Survival benefit of (neo-)adjuvant radiotherapy to patients with $T_{2-3}N_0M_0$ stage squamous cell esophagus carcinoma

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Abstract: Background and Aims: This study is designed to analyze survival benefit of (neo-)adjuvant radiotherapy to patients with $T_{2-3}N_0M_0$ stage squamous cell esophagus carcinoma (SCEC). Methods: $T_{2-3}N_0M_0$ stage SCEC patients were selected from the Surveillance Epidemiology and End Results data. Survival effect of (neo-)adjuvant radiotherapy to $T_{2-3}N_0M_0$ stage SCEC was explored. Results: Univariate and multivariate analysis showed age, sex, and neoadjuvant radiotherapy were the prognostic factors of survival (P<0.05). Further analysis showed that neoadjuvant radiotherapy significantly reduces risk of death in T3 stage (HR 0.445, P<0.05), but not significantly in $T_2N_0M_0$ stage (HR 1.159, P>0.05). Adjuvant radiotherapy showed no significant survival benefit in either $T_2N_0M_0$ or $T_3N_0M_0$ stage. Conclusions: sex, age, and neoadjuvant radiotherapy are independent prognostic factors of $T_{2-3}N_0M_0$ SCEC. Significant survival benefit of neoadjuvant radiotherapy is only observed in patients in $T_3N_0M_0$ stage SCEC, but not in $T_2N_0M_0$ stage. Adjuvant radiotherapy does not show survival benefit in either $T_2N_0M_0$ or $T_3N_0M_0$ stage SCEC.

Keywords: Esophageal cancer, squamous cell carcinoma, surgery, adjuvant radiotherapy, prognostic factor

Introduction

Squamous cell esophageal carcinoma (SCEC) is one of the most common malignancy of esophageal tumors. Treatment of SCEC varies by disease stages [1-3]. Chemotherapy with or without radiotherapy is the standard treatment of metastatic SCEC [2]. Multimodality therapy with chemoradiotherapy is the most rational treatment strategy of locally advanced SCEC [1, 4]. As for early stage of SCEC, surgery is the main treatment method, but whether (neo-)adjuvant radiotherapy should be given before or after surgery to the SCEC patients with $T_{2-3}N_0M_0$ stage is not clear.

The Surveillance, Epidemiology, and End Results (SEER) Program is a cancer related database founded by the National Cancer Institute (NCI) in the United States. It collects and reports cancer incidence and survival data from population-based cancer registries and covers approximately 28% of the US population. With large information of cancer, it is an important tool to analyze carcinoma.

In view of above, we used SEER data for the analysis of SCEC. Aim to explore the efficacy of adjuvant radiotherapy to the early stage ($T_{2-3}N_0M_0$) SCEC.

Patients and methods

Patients and clinical data

SEER data between 1973 and 2012 [“Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2014 Sub (1973-2012 varying)”] were chosen for this study. The National Cancer Institute’s SEER*Stat software (Version 8.2.1) was used for the identity of patients. We included: (1) cases of primary esophageal cancer (C15.0-C15.9) with a confirmed diagnosis of
(neo-)adjuvant radiotherapy to $T_{2-3}N_0M_0$ SCEC

microscopically, (2) entire squamous cell histology (Histologic/Behavior codes: 8070/3) based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), (3) year of diagnosis between 2004 and 2012, (4) stage 2a of ajcc6 ($T_{2-3}N_0M_0$) cancer, and (5) received surgery combined with or without radiation. We excluded patients with (1) unknown age, sex, race, T, N, M stage, (2) “radiation both before and after surgery”, “intraoperative radiation therapy”, “intraoperative radiation with other radiation given before or after surgery”, “surgery both before and after radiation” (for cases diagnosed 1/1/2012 and later), or “sequence unknown, but both surgery and radiation were given”, (3) cases diagnosed solely on autopsy or death certificate. Survival data were extracted at 1-month intervals for a maximal follow-up of 60 months.

This study was based on public data from the SEER database. The reference number we obtained for the permission to access research data files was 10612-Nov2014. No human subjects or personal identifying information were used in this study. No informed consent was required in this study. This study was approved by the Review Board of Huai’an First People’s Hospital, Huai’an, China.

**Statistical analysis**

The enrolled population was divided into three groups based on different treatments: patients who were treated with surgery alone (Surg group), surgery following with radiotherapy (RT + Surg group), and surgery followed by radiotherapy (Surg + RT group). Chi-square test was used to analyze the difference of these three groups. Univariate analysis with log-rank test and multivariate analysis with Cox proportional hazards regression model were performed to examine the clinical factors’ association with cause-specific survival (CSS) and overall survival (OS) respectively, with a statistically significant difference at $P<0.05$. Finally, stratified Cox regression survival analysis was performed based on different T stages. All analysis was performed in the population with a clear record of analytical variable. All analysis was performed with survival package [5, 6] of R [7] (version 3.2.1).

**Results**

A total of 369 cases were selected from the SEER database. Of which, 167 patients (45.3%) received surgery alone (Surg), 165 patients (47.7%) received surgery with neoadjuvant radiotherapy (RT + Surg), 37 (10.0%) patients received adjuvant radiotherapy with surgery (Surg + RT). Most of the patients were white race (75.1%) and T3 stage (63.1%). Percentage of male was 58.8%, and the median age of all patients was 64 years. Independence test of the patients’ treatment assignment and clinical characteristics indicated an obvious association between adjuvant treatment assignment and age. Patients with age younger than 65 years were more likely to receive neoadjuvant radiotherapy combined with surgery, those older than 65 years were more likely to receive

Table 1. Summary of characteristics and characteristics stratified by treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (%)</th>
<th>Surg</th>
<th>RT + Surg</th>
<th>Surg + RT</th>
<th>$\chi^2$</th>
<th>P-value $\psi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>152 (41.2)</td>
<td>78</td>
<td>58</td>
<td>16</td>
<td>4.646</td>
<td>0.098</td>
</tr>
<tr>
<td>Male</td>
<td>217 (58.8)</td>
<td>89</td>
<td>107</td>
<td>21</td>
<td></td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Black</td>
<td>60 (16.3)</td>
<td>26</td>
<td>25</td>
<td>9</td>
<td>6.755</td>
<td>0.149</td>
</tr>
<tr>
<td>White</td>
<td>277 (75.1)</td>
<td>123</td>
<td>131</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>32 (8.6)</td>
<td>18</td>
<td>9</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>T Stage</td>
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<tr>
<td>T2</td>
<td>136 (36.9)</td>
<td>63</td>
<td>63</td>
<td>10</td>
<td>1.715</td>
<td>0.424</td>
</tr>
<tr>
<td>T3</td>
<td>233 (63.1)</td>
<td>104</td>
<td>102</td>
<td>27</td>
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<tr>
<td>Age</td>
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<tr>
<td>65-</td>
<td>179 (52.3)</td>
<td>70</td>
<td>106</td>
<td>17</td>
<td>17.25</td>
<td>0.000***</td>
</tr>
<tr>
<td>65+</td>
<td>160 (47.7)</td>
<td>97</td>
<td>59</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Surg</td>
<td>167 (45.3)</td>
<td>167</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT + Surg</td>
<td>165 (47.7)</td>
<td>-</td>
<td>165</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surg + RT</td>
<td>37 (10.0)</td>
<td>-</td>
<td>-</td>
<td>37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RT + Surg = neoadjuvant radiotherapy + surgery; Surg + RT = surgery + adjuvant radiotherapy. $\psi$chi-square test. $***P<0.001$, chi-square est.
(neo-)adjuvant radiotherapy to $T_{2-3}N_{0}M_{0}$ SCEC

Finally, we performed further multivariate Cox regression analysis to assess the efficacy of (neo-)adjuvant radiotherapy to survival time based on different $T$ stages, by adjusting sex, race, age (Table 3). The results displayed that only neoadjuvant radiation therapy in $T_{3}N_{0}M_{0}$ stage can significantly improve survival time (HR 0.445, 95% CI 0.293-0.676).

Discussion

Squamous cell esophageal cancer is one of the two major histological subtypes of esophageal cancer in the world, with a highly incidence in so-called Asian belt, including Turkey, northeastern Iran, Kazakhstan, and northern and central China [1,8-10]. Its risk factors mainly contains tobacco use, alcohol consumption, injury, low socioeconomic status, and so on [11,12]. Treatment of SCEC varies depends on different stages [1]. As for local tumors, surgery is the standard procedure for patients with locally limited ($cT_{1}/T_{2}, N_{0}$) and some resectable advanced carcinoma ($cT_{3}, T_{4}, N_{x}$). Adjuvant or neoadjuvant treatment with chemoradiotherapy for patients with locally advanced tumors is well established [13-15]. While for some early stage esophageal cancer, chemotherapy is believed not to be a suitable adjuvant treatment of surgery [16], but the efficacy of radiation therapy before or after surgery to early stage esophagus cancer is not clear. Some studies proved radiotherapy before or after surgery benefits long-time survival [17,18], but others indicated no significant survival benefit of neoadjuvant [16,19,20] or adjuvant radiotherapy [16,20,21].

In this study, we summarized the clinical characteristics of $T_{2-3}N_{0}M_{0}$ stage operated SCEC with information provided by the population-based SEER database from 1973 to 2012. The characteristics used for analysis in our study contained sex, race, $T$ stage, age, and radiation therapy. We found that SCEC is more likely to present at $T_{3}$ stage, young, male, and white.
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patients. More than half of SCEC patients received adjuvant or neoadjuvant radiation therapy (57.7%), of which, neoadjuvant radiotherapy contained 47.7%. Independence chi-square test between radiation therapy and other factors showed that radiation therapy was associated with age. Younger patients are more likely to receive neoadjuvant radiotherapy combined with surgery, while the older were more likely to receive surgery alone. Univariate survival analysis of clinical characteristics showed that survival time was associated with sex, age, and radiotherapy ($P<0.05$), but of no association with T stage and race ($P>0.1$). Multivariate Cox proportional hazards regression analysis displayed that sex, age, and neoadjuvant radiation therapy were all significantly associated with survival ($P<0.05$). Death risk of female was lower than male (HR 0.643, 95% CI 0.477-0.867). Patients younger than 65 years had a lower risk of death (HR 0.618, 95% CI 0.457-0.835). Neoadjuvant radiotherapy could reduce nearly 40% of death hazards (HR 0.633, 95% CI 0.459-0.874). Further multivariate analysis of neoadjuvant or adjuvant radiotherapy based on different T stages showed that neoadjuvant radiotherapy can reduce more than 50% risk of death in T3 stage (HR 0.445, 95% CI 0.293-0.676), but not significantly reduce death risk in T2 stage (HR 1.159, 95% CI 0.686-1.958). Adjuvant radiotherapy could not significantly decrease death risk in either T2N0M0 or T3N0M0 stage SCEC.

In conclusion, our study demonstrates that age, sex, and neoadjuvant radiotherapy are prognostic associated factors in $T_{2-3}N_0M_0$ stage SCEC. Survival benefit of neoadjuvant radiotherapy is only significant in T3N0M0 stage SCEC, but not significant in T2N0M0 stage. Adjuvant radiotherapy shows no survival benefit to either T2N0M0 or T3N0M0 stage SCEC.

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Disclosure of conflict of interest

None.

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References

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