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*Original Article*

# Prognostic factors for survival of patients with esophageal squamous cell carcinoma following radiotherapy

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**Abstract:** Background: Prognostic factor is desperately needed to help predict outcomes of patients with esophageal cancer treated by radiotherapy. Materials and Methods: We retrospectively analyzed the probable prognostic factors which could be attained easily through general clinical examinations and imaging parameters without surgical approaches. General clinical features included sex, age, smoking, anemia, lesion location and radiation field. Imaging parameters included the lesion length defined by esophageal barium swallow and lesion characteristics on CT imaging, such as lymph nodes metastasis, volume of the primary lesion (GTV-E), the volume of positive lymph nodes (GTV-LN), and the total gross tumor volume (GTV-T = GTV-E + GTVLN). Results: The 3-year overall survival rate was 20.3%, with a median follow-up of 31.2 months (range: 8-54 months) for patients who were still alive. On univariate analysis, anemia, lesion location, lesion length by barium esophagogram, computed tomography imaging characteristics including lymph nodes metastasis, GTV-E, GTV-LN, GTV-T were prognostic for overall survival. By multivariate analysis, only anemia [hazard ratio (HR) 0.51, 95% CI 0.30-0.84, P = 0.02] and the GTV-T (HR 0.78, 95% CI 0.62-0.95, P = 0.01) were independent prognostic factors for survival. Conclusion: We recommend that GTV-T and anemia could be the best predictors for survival of ESCC patients who treated by 3D-CRT or IMRT.

**Keywords:** Esophageal squamous cell carcinoma, radiotherapy, prognostic factor

## Introduction

Esophageal cancer (EC) is the fifth most common cancer and the forth leading cause of cancer deaths in China. Different from the western countries, esophageal squamous cell carcinoma (ESCC) accounts for 95% of all Chinese EC patients [1]. Due to no typical symptoms in early stage, many patients are diagnosed at advanced stage in china. For these patients, the results of Radiation Therapy and Oncology Group (RTOG) 85-01 have made definitive chemoradiotherapy (CRT) to one standard treatment option [2]. However, not all patients are good candidates for chemoradiotherapy due to the presence of multiple co-morbid medical conditions. Thus, radiotherapy alone for ESCC is also a very important treatment in china. Prognostic factor is an important index for evaluating effectiveness of radiotherapy. The conventional tumor node metastasis (TNM) staging system has long been used to predict the outcomes of patients with esophageal cancer after non-surgical treatment. However, the current TNM staging category of esophageal cancer is wholly based on pathological findings from surgery [3]. It is inapplicable in patients treated with a non-surgical method, especially radiation therapy. Thus, prognostic factors other than pathological findings are desperately needed to help predict outcomes or make clinical decisions.

In this study, we retrospectively analyze prognostic the factors associated with survival of inoperable esophageal squamous cell carcinoma (ESCC) patients who treated by three dimensional conformal (3D-CRT) or intensity modulated radiotherapy (IMRT) and tried to find the probable prognostic factors which could be

attained easily through general clinical examinations without surgical approaches.

## Patients and methods

### *Patients*

79 patients with pathologically confirmed ESCC, who received 3D-CRT or IMRT treatment in the First Affiliated Hospital of Bengbu Medical College from January 2008 to June 2013, were retrospectively analyzed. The study was approved by ethics committee of the First Affiliated Hospital of Bengbu Medical College, and all patients gave their written informed consent. All patients underwent the following examinations: ultrasound examination of the lymph nodes of the neck, chest radiography; chest computed tomography (CT) scan, esophageal barium tomography, ultrasound examination of the abdomen, liver and renal function tests, electrocardiography and blood cell counts. Lymph nodes that were well vasculated, measured more than 8 mm in the short axes, and showed central necrosis or extracapsular extension in CT examination were considered malignant [4]. 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 [5]. 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. The patients were treated with definitive radiotherapy or chemoradiotherapy because the disease was not amenable to resection, patients had multiple medical co-morbidities that would preclude surgery or the patient declined surgery. The patients were treated with radiotherapy alone if aged over 75 or other co-morbid medical conditions precluded them from receiving concurrent chemotherapy or the patient declined chemotherapy.

### *Radiotherapy*

CT images were obtained from the angulus mandibular level to the lower border of the second lumbar vertebra and 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 total dose of GTV-E or GTV-LN was 58-66 Gy. 43 patients underwent elective nodal irradiation, the first clinical target volumes (CTV) with a total dose of 54-60 Gy and the second CTV with a total dose of 50-54 Gy. 36 patients underwent involved-field irradiation with a total dose of CTV 50-54 Gy. All patients received conventionally fractionated radiotherapy at 2 Gy per fraction five times every week throughout the treatment course. 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.

### *Chemotherapy*

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

### *Clinical variables for prognostic analysis*

General clinical features included sex, age, smoking, lesion location, anemia, chemotherapy and radiation field. Imaging parameters included the lesion length defined by esophageal barium swallow, lesion characteristics on CT imaging such as lymph nodes metastasis, volume of the primary lesion (GTV-E), the volume of positive lymph nodes (GTV-LN), and the total gross tumor volume (GTV-T = GTV-E + GTV-LN).

After radiation, patients were evaluated at 3-month intervals for 1 year and at 6-month intervals thereafter until the time of disease regression. Medical history, physical examination, toxicity assessment, complete blood cell count, serum chemistry profile, chest X-ray, barium swallow, CT scan of upper gastrointestinal, abdominal, and chest and PET-CT (partly) were examined. Biopsy of the primary tumor site or regional lymph nodes was performed in partial patients who had imaging evidence of local or regional recurrence. Overall survival (OS) was calculated from the first day of irradiation.

### *Statistical analysis*

Differences in patient, tumor and treatment characteristics were assessed using the chi-

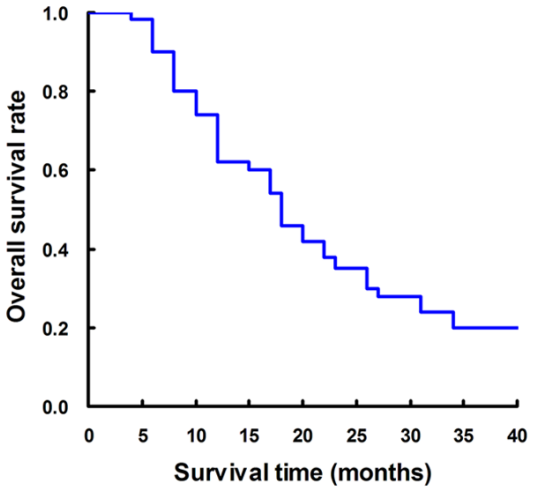


**Figure 1.** Overall survival of the 79 patients.

square test for categorical variables. Significant factors were extracted for further analysis. A univariate analysis was performed to identify factors for the multivariable model. A multivariate Cox-regression analysis was then performed to determine the relevant prognostic factors. The results are given as hazard ratios with their 95% confidence interval (CI). The overall cumulative probability of survival was calculated by the Kaplan-Meier method, and the difference of the survival curves was assessed by the Log-Rank test. For the analysis of 3-year overall survival, events were defined as death from any cause being estimated from first day of radiotherapy until date of death or date of last follow-up. All analyses were performed with SPSS (version 17.0; Chicago, IL). All reported *P* values were 2-sided with a value < 0.05 considered statistically significant.

## Results

*The clinical characteristic of the patients*

A total of 79 locally advanced ESCC patients (62 men, 17 women) were enrolled into this trial (median age 62 years, range 42-90 years). For 14 patients (17.7%), the tumors were located in the lower third of the esophagus. Meanwhile, the tumors were located in the middle third and upper third of the esophagus for 41 (51.9%) and 24 (30.4%) patients, respectively. The follow-up period ranged from 8 to 54 months for all patients with a median of 31.2 months. 2 of the patients were lost to follow-up.

*Overall survival rate*

Overall survival curves for the 79 patients are shown in **Figure 1**. The 1-, 2-, and 3-year overall survival rate was 62.0, 35.4 and 20.3%, respectively. The median overall survival time was 13.8 months (95% confidence interval (CI) 8.6, 56.6).

*Predictors of overall survival*

We performed an analysis to identify factors that predicted for OS for patients with ESCC. Sex, age, smoking, anemia, primary esophageal tumor location, tumor length, anemia, chemotherapy and radiation field, lymph nodes metastasis, GTV-E, GTV-LN and GTV-T were subjected to univariate analysis (**Table 1**). The results suggested that several variables including tumor location (P = 0.03), anemia (P = 0.001), lymph nodes metastasis (P = 0.02), tumor length (P = 0.03), GTV-E (P = 0.02), GTV-LN (P = 0.01) and GTV-T (P = 0.01) were significantly associated with the OS. To identify independent prognostic factors, the factors that were found to be significant on univariate analysis were subjected to multivariate analysis. Multivariate analysis revealed that anemia (P = 0.02) and GTV-T (P = 0.01) were independent factors affecting OS in ESCC patients (**Table 2**). The survival curves with different GTV-T and anemia status are shown in **Figures 2** and **3**.

## Discussion

Esophageal cancer is the eighth most common cancer worldwide [6]. In China, esophageal cancer is endemic and the majority of cases are squamous cell cancer (SCC). Radiation therapy is the most commonly used treatment method for patients with this disease under the following conditions: firstly, unresectable disease; secondly, resectable disease, but with medical co-morbidities that would preclude surgery; thirdly, patients declined surgery. Since the report of RTOG 85-01 trial in 1999, concurrent chemoradiotherapy has been widely accepted as the standard treatment for patients with EC who are treated with non-surgical methods. But in china, many ESCC patients can not tolerant chemotherapy for many reasons such as were diagnosed at age > 70 years old or at advanced stage.

**Table 1.** Univariate analysis of prognostic factors for survival of patients

| Feature | | Cases | 3-yr OS (%) | $\chi^2$ value | *P* value |
|---|---|---|---|---|---|
| Sex | Male | 62 | 19.4 | 1.35 | 0.98 |
| | Female | 17 | 23.5 | | |
| Age (y) | ≤ 60 | 22 | 22.7 | 1.24 | 0.75 |
| | > 60 | 57 | 19.3 | | |
| Smoking | Never | 41 | 22.0 | 1.30 | 0.86 |
| | Yes | 38 | 18.4 | | |
| Location | Upper | 24 | 25.0 | 4.35 | 0.03 |
| | Middle | 41 | 19.5 | | |
| | Lower | 14 | 14.3 | | |
| Hemoglobin (g/dl) | Anemia | 16 | 6.3 | 6.68 | 0.001 |
| | Non-anemia | 63 | 23.8 | | |
| Tumor length (cm) | ≤ 5 | 30 | 26.7 | 4.32 | 0.03 |
| | > 5 | 49 | 16.3 | | |
| Lymph node metastasis | N0 | 33 | 24.2 | 4.48 | 0.02 |
| | N+ | 46 | 17.4 | | |
| GTV-E ($cm^3$) | ≤ 45 | 37 | 24.3 | 4.46 | 0.02 |
| | > 45 | 42 | 16.7 | | |
| GTV-LN ($cm^3$) | ≤ 5 | 18 | 22.2 | 4.38 | 0.02 |
| | > 5 | 28 | 14.3 | | |
| GTV-T ($cm^3$) | ≤ 50 | 33 | 27.8 | 4.65 | 0.01 |
| | > 50 | 46 | 15.2 | | |
| Radiotherapy | 3D-CRT | 10 | 20.0 | 1.03 | 1.82 |
| | IMRT | 69 | 20.2 | | |
| Radiation field | ENI | 36 | 22.2 | 1.12 | 0.63 |
| | IFI | 43 | 18.6 | | |
| Chemotherapy | Yes | 29 | 24.1 | 1.06 | 0.36 |
| | No | 50 | 18.0 | | |

N0: No positive lymph node was observed; N+: Periesophageal lymph node with longest diameter of ≥ 5 mm, mediastinal lymph nodes or supraclavicular lymph nodes with shortest diameter of ≥ 10 mm; OS: Overall survival; GTV-E: Gross tumor volume of primary lesion; GTV-LN: Volume of positive lymph nodes; GTV-T: Total gross tumor volume. ENI: elective nodal irradiation; IFI: involved-field irradiation; anemia: Hb level of less than 12 g/dl for men and less than 11 g/dl for women.

In this study, we retrospectively analyzed 79 cases of ESCC that were treated with 3D-CRT or IMRT with or without chemotherapy. We selected general clinical features including gender, age, lesion location, chemotherapy, radiation field and imaging parameters of lesion characteristics on computed tomography imaging in the prediction analysis. These factors could be attained easily through general clinical examinations without surgical approaches. We found clinical features including sex, age, smoking, chemotherapy and radiation field were not prognostic factors for survival of non-surgical ESCC patients.

In many countries, surgical treatment should be considered for all localized esophageal cancer. However, surgical resection is possible in only 15-20% of patients because of the tumor site or comorbid disease. In addition, the outcome of surgery is not satisfactory with only 15-24% 2-year survival rate [7]. In this current retrospective review, a 3-year OS rate of 20.3% was observed. In this cohort, many patients were diagnosed at advanced stage or with medical co-morbidities. This was an encouraging result of non-surgical ESCC following definitive radiotherapy compared with conventional radiotherapy in last century. We hypothesize that the improvement in outcome may be a function of increased dose conformity and improved tumor targeting. These advances in 3DCRT or IMRT likely lead to decreased treatment related toxicities and reduced the potential for "marginal misses" [8, 9].

When considered high incidence of nodal failure and distant failure in combined modality therapy in local advanced ESCC, chemotherapy seems to play a limited role in preventing local regional or distant failure. In our study, we compared 3-year OS in radiotherapy and chemoradiotherapy, and found that there was no significant difference in OS rate between patients with or without chemotherapy. However, van Hagen et al. reported that the rate of complete pathological response was a relatively satisfactory 49% in patients who received preoperative chemoradiotherapy for esophageal or junctional SCC [10]. In our study, cohort consisted of a high proportion of patients with advanced stage and only 36.7% of patients received chemotherapy. Thus, it is difficult to define the precise role of chemotherapy in locally advanced ESCC due to the limitations of this retrospective study.

**Table 2.** Multivariate analysis of prognostic factors for survival of patients

| Variable | β | *P* value | HR | 95% CI for HR |
|---|---|---|---|---|
| Tumor location | 0.52 | 0.26 | 1.32 | 0.85-2.10 |
| Anemia | -2.64 | 0.02 | 0.51 | 0.30-0.84 |
| lymph nodes metastasis | -0.74 | 0.15 | 1.04 | 0.89-1.94 |
| tumor length | -0.68 | 0.35 | 1.26 | 0.90-1.58 |
| GTV-E | -1.22 | 0.08 | 1.21 | 0.81-1.49 |
| GTV-LN | -0.35 | 0.10 | 1.10 | 0.92-1.75 |
| GTV-T | -2.95 | 0.01 | 0.68 | 0.62-0.95 |

GTV-E: Gross tumor volume of primary lesion; GTV-LN: Volume of positive lymph nodes; GTV-T: Total gross tumor volume; anemia: Hb level of less than 12 g/dl for men and less than 11 g/dl for women.

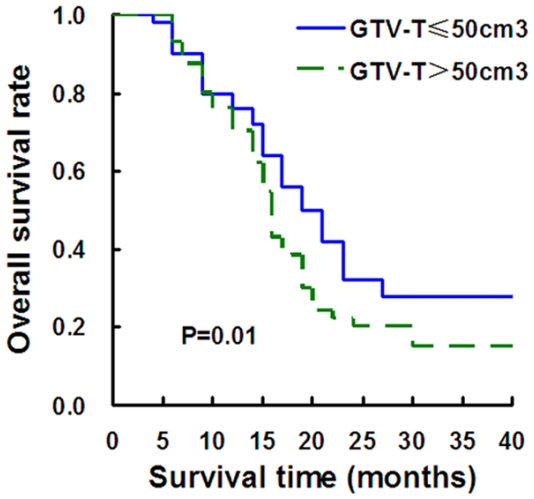


**Figure 2.** Overall survivals of the different total target volume (GTV-T) patients.

A few studies have reported that there is an association between tobacco smoking and poor prognosis in esophageal cancer epidemic countries [11, 12]. Particularly in Korea, more than 85% of esophageal cancer patients show squamous cell carcinoma, which is well-known to have an association with smoking or alcohol use [13]. Little information is available on the association between this habit and prognosis of ESCC. Tobacco may have a direct effect on tumor progression or may increase mortality from complications of treatment modalities. But in our study, we found no association between cigarette smoking and survival (P = 0.86).

For non-surgical ESCC, tumor length is still a controversial prognostic factor. Tachibana et al. evaluated 129 patients with ESCC and indicated that tumor length was related to survival but was not an independent prognostic factor on multivariate analysis [14]. Bollschweiler et al. demonstrated similar results [6]. However, several researchers have determined tumor length to be an important prognostic indictor of EC after surgery [15-17]. Eloubeidi et al. analyzed the outcomes of 10441 EC patients from the National Cancer Institute Surveillance, Epidemiology, and End Results database [18]. Their results demonstrated that tumor length was an important prognostic factor of overall survival for patients with EC. In our study, we found that the tumor length (≤ 5.0 cm versus > 5.0 cm) is a predictive factor for overall survival in advanced patients with ESCC but was not an independent prognostic factor on multivariate analysis.

In our study, many potential prognostic tumor factors such as lesion location, anemia, lymph nodes metastasis, tumor length, GTV-E, GTV-LN and GTV-T achieving significance in univariate analysis were identified. However, only anemia and GTV-T maintained independent prognostic factors for OS on multivariate analysis. The outcomes and factors that predict overall survival in patients treated with radiotherapy alone should also be considered in the management of esophageal cancer.

Anemia is known to be a common condition in cancer patients, and about 30% of cancer patients suffer from anemia. Disorders of iron metabolism, blood marrow insufficiency or metastases, malnutrition, bleeding at tumor site, catabolism of patients with tumor burden and relative deficiency of erythropoietin all play a role in anemic pathogenesis. Recent studies showed that anemia was associated with poor prognosis and an increased risk of relapse [19, 20]. In our study, we found that 3-year OS was 23.8% and 6.3% in the non-anemic and anemic group respectively. Similarly, Zhao et al. analyzed the effect of anemia on survival in 303 patients with locally advanced esophageal carcinoma undergoing irradiation and reported that there was a statistically significant reduction in survival and loco-regional control rates [21]. Several hypotheses have been proposed to explain the relationship between anemia and cancer. First, anemia is known to produce tumor hypoxia which has oncogenic actions

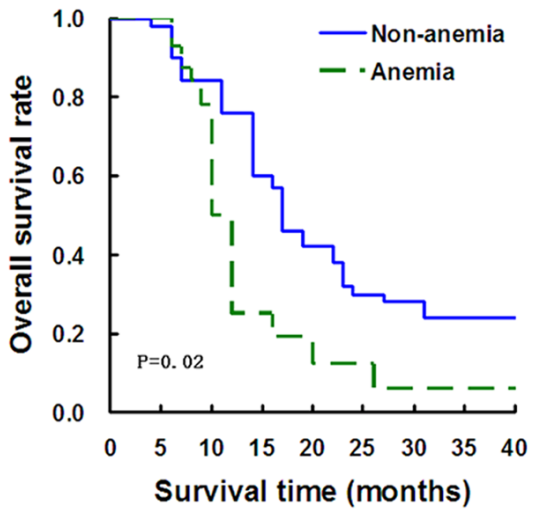


**Figure 3.** Overall survivals of the anemia and non-anemia patients.

through the associated genomic instability, mutagenesis and disordered cell growth [22]. Tumor hypoxia also confers radio-resistance through the hypoxia-associated reduction in free-radical production and consequent radiotherapy-induced DNA damage [23]. Second, bulky tumors might have a more anemic condition compared with small volume tumors.

The total gross tumor volume (GTV-T) is an important prognostic factor following radiotherapy. Perhaps, larger GTV-T means heavier tumor load, increasing numbers of radio resistant hypoxic tumor cells and clonogenic cells and greater limitation of relevant organs at risk that lead to poor survival, which has been regarded as an important predictive factor for cancer such as lung, breast and head and neck [4]. In recent years, many documents regarded GTV-T as an important prognostic factor for non-surgical ESCC. Xu et al. retrospectively analyzed 607 cases of esophageal carcinoma and found that there was a significant difference of the GTV-T volumes of EC patients with lymph node metastasis [24]. Cox regression model analysis showed that GTV-T volume was an independent prognostic factor of OS. Chen et al. [4] retrospectively analyzed 153 ESCC patients treated with 3D-CRT and found that the GTV-T was the best predictor for OS. In our study, we found significant difference of overall survival between GTV-T $\leq$ 50 $cm^3$ and GTV-T > 50 $cm^3$ patients by multivariate analysis, which was similar to other relative researches. So we regarded GTV-T as an independent prognostic factor of OS for ESCC.

## Conclusion

In conclusion, our study found that 3D-CRT or IMRT with or without chemotherapy should be considered as a definitive treatment option for patients with inoperable ESCC. Anemia or large GTV-T predicted for worse survival which may provide additional prognostic information to the non-surgical staging system and clinical decision making for ESCC. However, in our study, cohort consisted of a high proportion of patients with advanced stage, who had worse prognosis. Moreover, this was a retrospective study with a relatively small sample size, which may limit the generalizability of our findings. Further observations with large-scale, multi-center, prospective trials are needed to verify the best prognostic factors for non-surgical ESCC population.

## Disclosure of conflict of interest

None.

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