Time distribution of recurrence risk of oesophageal squamous cell carcinoma with complete resection (R0) in a Chinese population

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Abstract

OBJECTIVES: We aimed to clarify the correlation between clinic-pathological characteristics and the distribution of recurrence probability during follow-up of oesophageal squamous cell carcinoma (OSCC) patients with complete resection analysis by hazard function, and to try to provide evidence-based data for optimal timing for adjuvant therapy.

METHODS: A single-institution, retrospective study was conducted on 553 Chinese patients with OSCC who underwent R0 resection between January 2005 and October 2007. Survival curves were generated using the Kaplan–Meier method, and hazard function was used to analyse the annual recurrence hazard.

RESULTS: The median recurrence-free survival time of these patients was 3.4 years. In univariate analysis, the favourable prognostic factors were gender, smoking status, a tumour length of ≤4.0 cm, tumour invasion thickness, normal level of squamous cell carcinoma (SCC) antigen, pathological T category and pathological N category. In multivariate analysis, pathological T category and pathological N category were independent prognostic factors. Overall, the recurrence hazard curve for the entire cohort showed that the first major recurrence surge began to increase from the first year at 22.97% and peaked at 1.3 years at 27.4% during follow-up. The second recurrence surge peaked during the seventh year at 13.0%. A lower recurrence risk was observed in patients with the following clinic-pathological characteristics: gender, smoking status and N0.

CONCLUSIONS: We identify the presence of two peaks for recurrence risk in Chinese patients with resectable OSCC, which might contribute to choosing the optimal timing for adjuvant therapy after an operation to decrease or delay the recurrence hazard for patients with resectable OSCC.

Keywords: Recurrence risk-free survival • Oesophageal squamous cell carcinoma • Surgery

INTRODUCTION

Oesophageal squamous cell carcinoma (OSCC) is the most common histological type of oesophageal cancer and is characterized by a high mortality rate in China [1]. The main treatment of OSCC is still complete surgical resection. Nevertheless, disease recurrence after curative resection cannot be ruled out, and the overall survival remains poor [2, 3]. A multimodal approach for OSCC patients after operation, including adjuvant chemotherapy or adjuvant chemoradiotherapy, was essential to prolong the patients’ survival [4, 5]. However, how to screen the patients with high risk of recurrence after complete surgical resection was still in exploration.

In previous studies, survival curves were used most frequently to evaluate the risk of recurrence rather than hazard functions. Compared with survival curves, hazard function calculated the rate of recurrence at any point in time among the remaining patients survived [6, 7]. This method first brought insights into the recurrence analysis of breast cancer [8-10]. Despite the controversy, the findings demonstrated that double-peaked recurrence risk of breast cancer was existing.

†The first two authors contributed equally to this work.
Patterns of recurrence and death after surgery

Table 1: Kaplan–Meier survival analysis (log-rank test) according to clinic-pathological factors in Chinese patients with oesophageal squamous cell carcinoma after surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 553</th>
<th>RFS = 3.408</th>
<th>95% CI = 2.759–4.057</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>406</td>
<td>3.003</td>
<td>2.372–3.643</td>
<td>0.037</td>
</tr>
<tr>
<td>Female</td>
<td>147</td>
<td>4.372</td>
<td>2.168–6.576</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>449</td>
<td>3.417</td>
<td>2.716–4.118</td>
<td>0.466</td>
</tr>
<tr>
<td>&gt;65</td>
<td>104</td>
<td>2.956</td>
<td>1.468–4.448</td>
<td></td>
</tr>
<tr>
<td>Smoking statusa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>205</td>
<td>4.372</td>
<td>2.490–6.254</td>
<td>0.028</td>
</tr>
<tr>
<td>Ever</td>
<td>348</td>
<td>3.003</td>
<td>2.363–3.642</td>
<td></td>
</tr>
<tr>
<td>Tumour location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>47</td>
<td>2.256</td>
<td>1.844–2.667</td>
<td>0.588</td>
</tr>
<tr>
<td>Middle</td>
<td>351</td>
<td>3.531</td>
<td>2.613–4.448</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>155</td>
<td>3.572</td>
<td>2.360–5.784</td>
<td></td>
</tr>
<tr>
<td>Tumour length (cm)b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4.0</td>
<td>276</td>
<td>3.761</td>
<td>2.947–4.575</td>
<td>0.045</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>277</td>
<td>2.564</td>
<td>1.757–3.371</td>
<td></td>
</tr>
<tr>
<td>Approach of operationc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>383</td>
<td>3.450</td>
<td>2.797–4.103</td>
<td>0.752</td>
</tr>
<tr>
<td>Right</td>
<td>170</td>
<td>2.808</td>
<td>1.294–4.322</td>
<td></td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>311</td>
<td>3.314</td>
<td>1.677–4.951</td>
<td>0.999</td>
</tr>
<tr>
<td>G2</td>
<td>262</td>
<td>3.483</td>
<td>2.394–4.573</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>131</td>
<td>3.003</td>
<td>1.991–4.014</td>
<td></td>
</tr>
<tr>
<td>Pathological T category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Tis</td>
<td>10</td>
<td>6.099</td>
<td>4.286–7.911</td>
<td>0.001</td>
</tr>
<tr>
<td>p T1</td>
<td>54</td>
<td>5.204</td>
<td>4.457–5.950</td>
<td></td>
</tr>
<tr>
<td>p T2</td>
<td>116</td>
<td>4.736</td>
<td>4.194–5.278</td>
<td></td>
</tr>
<tr>
<td>p T3</td>
<td>365</td>
<td>3.766</td>
<td>3.453–4.079</td>
<td></td>
</tr>
<tr>
<td>p T4</td>
<td>8</td>
<td>3.921</td>
<td>1.694–6.148</td>
<td></td>
</tr>
<tr>
<td>Pathological N category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p N0</td>
<td>305</td>
<td>6.833</td>
<td>5.573–8.194</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p N1</td>
<td>151</td>
<td>2.717</td>
<td>1.919–3.515</td>
<td></td>
</tr>
<tr>
<td>p N2</td>
<td>83</td>
<td>1.172</td>
<td>0.926–1.419</td>
<td></td>
</tr>
<tr>
<td>p N3</td>
<td>14</td>
<td>0.897</td>
<td>0.439–1.356</td>
<td></td>
</tr>
<tr>
<td>AJCC of p TNM stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p 0 stage</td>
<td>9</td>
<td>6.290</td>
<td>4.316–8.265</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p I stage</td>
<td>89</td>
<td>4.911</td>
<td>4.290–5.533</td>
<td></td>
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<tr>
<td>p II stage</td>
<td>238</td>
<td>4.934</td>
<td>4.553–5.315</td>
<td></td>
</tr>
<tr>
<td>p III stage</td>
<td>217</td>
<td>2.916</td>
<td>2.549–3.282</td>
<td></td>
</tr>
</tbody>
</table>

RFS: recurrence-free survival; CI: confidence interval.
aSmoking status: patients had smoked ≥10 cigarettes per week.
bBaseline length of tumor.
cApproach of operation: left approach: left transthoracic with anastomosis in the chest or neck; right approach: Ivor-Lewis oesophagogastrectomy and McKeown oesophagogastrectomy.

Patterns of recurrence after operation on patients with OSCC. To our knowledge, our study was the first one conducted on Chinese patients with OSCC, concerning the time distribution of tumour recurrence hazard. We aimed to clarify the time-varying pattern of tumour recurrence hazard for patients with radical resection and tried to determine the optimal timing for administering adjuvant therapies in an effort to decrease or delay the recurrence hazard for patients with resectable OSCC.

**MATERIALS AND METHODS**

**Study design**

Between January 2005 and October 2007, 692 patients with primary oesophageal carcinoma treated with surgical resection were included in our cohort, according to our institute’s policy. After a review of all of the clinical and pathological records, 553 patients were included in the analysis. The main eligible criteria were as follows: (i) histologically confirmed primary thoracic OSCC; (ii) previous treatment naive; (iii) no distant metastases, including supra-clavicular or celiac lymph node metastases; (iv) underwent complete resection (R0) and (v) at least 3 months of follow-up. All of the medical records were reviewed for gender, age, smoking status [12], tumour length, tumour location, TNM staging and histological grade according to the seventh edition of the AJCC Cancer Staging Manual [13], tumour biomarkers and the approach of the operation. Approaches of the operation were administered as a left (left transthoracic with anastomosis in the chest or neck) or right (Ivor-Lewis oesophagogastrectomy and McKeown oesophagogastrectomy) approach. This study was conducted in accordance with the Declaration of Helsinki, and all of the patients signed a consent form approved by the Research Ethics Committee of the Sun Yat-Sen University Cancer Center.

**Patients’ follow-up**

All patients were monitored as follows: Tumour biomarkers were tested per month and thoraco-abdominal computed tomography (TACT) was conducted every 3 months for the first 6 months, 3-month interval measurement of tumour biomarkers and 6-month

Table 2: Patterns of recurrence and death after surgery

<table>
<thead>
<tr>
<th>Years at follow-up</th>
<th>Patterns of recurrence</th>
<th>Patterns of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at risk</td>
<td>No. of recurrence</td>
</tr>
<tr>
<td>0–1</td>
<td>553</td>
<td>63</td>
</tr>
<tr>
<td>1–2</td>
<td>431</td>
<td>34</td>
</tr>
<tr>
<td>2–3</td>
<td>325</td>
<td>17</td>
</tr>
<tr>
<td>3–4</td>
<td>270</td>
<td>12</td>
</tr>
<tr>
<td>4–5</td>
<td>234</td>
<td>9</td>
</tr>
<tr>
<td>5–6</td>
<td>213</td>
<td>4</td>
</tr>
<tr>
<td>6–7</td>
<td>198</td>
<td>3</td>
</tr>
<tr>
<td>≥7</td>
<td>191</td>
<td>0</td>
</tr>
</tbody>
</table>

Total no.          | 142        | 92              | 50         |       |          | 306        | 291           | 15          | 41             |       |          |
TACT for the next 2–3 years and once a year thereafter. Survival status was obtained from our cancer center surveillance system. Final surviving status was double-checked at the last follow-up of January 2013 for all of the cases.

**Statistical analysis**

Recurrence-free survival (RFS) was calculated from the date of surgery to the date of loco-regional or distant relapse related to

Figure 1: Kaplan–Meier curves for recurrence-free survival (RFS) in 553 Chinese patients with resectable oesophageal squamous cell carcinoma analysis by clinic-pathological factors. (A) Overall RFS; (B) RFS analysis by gender; (C) RFS analysis by smoking status; (D) RFS analysis by tumour length; (E) RFS analysis by pathological T category and (F) RFS analysis by pathological N category.
oesophageal carcinoma or death from cancer. RFS curves were generated using a log-rank test. A Kernel Smoothing method was used to estimate annual hazard rates. All statistical tests were two-tailed, and a $P$-value of $\leq 0.05$ was considered statistically significant. All prognostic factors identified in the univariate analyses with a $P$-value of $<0.20$ were included in the Cox regression multivariate analyses. The Stata Statistical Software Package (release 9.0; Stata Corporation, College Station, TX, USA) was used to perform data analysis.

RESULTS

Patient characteristics

The details of the patients are given in Table 1.

The median age was 65 years (range: 30–78 years), and there were 406 males and 147 females. Patients in Stages II (238 cases) and III (217 cases) accounted for 82% of all cases. The median length of tumours was 4 cm. The majority (63%) of the tumours were located in the middle segment of the oesophagus (351/553). Approximately, half (47%) of the patients were diagnosed with histological grade 2 (262/553). Operations using the left approach were performed for 69% of all patients (383/553). Sixty-nine percent (379/553) and 68% (374/553) of the patients tested had normal levels of carcino-embryonic antigen (CEA) and SCC, respectively. Only 13 patients received adjuvant chemoradiotherapy and 73 received adjuvant chemotherapy. Adjuvant therapy was performed in 86 (15.6%) patients identified with pathologically lymph node metastasis (N stage $\geq 1$), tumours involved with proper muscle layer (T stage $\geq 3$) and good performance status $\leq 2$.

The median follow-up time was 3.8 years, and relapse was observed in 142 patients (locoregional or distant). The local recurrence was twice more than the distant recurrence in the first 3 years after surgery (Table 2). At the time of the last follow-up, 37% (206/553) of the patients were alive, 53% (291/553) of the patients had died due to a cancer-related disease and 2.7% (15/553) of the patients had died due to a non-cancer-related disease (Table 2).

Survival analysis

Overall, the median RFS was 3.4 years. In univariate analysis, clinicopathological characteristics including gender ($P = 0.037$), smoking status ($P = 0.028$), tumour length $\leq 4$ cm ($P = 0.045$), Tis ($P = 0.001$) and N0 ($<0.001$) staging favoured RFS (Table 1 and Fig. 1). The patients with normal levels of SCC had a longer RFS of 3.7 years compared with those with abnormal levels, 1.9 years ($P = 0.028$). However, the patients with normal levels of CEA showed a non-significant but slightly longer RFS—3.5 years compared with 2.6 years.

Figure 2: Annual recurrence hazard rate for 553 Chinese patients with resectable oesophageal squamous cell carcinoma. The hazard rates describe recurrence hazard for each 1-year interval.
years—of the patients with elevated levels of CEA ($P = 0.928$; Table 3). After multivariate analysis, the remaining common independent prognostic factors for RFS were pathological T ($P = 0.017$) and N staging ($P < 0.001$; Table 4).

**Recurrence hazard analysis**

Overall, the recurrence hazard curve for the entire cohort showed that the first major recurrence peak began to increase from the

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**Figure 3:** Recurrence hazard rate analysis for 553 Chinese patients with oesophageal squamous cell carcinoma undergoing surgery-related to clinic-pathological factors. (A) Gender; (B) smoking status; (C) pathological N category; (D) pathological T category; (E) histological grade and (F) surgical approaches.
Concerning the surgical approaches, the recurrence risk for the patients receiving a left approach was lower than for those receiving a right approach until 2.5 years of follow-up, when these two curves crossed at that point and the risk then became opposite of the initial one until 6.4 years. The recurrence risk for the patients receiving a right approach continued to rise afterwards (Fig. 3F).

When the hazard rate was analysed with the level of SCC, the curves also suggested that a double-peaked pattern recurrence risk was existing. Compared with lower levels of SCC, the patients with higher levels of SCC were more likely to recur earlier and higher for the second peak (Fig. 4A). Furthermore, the hazard curves for different levels of CEA (Fig. 4B) proved that despite a first higher peak for high levels of CEA, the patients with low levels of CEA had a higher recurrence risk than those with high levels of CEA after the cross-over point at 3.5 years of follow-up.

DISCUSSION

In the present study, we demonstrated the presence of two peaks for recurrence risk among Chinese patients with OSCC after complete resection. This similar pattern was observed in various subgroup analyses regarding age, gender, smoking status, N or T staging, histological grade and surgical approaches.

The mechanism of early postoperative metastasis and/or recurrence for cancer patients after radical resection is unclear. 'Tumor dormancy' hypothesis [14, 15] postulated that most of micrometastatic foci were in biological steady states; however, surgery may stimulate these tumour cells in dormancy to growth in accelerating the relapse process and eventually lead to recurrence. This might be an explanation for the double-peaked pattern of recurrence risk in cancer treatment.

The number of metastatic lymph nodes was considered for node classification [12]. Compared with lymph node (LN)-negative, LN-positive patients with OSCC were more likely to recur earlier for the double peaks, and the first peak was much higher. A similar result was also shown in different pathological T stages, but there was an intersection between the two curves.

In our study, the double peaks were much obvious in smokers than in non-smokers. Smoking is not only a well-known risk factor for oesophageal cancer, especially in adenocarcinomas of the oesophagus [16–18], but is also as a prognostic factor [19, 20]. In our study, the hazard rate curves regarding smoking status between smokers and non-smokers were separated from the beginning of follow-up and virtually parallel to each other. Hazard rates remained lower in non-smokers than in smokers at all follow-up times. One possible explanation is that nicotine has significant immunomodulatory effects on the cytotoxic activities of human lymphocytes, which may be of clinical relevance, leading to an inability to destroy cancer cells [21]. It seemed that pre-diagnostic smoking status was a prognostic factor for OSCC patients.

Some studies showed that patients with OSCC with poor histological differentiation have a poor prognosis, whereas others did not [22–24]. In our data, although the curves of the two groups, divided by the degree of histological differentiation, were almost identical in the first peak, the poorly differentiated tumours had an earlier and higher second peak than well-differentiated ones during all of the follow-up time.

The surgical approach might impact the shape of the curves. In the patients who underwent left thoracotomy, compared with those with right thoracotomy, the first peak remained lower and the curve occurred later; however, after 2.5 years, the curve of the
patients receiving a left thoracotomy was higher than that of the patients receiving a right thoracotomy during the follow-up. To our knowledge, surgical approaches were not a prognostic factor for OSCC [24, 25]. In our graphics, the first peak of recurrence might be stimulated by the surgery, and the patients receiving a left thoracotomy had less damage than those with a right thoracotomy, which might explain the pattern for the first peaks of these two curves. Afterwards, the curves started to change, reversing the previous trends. The recurrence risk for the patients with a right thoracotomy eventually changed to a lower level than those with a left thoracotomy, which might be due to a more complete lymphadenectomy with right thoracotomy than left thoracotomy.

Our results need to be interpreted with caution because of a relatively limited follow-up and the study’s retrospective nature. Still, 198 cases died without recurrence. Moreover, it was unable to do subgroup analysis for the limited sample of the patients receiving postoperative therapy. A prospective, randomized clinical trial should be performed to prove our findings.

In conclusion, the double-peaked patterns of recurrence risk exist in the patients with OSCC after complete resection. Hazard functions should be used for selecting the high recurrence risk OSCC patients. Adjuvant therapy might be beneficial for OSCC patients with complete resection in decreasing or delaying recurrence risk.

Funding

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Conflict of interest: none declared.

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