RESEARCH ARTICLE

Prognosis impact of clinical characteristics in patients with inoperable esophageal squamous cell carcinoma

Ying Yang, Jun Jia, Zhiwei Sun, Feng Du, Jing Yu, Chuanling Liu, Yanjie Xiao, Xiaodong Zhang*

Key laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), VIP-II Gastrointestinal Cancer Division of the Department of Medicine, Peking University Cancer Hospital and Institute, Haidian District, Beijing, China

*zhangxd0829@163.com

Abstract

Background

Patients with inoperable esophageal squamous cell carcinoma (ESCC) were not homogeneous and their outcomes were widely divergent. There was a lack of identified clinical factors related to prognosis; and there were no previous studies constructing prognosis score to predict survival and guide treatment.

Methods

In this retrospective cohort study, twelve clinical characteristics of one hundred and twenty inoperable ESCC patients were collected at diagnosis and analyzed by Cox regression model. Various methods including univariate analysis, confounding adjusted multivariate analysis and model selection were applied to determine factors associated with poor prognosis; and prognosis score was built on established factors.

Results

Four characters were identified as poor prognosis factors, including mid- and low-thoracic tumor (aHR = 2.20, 95% CI = 1.03, 4.72), abdominal and retroperitoneal lymph node metastasis (aHR = 1.62, 95% CI = 1.00, 2.64), albumin no more than 39g/L (aHR = 2.81, 95% CI = 1.24, 6.41) and hematogenous metastasis (aHR = 1.61, 95% CI = 0.97, 2.69). Patients were stratified into three groups by prognosis score, that was, good survival with none of four identified factors (score zero), poor survival with three to four factors (score three to four) and median with one to two factors (score one to two), survival of three groups were statistically different ($p_{\text{trend}} = 0.020$).

Conclusion

Prognosis score based on selected clinical characteristics could predict survival among inoperable ESCC patients, which was critical for individualized treatment and central of precise medicine.
Introduction

Esophageal cancer is a malignant disease seriously threatening human health and lives. In 2012, it was estimated that 455,800 new cases and 400,200 deaths of esophageal cancer occurred globally, which ranked the eighth in incidence and the sixth in mortality of cancers [1]. The mortality of esophageal cancer in China was the highest in the world. Chinese epidemiology data showed that there were estimated 477,900 incident cases and 375,000 deaths of esophageal cancer in 2015, which ranked the third in incidence and the fourth in mortality, respectively [2–4].

The major pathology types of esophageal cancer comprise of squamous cell carcinoma, adenocarcinoma and neuroendocrine carcinoma. In western countries and the US, approximately 50% of esophageal cancers are adenocarcinoma [5]; while in Asian countries especially in China, about 90% are squamous cell carcinoma and incidence is increasing [6, 7]. In general, the overall survival of esophageal cancer is as low as about 20% [8].

Surgery is the recognized best option to eradicate localized esophageal cancer. However, due to diverse impacts such as tumor location, comorbidities and patients’ will, only 15–20% of patients eventually receive surgical procedure, leaving quite a number of patients inoperable [8–12].

Although there is a lack of Chinese research data, taking international studies and our practice experience into account, it should be aware of that inoperable patients are the majority of esophageal squamous cell carcinoma (ESCC) with very poor prognosis in China; meanwhile, by our clinical observations, patients not receiving surgery are a heterogeneous population, with prominently different prognoses; and for the most benefit of patients, it is worthwhile to find factors predicting their survival and classify them by their prognoses, which would provide the basis and evidence for future precise treatment decisions.

To our knowledge, there were no widely accepted molecular markers related to ESCC survival, and even research on clinical factors in ESCC prognosis was little; thus in this study we tried to explore the association between the clinical features and survival in patients with inoperable ESCC, and also to stratify patients by their prognosis prediction factors, which might be of help to future treatment guidance.

Methods

Study population

A total of 196 esophageal cancer patients were treated in the VIP-II Gastrointestinal Cancer Division of the Department of Medicine, Peking University Cancer Hospital and Institute, from August 2012 to February 2016. Two patients rejected to attend the investigation and were excluded from our further analysis. The response rate was 98%. Of all included participants, 181 were squamous cell carcinomas, 11 were neuroendocrine carcinomas and 2 were adenocarcinomas. All were historically confirmed cases. Of the 181 ESCC patients, 61 received surgery and the other 120 patients did not because of advanced stages, tumor locations, comorbidities or refusal. All 120 inoperable patients were included in our study.

Study design

It was a retrospective cohort study. The outcome was overall survival (OS), which was calculated as the number in months from the date of diagnosis to the date of death or the date of last follow-up on November 16th, 2016. The average follow-up was 40 months, ranging from 6 to 104 months. The exposures were twelve clinical and pathologic characteristics at diagnosis, including age, gender, comorbidities, and family history of cancers, multiple lesions, tumor
location, differentiate grade, and lymphatic metastasis, hematogenous metastasis, and loss of weight, albumin and hemoglobin.

Some exposures were defined as follows. By endoscopy examinations, “multiple lesions” referred to more than one spot of malignant lesions that were separated by grossly normal tissues; and “tumor location” was measured in centimeters (cm) from the incisor to the superior boarder of tumor. 25cm was set as the cut-off and it was dealt as “non-applicable (NA)” if multiple lesions spread across the boundary of 25cm. Lymphatic and hematogenous metastasis was assessed by a variety of means such as esophagoscopy, esophageal ultrasonography, computed tomography (CT), Magnetic Resonance Imaging (MRI) or positron emission tomography-computed tomography (PET-CT) scans. We took “lymphatic metastasis” as four fields—cervical and supraclavicular lymph nodes, mediastinum lymph nodes, abdominal and retroperitoneal lymph nodes and other areas.

**Statistical analysis**

Univariate analysis and multivariate analysis adjusting for confounders were used to identify prognosis related factors. We also applied model selection to opt for factors significantly related to survival. All survival analyses were performed by Cox proportional hazard regression model. All factors included in the regression model were tested for proportional hazard assumptions and no violations were detected. Integrated the results of univariate analysis, multivariate analysis and model selection into account, factors statistically significantly associated with poor prognosis were established as prognosis factors and the count of prognosis factors served as prognosis score. Furthermore, patients were stratified by their prognosis score; and the corresponding survival intervals were compared by the log-rank test and the survival curves were plotted by the Kaplan-Meier method. All statistical analyses were two-sided, and $p < 0.05$ were treated as statistical significance. Results were presented by hazard ratios (HRs) and 95% confident intervals (95% CIs). All analyses and plots were conducted by SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

The study was approved by the Institutional Review Board of Peking University Cancer Hospital and Institute.

**Results**

The median age at diagnosis was 60 years of age, varying from 44 to 79 years. 78% of patients were male while 22% were female. 11% of patients were with multiple lesions. In terms of tumor location, about 70% located at 25cm and lower, that was mid- and low- thoracic ESCC. 87% of inoperable ESCC patients were with lymphatic metastasis, and among these patients 50% were with abdominal and retroperitoneal lymph node invasion. Hematogenous metastasis was found in 23% of patients, and further stratification revealed that 52% were lung metastasis, 22% were liver metastasis and 11% were bone metastasis. The mean albumin was 43.5g/L, with a range of 29.9g/L to 51.0g/L. The mean hemoglobin was 141.4g/L and the range was from 92.0 g/L to 175.0g/L. OS was from 0 to 63 months and its median was 16 months. By the date of last follow-up, 62% of patients died and 7% were loss of follow-up; and the others were still alive. As for treatment, 5% received solely radiotherapy and 24% received chemotherapy only; and 71% received multidisciplinary treatment that centered on chemoradiotherapy (CRT) and included other modalities such as radiofrequency ablation and “gamma knife”. The results were shown in Table 1.

Univariate analysis showed that tumor located at 25cm and lower (cHR = 2.39, 95% CI = 1.13, 5.05), lymphatic metastasis (cHR = 2.64, 95% CI = 1.06, 6.56), hematogenous metastasis (cHR = 1.71, 95% CI = 1.03, 2.84), and albumin $\leq$39g/L (cHR = 2.46, 95% CI = 1.10, 5.51)
Table 1. Clinical characteristics of inoperable ESCC patients (n = 120).

| Characteristics                                      | Counts | Percentage (%) |
|------------------------------------------------------|--------|----------------|
| Age (years) (median) (range)                         | 60 (44–79) |                |
| Gender                                               |        |                |
| Male                                                 | 93     | 78             |
| Female                                               | 27     | 22             |
| Past medical history                                 |        |                |
| No                                                   | 54     | 45             |
| Yes                                                  | 66     | 55             |
| Cancer family history                                |        |                |
| No                                                   | 86     | 72             |
| Yes                                                  | 34     | 28             |
| Multiple lesions                                     |        |                |
| No                                                   | 104    | 89             |
| Yes                                                  | 13     | 11             |
| Tumor location                                       |        |                |
| <25cm                                                | 23     | 20             |
| ≥25cm                                                | 82     | 70             |
| NA                                                   | 12     | 10             |
| Differentiation                                      |        |                |
| High                                                 | 6      | 6              |
| Median                                               | 58     | 56             |
| Low                                                  | 40     | 38             |
| Lymphatic metastasis                                 |        |                |
| No                                                   | 16     | 13             |
| Yes                                                  | 104    | 87             |
| Abdominal and retroperitoneal lymph node metastasis  | 52     | 50             |
| Other lymph node metastasis                          | 52     | 50             |
| Hematogenous metastasis                              |        |                |
| No                                                   | 92     | 77             |
| Yes                                                  | 27     | 23             |
| Liver                                               | 6      | 22             |
| Lung                                                 | 14     | 52             |
| Bone                                                 | 3      | 11             |
| Multiple                                             | 4      | 15             |
| Loss of body weight                                  |        |                |
| No                                                   | 47     | 45             |
| Yes                                                  | 58     | 55             |
| Albumin (g/L) (mean±SD) (range)                      | 43.5±3.94 (29.9–51.0) | |
| Albumin                                              |        |                |
| <39g/L                                                | 11     | 10             |
| >39g/L                                                | 95     | 90             |
| Hemoglobin (g/L) (mean±SD) (range)                   | 141.4±16.7 (92.0–175.0) | |
| Treatment                                            |        |                |
| Chemotherapy only                                    | 28     | 24             |
| Radiotherapy only                                    | 6      | 5              |
| Comprehensive therapy                                | 82     | 71             |
| OS (months) (median) (range)                         | 16 (0–63) |                |

(Continued)
were associated with poor prognosis. It was worth noting that abdominal and retroperitoneal lymph node metastasis (cHR = 1.76, 95% CI = 1.10, 2.83) was related to unfavorable prognosis. Next, we adjusted for age and gender whenever possible, the adjusted analyses revealed very similar results. Specifically speaking, mid- and low-thoracic tumor (aHR = 2.20, 95% CI = 1.03, 4.72), abdominal and retroperitoneal lymph node metastasis (aHR = 1.62, 95% CI = 1.00, 2.64) and low albumin (aHR = 2.81, 95% CI = 1.24, 6.41) were statistically significantly related to lower survival; while lymphatic metastasis (aHR = 2.36, 95% CI = 0.93, 5.98) and distant metastasis (aHR = 1.61, 95% CI = 0.97, 2.69) were marginally significant. All analyses were presented in Table 2.

In addition, we put all twelve exposure variables that included age, gender, past medical history, and family history of cancer, multiple lesions, tumor location, and differentiation, lymphatic metastasis, hematogenous metastasis, and loss of weight, albumin and hemoglobin into one multivariate model, and applied stepwise selection. After model selection, hematogenous metastasis and low albumin entered into the final model; and the aHRs were 1.68 (95% CI = 1.00, 2.84) and 2.35 (95% CI = 1.05, 5.29), respectively.

Taking results of univariate analysis, adjusted analysis and model selection into consideration, tumor location $\geq 25$cm, abdominal and retroperitoneal lymph node metastasis, hematogenous metastasis and albumin $\leq 39g/L$ were determined as poor prognosis factors. Each factor scored one point and a patient’s “prognosis score” was the sum of all factors, ranging from 0 to 4. The corresponding cases and median OS were shown in Table 3. The $P_{\text{trend}}$ for groups was 0.012.

Besides, we stratified patients into three groups by their prognosis score—good with score zero, median with score one to two and poor with score three to four. 15% of patients were good prognosis with median OS of 20 months; and 19% were poor prognosis with median OS of 9 months. Results were listed in Table 4 and the corresponding Kaplan-Meier curves were presented in Fig 1. The three prognosis groups separated clearly and $P_{\text{trend}}$ was 0.020.

In the end, we analyzed the association between treatment modalities and prognosis. By adjusting for age, gender, tumor location, and hematogenous metastasis, abdominal and retroperitoneal lymph node invasion and albumin level, comprehensive therapy, primarily CRT was significantly related to longer survival, compared with chemotherapy only (aHR = 0.27, 95% CI = 0.15, 0.51), Results were seen in Table 5.

**Discussion**

In patients with inoperable ESCC, we built prognosis score based on four clinical factors including tumor located at 25cm and lower, abdominal and retroperitoneal lymph node invasion, hematogenous metastasis and albumin level no more than 39g/L; and found that survival of patients with none of the four factors was significantly better than those with three to four factors.

There had been an assortment of prognosis score systems derived from cancer features and host properties, such as the Physiologic and Operative Severity Score for the Enumeration of
Mortality and Morbidity (POSSUM) [13], POSSUM adjusted for esophagogastric surgery [14], and Portsmouth POSSUM (P-POSSUM) [15], Glasgow Prognostic Score (GPS) [16], and Association of Coloproctology of Great Britain and Ireland scoring system [17]. Nevertheless, all those prognosis score models were to estimate post-operation comorbidity and mortality, and none of them were particularly for ESCC; thus their accuracy and application for prediction of inoperable ESCC long-term survival were equivocal.

### Table 2. Association between clinical characteristics and prognosis of inoperable ESCC patients.

| Characteristics                          | Univariate analysis | Adjusted analysis * |
|------------------------------------------|---------------------|---------------------|
|                                          | cHR (95% CI)        | p value             | aHR (95% CI)        | p value             |
| Age                                      | 0.99 (0.96, 1.02)   | 0.546               | 0.99 (0.96, 1.02)   | 0.509               |
| Gender                                   |                     |                     |                     |                     |
| Male                                     | 1.00                |                     | 1.00                |                     |
| Female                                   | 0.61 (0.33, 1.12)   | 0.108               | 0.61 (0.33, 1.10)   | 0.104               |
| Past medical history                     |                     |                     |                     |                     |
| No                                       | 1.00                |                     | 1.00                |                     |
| Yes                                      | 1.08 (0.67, 1.74)   | 0.743               | 1.09 (0.66, 1.82)   | 0.738               |
| Cancer family history                    |                     |                     |                     |                     |
| No                                       | 1.00                |                     | 1.00                |                     |
| Yes                                      | 0.87 (0.51, 1.49)   | 0.605               | 0.93 (0.54, 1.60)   | 0.782               |
| Multiple lesions                         |                     |                     |                     |                     |
| No                                       | 1.00                |                     | 1.00                |                     |
| Yes                                      | 1.73 (0.87, 3.42)   | 0.116               | 1.65 (0.83, 3.28)   | 0.156               |
| Tumor location                           |                     |                     |                     |                     |
| <25cm                                     | 1.00                |                     | 1.00                |                     |
| ≥25cm                                     | 2.39 (1.13, 5.05)   | 0.022               | 2.20 (1.03, 4.72)   | 0.042               |
| Differentiation                          |                     |                     |                     |                     |
| Low                                      | 1.00                |                     | 1.00                |                     |
| Median                                   | 1.22 (0.71, 2.08)   | 0.474               | 1.26 (0.74, 2.17)   | 0.394               |
| High                                     | 1.18 (0.35, 3.94)   | 0.791               | 1.20 (0.36, 4.04)   | 0.771               |
| Lymphatic metastasis                     |                     |                     |                     |                     |
| No                                       | 1.00                |                     | 1.00                |                     |
| Yes                                      | 2.64 (1.06, 6.56)   | 0.037               | 2.36 (0.93, 5.98)   | 0.072               |
| Abdominal and retroperitoneal lymph node metastasis |   |                     |                     |                     |
| No                                       | 1.00                |                     | 1.00                |                     |
| Yes                                      | 1.76 (1.10, 2.83)   | 0.019               | 1.62 (1.00, 2.64)   | 0.053               |
| Hematogenous metastasis                  |                     |                     |                     |                     |
| No                                       | 1.00                |                     | 1.00                |                     |
| Yes                                      | 1.71 (1.03, 2.84)   | 0.038               | 1.61 (0.97, 2.69)   | 0.068               |
| Loss of body weight                      |                     |                     |                     |                     |
| No                                       | 1.00                |                     | 1.00                |                     |
| Yes                                      | 1.25 (0.75, 2.07)   | 0.395               | 1.23 (0.74, 2.05)   | 0.415               |
| Albumin                                  |                     |                     |                     |                     |
| >39g/L                                    | 1.00                |                     | 1.00                |                     |
| ≤39g/L                                    | 2.46 (1.10, 5.51)   | 0.028               | 2.81 (1.24, 6.41)   | 0.014               |
| Hemoglobin                               | 1.01 (1.00, 1.03)   | 0.140               | 1.00 (0.99, 1.02)   | 0.551               |

*Adjusted for age and gender.

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A few of previous studies on the association between clinical characteristics and ESCC prognosis were inconsistent and inconclusive. For example, in thoracic ESCC patients, one study found that performance status, initial weight loss, lymph node stage, and serum C-reactive protein (CRP) level, cigarette smoking, and differentiation grade were related to prognosis [18]; and another reported that swallowing difficulty, cigarette smoking, number of invasive lymph nodes, and gastric cardia involvement were independent prognostic factors [19]. For another example, in patients treated with definitive CRT, a study reported that smoking history, poor differentiation and short progression free survival (PFS) were associated with unfavorable outcome [20].

In our study, we found that mid- and low-thoracic tumor, lymphatic metastasis especially abdominal and retroperitoneal lymph node invasion, distant metastasis and low albumin level were associated with poor prognosis in patients with inoperable ESCC. These findings were generally in accordance with clinical observations and consensus. Still, it should be noted that low albumin might be controversial. Several studies showed that hypoalbuminemia was related to more advanced T stage or decreased survival [21, 22]; while others revealed that decreased albumin solely was not associated with poor prognosis [23]; therefore, GPS containing CRP and albumin was introduced to estimate survival, which functioned well in some gastrointestinal cancers [24–26]. However, since CRP was easily influenced by kinds of diseases such as cardiovascular and cerebrovascular diseases, rheumatoid systemic diseases and infection, we did not take it as a reliable indicator of malignant cancer survival. Therefore, we did not adopt GPS or CRP as our prognosis factors; and we believed that low albumin was poor prognosis related and was the only modifiable factor among all four. Early intervention to boost albumin level might improve patients’ long-term outcome.

Additionally, we analyzed the impact of treatment on survival. In the RTOG 85–01 randomized trial, concurrent CRT showed beneficial 5-year survival over radiotherapy alone; and toxicity was tolerable [27, 28]. In our study, we found that patients would be benefit more from comprehensive treatment primarily CRT, comparing to chemotherapy only. Since most ESCC patients were aged and quite a number were not eligible for surgery due to complications, CRT should be considered as an optimal alternative. Taking account of our results, for

| Prognosis stratification | Prognosis score | Cases | Percentage (%) | OS (median (range)) (months) |
|-------------------------|----------------|-------|----------------|-------------------------------|
| Good                    | 0              | 14    | 15             | 20 (7–48)                     |
| Median                  | 1–2            | 62    | 66             | 16 (2–63)                     |
| Poor                    | 3–4            | 18    | 19             | 9 (0–44)                      |

$p_{\text{trend}} = 0.020$

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inoperable patients with good prognosis, comprehensive treatment should be considered as the priority, which would prolong survival even achieve cure; meanwhile, for patients with high prognosis score indicating poor survival, it might be inappropriate to administer aggressive treatment and further larger sample studies should be carried on to set up proper therapeutic models, with the aim of improving quality of life and lengthening survival to some extent.

As a retrospective cohort study, our analyses were affected by various kinds of biases. Known confounders like age and gender were adjusted in multivariate analysis and unknown confounding factors would pull results into either direction. Most interested characteristics in the study were objective measurements, so it was less likely that our results were influenced by recall bias; and measurement bias mainly pulled results into the null. Selection bias did exist and might either exaggerate or weaken the results. Besides, the sample size was small.

In the era of precision medicine, compared with other gastrointestinal tumors, research on ESCC that was one of the most important cancers in the Asian area, especially in China was...
falling far behind. Our study was the first to explore associations between clinical features and prognosis and to predict survival by the total of prognostic factors in Chinese patients with inoperable ESCC. With the consciousness that inoperable ESCC was not a homogeneous disease but without definite molecular markers for its prognosis, stratifying patients by clinical characteristics was also a means of precision medicine, which was critical and realistic in individualized treatment. Since all prognostic factors identified in our study were routinely measured at the time of diagnosis in clinical settings, prognosis score constructed in our study was practical and convenient. However, limited by sample size and inherent defects of an observational study, further larger prospective trials are warranted to confirm our findings.

Author Contributions
Conceptualization: Ying Yang, Xiaodong Zhang.
Data curation: Ying Yang, Jun Jia, Xiaodong Zhang.
Formal analysis: Ying Yang.
Funding acquisition: Ying Yang, Xiaodong Zhang.
Investigation: Ying Yang, Jun Jia, Zhiwei Sun, Feng Du, Jing Yu, Chuanling Liu, Yanjie Xiao, Xiaodong Zhang.
Methodology: Ying Yang, Xiaodong Zhang.
Project administration: Xiaodong Zhang.
Supervision: Xiaodong Zhang.
Writing – original draft: Ying Yang.
Writing – review & editing: Ying Yang, Jun Jia, Zhiwei Sun, Feng Du, Jing Yu, Chuanling Liu, Yanjie Xiao, Xiaodong Zhang.

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