In the CRT group, RT was performed with conventional fractionation on the first day of week 1. Patients were treated with 5 daily fractions of 2.0 Gy per week over a 5-week period. The total radiation dose was 50 Gy.

Details regarding the LAFR regimen were previously published (10). In the LAFR group, patients received conventional fractionation RT at 2 Gy per fraction, to a dose of 30 Gy in 15 fractions over 3 weeks during the first RT course, followed by accelerated fractionation RT, twice daily, at 1.5 Gy per fraction, with a minimal interval of 6 h between fractions and an overall treatment time of 5 weeks. The total dose was 60 Gy.

*Chemotherapy*. Chemotherapy regimens, defined specifically for Chinese individuals with esophageal carcinoma have

been published in detail (9). Chemotherapy was commenced on Day 1 of RT using MTD: CDDP 52.5 mg/m$^2$ on Day 1 and 5-FU 700 mg/m$^2$ on Days 1-5, repeated four times every 28 days. The first and second cycles were concurrent with CRT. CDDP was administered at an infusion rate of 1 mg/min on Day 1, followed by a continuous daily intravenous infusion of 5-FU (at least 8 h) from Day 1 to Day 5.

*Evaluation of adverse events*. Radiation-induced adverse events were graded according to the RTOG criteria (11), which included acute reactions occurring within the first 90 days of treatment or late reactions occurring after 90 days of treatment. Chemotherapy-induced adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0) (12), with the exception of hand-foot syndrome, which was graded using protocol-specific definitions. Hand-foot syndrome grades were defined as (13): Grade 1: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema. Discomfort did not disrupt normal activities. Grade 2: painful erythema, with swelling. Discomfort affected activities of daily living. Grade 3: moist desquamation, ulceration, blistering and severe pain. Severe discomfort made it impossible for the patient to work or perform activities of daily living.

*Dose attenuation*. Dose modifications were based on the most serious toxicities occurring on any day after treatment initiation.

The irradiation dose was not allowed to be modified. However, RT was withheld for Grade 3 or higher toxicities until the toxicities were no longer present. RT was continued, but chemotherapy was withheld in cases where Grade 3 or higher toxicities, unrelated to RT, occurred; for example, mucositis, genitourinary toxicity and hand-foot syndrome. Chemotherapy was resumed once these toxicities had been eradicated.

The CDDP dose was reduced by 50% if the serum creatinine was between 1.6 and 2.0 mg/dl. Both CDDP and 5-FU were stopped if the serum creatinine was >2 mg/dl, but RT was continued. Chemotherapy was restarted once the toxicities had been eradicated.

For hand-foot syndrome, only the 5-FU dose was modified. For Grade 2 toxicity the 5-FU dose was reduced by 25% for the following chemotherapy cycle, and for Grade 3 toxicity 5-FU was stopped and the dose was reduced by 50% in the following chemotherapy cycle.

In other cases, doses were also modified. If Grade 3-4 thrombocytopenia, Grade 3-4 anemia, Grade 4 neutropenia, or Grade 3-4 non-hematologic toxicity occurred (with the exception of Grade 3 nausea, vomiting and anorexia), both RT and CDDP with 5-FU were withheld until the toxicities were no longer present. If this did not occur within 2 weeks, the patient was withdrawn from the study. The CDDP and 5-FU doses of the following chemotherapy cycle were reduced by 25%. Prophylactic recombinant-human granulocyte colony stimulating factor was used following the reduced chemotherapy cycle. If Grade 3 neutropenia or Grade 2 thrombocytopenia alone occurred, chemotherapy was stopped and RT was continued. The CDDP and 5-FU doses of the following chemotherapy cycle were the same as those in the original regimen. Prophylactic recombinant-human granulocyte colony stimulating factor was used following that chemotherapy cycle.

*Follow-up and therapeutic effects evaluation*. Following treatment, patients were followed up every 3 months for the first year, every 6 months for the second year and annually thereafter. Each follow-up included history, physical examination, complete blood count, blood biochemical examination, chest X-ray or chest CT, esophageal barium radiography or esophagoscopy. A biopsy of the primary tumor site was required if locoregional recurrence was suspected following the X-ray or CT.

The endpoints of this study were survival, locoregional control and distant metastasis. Death from any cause was calculated from the date of treatment until the patient succumbed to the disease or the last follow-up evaluation. All endpoints were observed from the first day of treatment until death or the last follow-up time.

*Statistical analysis*. Statistical analyses were performed using the SPSS13.0 software package. Constituent ratios were assessed using the Chi-square test or the Fisher's exact probability test. The means between the two groups were compared using the t-test or rank-sum test. The survival, local control and metastasis rates were estimated using the Kaplan-Meier method. Statistical significance was assessed using the log-rank test. $P<0.05$ was considered to be statistically significant.

## Results

*Patient characteristics*. Between July 2006 and June 2007, 22 sequential untreated patients with pathologically confirmed esophageal squamous cell carcinoma were treated with LAFR (LAFR group). Concomitantly, 25 patients were treated with CRT (CRT group). The 47 patients, comprising 29 males and 18 females, were between the ages of 40 and 70 years (median 64). Of the 47 patients, 19 had stage II disease and 28 had stage III disease. As shown in Table II, although the percentage of stage III patients in the LAFR group (63.6%) was slightly higher than that in the CRT group (56%), the difference was not significant ($P=0.595$). No significant statistical difference was noted in other patient characteristics such as gender, age, location in the esophagus, KPS score, weight loss and largest tumor diameter.

All 47 patients were followed up until they succumbed to the disease or until the time of the last follow-up evaluation. Until August 31, 2008, no patients were lost to follow-up. The median follow-up time for the patients was 17 months (range 4-25).

*Treatment compliance*. In the LAFR group, one patient refused subsequent treatment after receiving an irradiation dose of 57 Gy due to personal reasons, while the remaining patients completed the treatment as planned. In the CRT group, 5 patients failed to complete all four cycles of chemotherapy (including one who received only 32 Gy of irradiation). The planned treatment was terminated for the following reasons: esophago-mediastinal fistula in one patient who only completed one cycle of chemotherapy and received only 32 Gy of irradiation; intolerable fatigue and gastrointestinal adverse events in one patient who completed three cycles of chemotherapy; disease progression in one patient who completed one cycle of chemotherapy; and

Table II. Patients characteristics.

| Characteristics | LAFR group | CRT group | Statistical value | P-value |
|---|---|---|---|---|
| Gender | | | $\chi^2$=0.099 | 0.753 |
| Male | 14 | 17 | | |
| Female | 8 | 8 | | |
| Age (years) | | | t=2.425 | 0.635 |
| Range | 53-70 | 40-70 | | |
| Median | 66 | 64 | | |
| Location in the esophagus | | | $\chi^2$=0.619 | 0.445 |
| Upper | 9 | 6 | | |
| Median | 12 | 17 | | |
| Lower | 1 | 2 | | |
| Clinical stage | | | $\chi^2$=0.283 | 0.595 |
| II | 8 | 11 | | |
| III | 14 | 14 | | |
| KPS score | | | t=1.340 | 0.187 |
| Range | 60-90 | 60-90 | | |
| Median | 80 | 80 | | |
| Weight loss | | | $\chi^2$=0.091 | 0.763 |
| Yes | 12 | 10 | | |
| No | 10 | 15 | | |
| Largest tumor diameter (cm) | 3.8±1.2 | 4.1±1.9 | t=0.457 | 0.639 |

LAFR, late-course accelerated hyperfractionated radiotherapy; CRT, concurrent chemoradiotherapy.

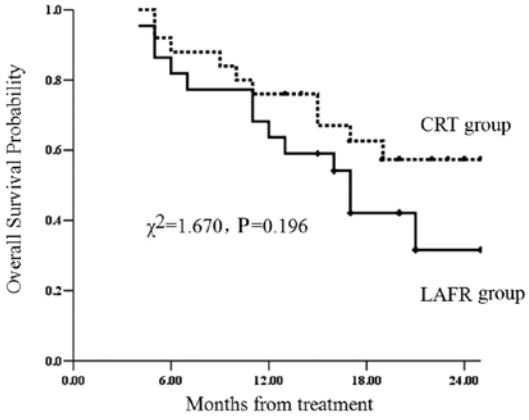


Figure 1. The 1- and 2-year overall survival rates were 63.6, 31.6 and 76%, 57.4% in the LAFR and CRT groups, respectively. The survival rate in the LAFR group was lower than that in the CRT group, but the difference was not significant ($\chi^2$=1.670; P=0.196).

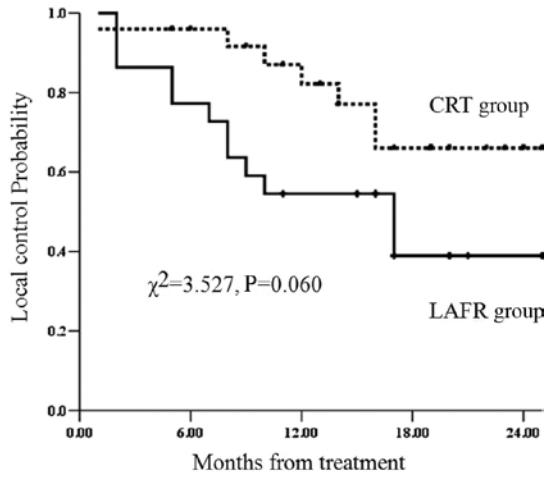


Figure 2. The 1- and 2-year local control rates were 54.5, 39 and 82.2, 66.1% in the LAFR and CRT groups, respectively. The local control rate in the LAFR group was lower than that in the CRT group, but the difference was not significant ($\chi^2$=3.527; P=0.060).

refusal of subsequent treatment after symptom remission in two patients. Of note is that although the patient developing esophago-mediastinal fistula completed only one cycle of chemotherapy and received only 32 Gy of irradiation, he was included in the evaluation of treatment efficacy, since his symptom of swallowing difficulty was significantly relieved. Subsequently, all 47 patients were subjected to the evaluation of efficacy and toxicity.

*Survival and causes of death*

*Survival rates*. For all 47 eligible patients, the median survival time from treatment initiation was 21 months, whereas the 1- and 2-year survival rates were 70.2 and 45%, respectively. The median survival time in the LAFR group was 17 months, while that in the CRT group was 21 months. The 1- and 2-year survival rates were 63.6 and 31.6%, respectively, in the LAFR group and 76 and 57.4%, respectively, in the CRT group. The survival rate in the LAFR group was lower than that in the CRT group, but the difference was not significant ($\chi^2$=1.670; P=0.196) (Fig. 1).

*Local control rates*. A total of 12 patients in the LAFR group and 7 in the CRT group showed local control failure or recurrence. The median local control in the LAFR group was 17 months, while the corresponding result for the CRT group was not obtained. The 1- and 2-year local control rates were 54.5 and 39%, respectively, in the LAFR group and 82.2 and 66.1%, respectively, in the CRT group. The local control rate in the LAFR group was lower than that in the CRT group, but the difference was not significant ($\chi^2$=3.527; P=0.060) (Fig. 2).

*Metastasis rates*. Nine patients in the LAFR group and 11 in the CRT group showed distant metastasis. The median non-metastasis time in the LAFR group was not obtained, while the value in the CRT group was 20 months. The 1- and 2-year metastasis rates were 40.8 and 46.7%, respectively, in the LAFR group and 33 and 52.4%, respectively, in the CRT group. The metastasis rates in the LAFR and CRT groups were equal ($\chi^2$=0.030; P=0.862) (Fig. 3).

*Causes of death*. As of the last follow-up, 24 patients were alive and 23 had succumbed to the disease. A total of 13 patients in the LAFR group had succumbed to the disease, including 6 (46.2%) who died of local control failure, 2 (15.4%) of distant metastasis and 5 (38.5%) of a combination of the two causes. A total of 10 patients in the CRT group had succumbed to the disease, including 5 (50%) who died of distant metastasis,

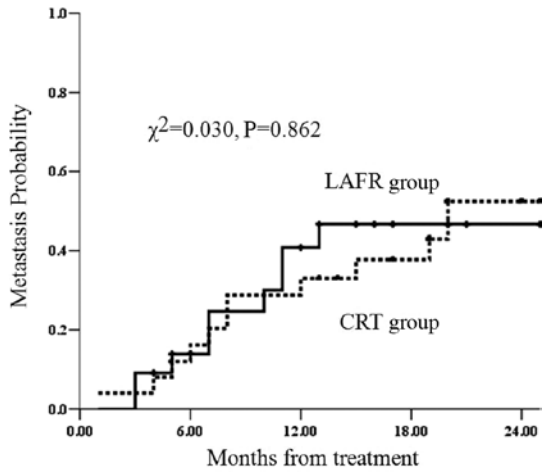


Figure 3. The 1- and 2-year metastasis rates were 40.8%, 46.7% and 33%, 52.4% in the LAFR and CRT groups, respectively. The metastasis rates in the LAFR and CRT groups were equal ($\chi^2$=0.030; P=0.862).

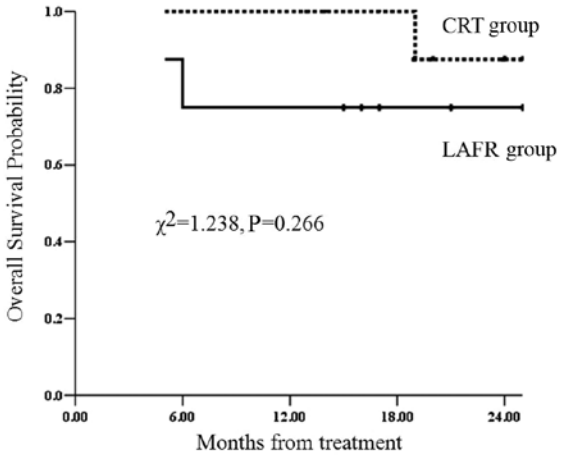


Figure 5. The 2-year overall survival rates of patients with clinical stage II in the LAFR and CRT groups were 75.5% and 87.5%, respectively. No significant difference was observed between the two groups ($\chi^2$=1.238; P=0.266).

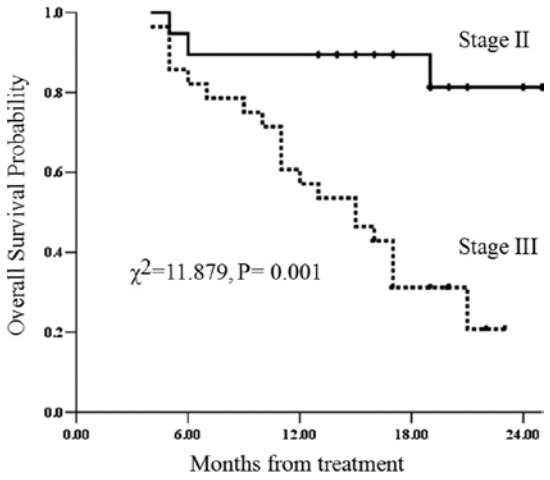


Figure 4. The survival rate in patients with stage II disease (CT-based staging) was significantly superior to that of patients with stage III disease ($\chi^2$=11.879; P=0.001).

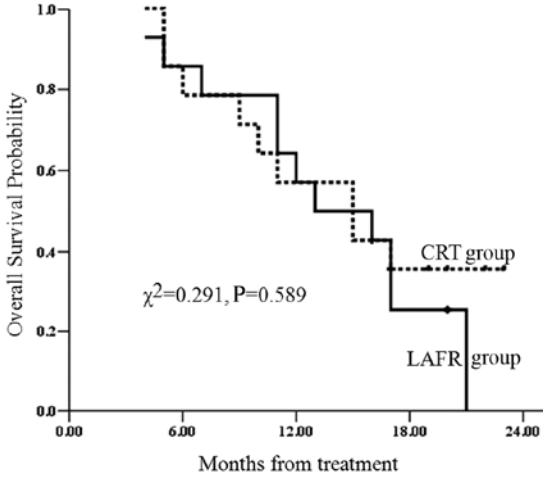


Figure 6. The 2-year overall survival rate of patients with clinical stage III in the LAFR group was 0%. The corresponding rate for the CRT group is not yet known; however, the 23-month survival rate was 35.7%. No significant difference was observed between the two groups ($\chi^2$=0.291; P=0.589).

2 (20%) of local control failure and 3 (30%) of a combination of the two causes. Local control failure was the major cause of death in the LAFR group, since it contributed to 46.2% of deaths, while distant metastasis was the major cause of death in the CRT group, contributing to 50% of deaths.

*Survival rates of patients with different clinical stages*. Of the whole group, the survival rate in patients with stage II disease (CT-based staging) was significantly superior to that of patients with stage III disease ($\chi^2$=11.879; P=0.001) (Fig. 4).

*Survival rates of patients with clinical stage II*. The 2-year survival rates of patients with clinical stage II in the LAFR and CRT groups were 75 and 87.5%, respectively. No significant difference was observed between the two groups ($\chi^2$=1.238; P=0.266) (Fig. 5).

*Survival rates of patients with clinical stage III*. The 2-year survival rate of patients with clinical stage III in the LAFR group was 0%. The 2-year overall survival rate with clinical stage III in the CRT group has yet to be determined; however, the 23-month survival rate was 35.7%. No significant difference was observed between the two groups ($\chi^2$=0.291; P=0.589) (Fig. 6).

*Adverse events*. The major acute adverse events observed in the two groups were radiation-induced esophagitis and radiation-induced pneumonia. No significant difference in the rates of these adverse events was noted between the two groups. The rates of Grade III or above radiation-induced esophagitis in the LAFR and CRT groups were 4.5 and 4%, respectively. Grade III or above radiation-induced pneumonia was not observed. The rates of all hematological toxicities, Grade III nausea and vomiting, and Grade III anorexia were significantly lower in the LAFR group compared to the CRT group. The results are shown in Table III.

Grade V late esophageal injury was observed in only one patient in the CRT group, while no other Grade III or above late adverse events were observed. No significant difference in late injury in the esophagus and lungs was noted between the two groups. Serious late adverse events, such as radiation-induced

Table III. Acute adverse events.

| Acute adverse event | LAFR group (%) | CRT group (%) | $\chi^2$-test | P-value |
|---|---|---|---|---|
| Radiation-induced esophagitis | | | 1.177 | 0.734[a] |
| 0 | 6 (27.3) | 4 (16.0) | | |
| I-II | 15 (68.2) | 20 (80.0) | | |
| III-IV | 1 (4.5) | 1 (4.0) | | |
| Radiation-induced pneumonia | | | 2.736 | 0.203[a] |
| 0 | 16 (72.7) | 13 (52.0) | | |
| I | 6 (27.3) | 10 (40.0) | | |
| II | 0 (0.0) | 2 (8.0) | | |
| Hematology | | | 16.780 | 0.000[a] |
| 0 | 13 (59.1) | 1 (4.0) | | |
| I-II | 9 (40.9) | 20 (80.0) | | |
| III-IV | 0 (0.0) | 2 (8.0) | | |
| Nausea and vomiting III | 0 (0.0) | 7 (28.0) | 9.913 | 0.002 |
| Anorexia III | 0 (0.0) | 9 (36.0) | 13.236 | 0.002 |
| Sarcitis/myasthenia III | 0 (0.0) | 1 (4.0) | | 1.000[a] |

[a]Fisher's exact test.

Table IV. Late adverse events.

| Late adverse event | LAFR group (%) | CRT group (%) | $\chi^2$-test | P-value |
|---|---|---|---|---|
| Late esophageal injury | | | 2.491 | 0.507[a] |
| 0 | 12 (54.5) | 11 (44.0) | | |
| I | 9 (40.9) | 9 (36.0) | | |
| II | 1 (4.5) | 4 (16.0) | | |
| V | 0 (0.0) | 1 (4.0) | | |
| Late lung injury | | | 0.435 | 0.805 |
| 0 | 15 (68.2) | 15 (20.0) | | |
| I | 6 (27.3) | 8 (32.0) | | |
| II | 1 (4.5) | 2 (8.0) | | |

[a]Fisher's exact test.

myelitis and radiation-induced pericarditis, were not observed. The results are shown in Table IV.

## Discussion

LAFR for esophageal carcinoma has been widely adopted in China. Early studies (4,5) of LAFR from various individual medical centers have reported achieving a 5-year survival rate of more than 30%, which is significantly superior to conventional fraction RT. However, a direct comparison cannot be made between these outcomes due to the different recruitment criteria and study background used in the studies.

Most early studies of LAFR have two obvious shortcomings. First, there was a selection bias; for example, a Karnofsky performance status of ≥80 (14), the ability to have a semi-liquid diet (14), lesions of esophagus ≤8 cm (4,6) or esophageal lumen not completely obstructed (4). Moreover, no original data exist relating to disease stage in those studies. If patients with a 5-year survival rate of 33% were recruited in the early stage, a favorable prognosis may have been obtained. Those cases therefore did not represent all esophageal carcinomas of different stages. Secondly, data regarding the TNM stage were not available when patients were randomized into treatment and control groups, thus the process used for randomization did not guarantee stage balance between the two groups. Since TNM stage is a crucial factor related to prognosis (15), randomization without the stage factor renders these outcomes (4-6) discouraging. A previous LAFR study using a large sample group of 201 cases showed that LAFR achieved 3- and 5-year overall survival rates of 34 and 26%, respectively, while the 3-year overall survival rate in this study was only the same as the previous 5-year overall survival rate of 33% reported from the same cancer center (4). Two other studies (16,17) have reported long-term survival outcomes

from a well-known cancer center in China. The 5-year overall survival rate was only approximately 20%. None of the abovementioned survival outcomes are comparable to early results (4,5), which have shown 5-year overall survival rates of more than 30%. These survival rate results are inconsistent. A significant reason for this inconsistency may be the different stages of disease in the patients at the point when they were recruited for the different studies.

Zhao e*t al* (7) reported that LAFR provides a 5-year overall survival rate of 26% and concluded that the LAFR regimen offers a similar survival rate to standard chemoradiotherapy (1,2). In this study, the esophageal carcinomas were staged by CT and ultrasound, and more than 60% of patients who began the study with stage I-IIA of the disease had favorable survival outcomes. The survival rates of stage III patients were not available in this study. Since most of the patients with esophageal carcinoma had advanced disease at the time of presentation (15,18), the results of this study do not guarantee that LAFR provides a favorable outcome in the treatment of esophageal carcinoma of all stages.

No results from multi-center randomized controlled trials have confirmed the survival outcomes of LAFR thus far. The role of LAFR in the treatment of esophageal carcinoma remains to be evaluated. A multi-center prospective randomized controlled phase III trial should therefore be conducted to compare the efficacy of LAFR and CRT. Prior to this phase III trial, however, we conducted this preliminary small-sample study to test the efficacy and side effects of LAFR. Since no standard CRT schemas are currently available in China, a phase I trial was performed to obtain the MTD of CRT for Chinese patients with esophageal carcinoma (9). The MTD was used as the CRT regimen, making it feasible to carry out this study.

Results of the present study showed that the overall survival and local control rates of LAFR were lower than those of CRT, but the difference was not significant. Due to the small sample size and the relatively short follow-up period, the effects of LAFR on survival remain to be elucidated. However, LAFR achieved substantial efficacy in this study, considering that more than 60% of patients were classified as having stage III disease. The 1- and 2-year overall survival rates in the LAFR group were 63.6 and 31.6%, respectively, while the 1- and 2-year local control rates were 54.5 and 39%, respectively.

The survival rates of LAFR patients in our study was not comparable to that reported previously (7). However, only 36.4% of patients were classified as having stage II disease in our LAFR group, and this proportion was much lower than that of the previous study, in which more than 60% of patients had stage I-IIA of the disease. However, the subgroup analyses showed that patients with stage II in the LAFR group achieved favorable survival rates. The 2-year overall survival rate in the LAFR group was 75%, similar to the 87.5% in the CRT group ($\chi^2$=1.238; P=0.266). Therefore, LAFR was found to be as effective as in a previous study for treating early-stage esophageal carcinoma (7). The overall survival rate of stage II patients in this study was also higher than that of stage III patients (P=0.001). These results indicate that esophageal carcinoma can be staged relatively accurately based on CT without ultrasound. Moreover, stage II patients achieved similar survival rates to those in a previous LAFR trial that recruited only T2N0M0 patients and for which the 2-year overall survival rate was 66.8% (19). Therefore, LAFR results from our study are consistent with those from previous studies (7-19), at least with regards to early-stage esophageal carcinoma.

The incidence of hematological toxicities, severe nausea and vomiting, and severe anorexia in the LAFR group was found to be significantly lower than that in the CRT group, indicating that LAFR is associated with fewer side effects in patients, thus making it more clinically feasible. Since fewer side effects were observed, patients in the LAFR group required less supportive treatment. In addition, LAFR is more cost-effective than CRT in China, which is of great significance to Chinese patients presenting with esophageal carcinoma since the majority of patients are from poverty-stricken regions.

In our study, the outcome of clinical stage III patients was discouraging. The 2-year overall survival rate in the LAFR group was 0%. On the other hand, although the 2-year overall survival rate in the CRT group has yet to be determined, the 23-month survival rate was 35.7%. Consequently, it is imperative to improve the outcome of clinical stage III patients. In patients treated with LAFR, locoregional failure is one of the main patterns of failure in esophageal carcinoma treatment, based on our study and those of other authors (4,7). Intensity-modulated radiotherapy (IMRT) technology improves the irradiation dose for tumors while sparing normal tissues (20). Wang e*t al* (21) have reported that the results of an IMRT study for esophageal carcinoma and the preliminary survival outcomes were encouraging. If IMRT technology is used in the LAFR regimen, higher doses may be delivered to the tumors and better local control may be obtained. More and more molecular-targeted therapies are used for esophageal carcinoma due to the over-expression of epidermal growth factor receptors associated with this disease (22,23). In the future, LAFR with IMRT technology combined with cetuximab (C225), gefitinib and erlotinib is a potential treatment modality for patients with esophageal carcinoma. However, in the present study, the major cause of death in the CRT group was distant metastasis, indicating that for CRT more attention should be focused on developing new chemotherapeutic drugs, such as paclitaxel (24,25) and irinotecan (26), to reduce metastasis.

In our small-sample exploratory study, the overall survival and local control rates of LAFR patients were lower than those of CRT patients, but the difference was not significant. LAFR achieved a positive outcome for clinical stage II patients, similar to those for CRT. LAFR is also more cost-effective than CRT. Considering that more than 60% of patients were classified as having stage III disease, LAFR achieved substantial efficacy with fewer side effects when compared to CRT. Based on this study, the effectiveness of LAFR in treating esophageal cancer is currently being evaluated in a prospective phase III trial.

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