Review Article
Clinicopathological and prognostic significance of cd133 in esophageal cancer: a meta-analysis

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Received August 20, 2016; Accepted October 15, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Objective: CD133 has been recognized as a marker of cancer stem-like cells in esophageal cancer. However, its promising value still remains controversial. Therefore, we performed a meta-analysis to evaluate the association between the expression of CD133 and clinicopathological features and the prognosis of esophageal cancer. Methods: A systematic literature search for relevant articles published from 2010 to 2015 was conducted in PubMed, Embase and Cochrane databases. Electronic searches were conducted by hand searching reference lists, abstracts and conferences. Outcomes included clinicopathological features. Publication bias was assessed by the funnel plots, and heterogeneity and sensitivity were analyzed as well. Results: Seven articles with a total of 538 patients were subjected to the final analysis. High expression of CD133 was associated with lymph node metastasis, clinical stage and histopathological grade cases, leading to a risk difference of 1.75 (95% CI 1.17-2.61), 1.91 (95% CI 1.08-3.38) and 1.55 (95% CI 1.11-2.18), respectively. And there was no statistically significant association of CD133 with depth of invasion (OR=1.24, 95% CI: 0.53-2.92). Conclusion: This study indicated that CD133 could be recommended as a useful prognostic factor in esophageal cancer. Higher CD133 expression is significantly associated with lymph node metastasis, distant metastasis and clinical stage. More well-designed prospective studies are needed to confirm the findings.

Keywords: CD133, cancer stem cell, esophageal cancer, meta-analysis

Introduction

As of 2012, esophageal cancer is the eighth-most common cancer globally with 456,000 new cases during the year [1]. It caused about 400,000 deaths that year, up from 345,000 in 1990 [1]. Rates vary widely among countries, with about half of all cases occurring in China. It is around three times more common in men than in women [1]. In the near decades, its incidence, diagnostic options and therapeutic therapies have undergone significant changes, but the prognosis for esophageal cancer patients remains poor, especially in more advanced stages.

Previous work showed that only CSCs could reconstitute tumors with similar histopathological characteristics to the primary cancer, whereas non-stem cancer cells failed to effect tumor initiation. And, CSCs are believed to play a key role in resistance to chemotherapy and radiotherapy [2, 3]. This new paradigm has promising implications for cancer therapy, as our recently available therapies are more successful at eradicating non-cancer stem cells rather than cancer stem cells [4, 5]. In other words, identification and characterization of CSCs could lead to development of directed and more effective treatments for cancer [6].

Recently, several cell surface markers have been identified as stem cell markers in esophageal cancer. Among these markers, CD133 is believed to be the most robust surface marker for cancer stem cells by now. CD133 molecule (also known as prominin-1) is a five transmembrane glycoproteins with a molecular weight of 120 kDa and it is shown to be mainly localized in membrane protrusions [7].

Thus, based on current evidences, we performed a meta-analysis to determine the association between CSCs marker CD133 and the
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Methods

Literature search

We searched PUBMED, EMBASE and Cochrane Library digital databases for all relevant articles. The search was performed in each database by two independent investigators. The medical subject headings (MeSH) and keywords collected for individually and in combination were as follows: ('esophageal cancer' 'cancer' or 'esophageal adenocarcinoma') AND ('cancer stem cell' or 'neoplastic stem cells) AND ('CD-133' or 'prominin-1' or 'AC133'). No language restrictions were imposed. The reference lists in all identified articles were checked for further relevant articles.

Study selection

Eligibility of studies for inclusion was assessed independently by two investigators. Studies were eligible for inclusion if all the following criteria were fulfilled: (1) Diagnosis of esophageal cancer was proven by histopathologic analysis. (2) CD133 expression should be evaluated in primary esophageal cancer tissue. (3) Articles were published as original research. Reviews, comments, and letters were excluded.

Data extraction

Data was extracted by two of the authors independently using the same standardized form. The fields extracted included first author, year of publication, country of origin, number of patients, research techniques, tumor stage, histopathological type and tumor location. For the articles with the same population resources or overlapping data sets, the paper which included the largest population or contained more useful information was included. If some articles revealed the prognosis of esophageal cancer only by Kaplan-Meier curve, the software Engauge Digitizer 4.1 (http://sourceforge.net/projects/digitizer/) was utilized to extract the relevant data.
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### Statistical analysis

Statistical calculations were all performed using STATA version 13.0. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the association between the expression of the stem cell marker CD133 and the clinicopathological parameters of esophageal carcinoma. Statistical heterogeneity between studies was assessed with the chi-square statistic and quantified by $I^2$, a statistic that represents the percentage of total variation contributed by between-study variation. If the Q test showed a $P < 0.05$ or the $I^2$ test exhibited $> 50\%$, indicating significant heterogeneity between studies, the random-effect model was conducted, or the fixed-effect model was used. Publication bias was examined by using the Begg rank correlation method and the Egger weighted regression method.

### Results

#### Study selection and characteristics

Detailed search steps were described in Figure 1. The initial search algorithm retrieved a total of 118 studies according to the inclusion criteria stated above. After titles and abstracts were previewed, only 27 identified studies concerning CD133 and the risk of esophageal cancer were further evaluated. After the removal of all studies that did not meet our criteria, 7 studies

### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>Country</th>
<th>Tumor stage (TNM)</th>
<th>Median age (years)</th>
<th>Histopathological type</th>
<th>Technique</th>
<th>No. of patients</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang [8]</td>
<td>2010</td>
<td>China</td>
<td>I-IV</td>
<td>52.8</td>
<td>SCC</td>
<td>IHC</td>
<td>90</td>
<td>Esophagus or bone</td>
</tr>
<tr>
<td>Cao [9]</td>
<td>2009</td>
<td>China</td>
<td>II-III</td>
<td>54.3</td>
<td>SCC</td>
<td>IHC</td>
<td>68</td>
<td>Esophagus or bone</td>
</tr>
<tr>
<td>Fei [10]</td>
<td>2011</td>
<td>China</td>
<td>I-IV</td>
<td>55.4</td>
<td>SCC</td>
<td>IHC</td>
<td>90</td>
<td>Esophagus or liver</td>
</tr>
<tr>
<td>Feng [11]</td>
<td>2014</td>
<td>China</td>
<td>I-IV</td>
<td>68.8</td>
<td>SCC</td>
<td>IHC</td>
<td>28</td>
<td>Esophagus or bone</td>
</tr>
<tr>
<td>Wang [12]</td>
<td>2014</td>
<td>China</td>
<td>I-IV</td>
<td>69</td>
<td>SCC</td>
<td>IHC</td>
<td>40</td>
<td>Esophagus or brain</td>
</tr>
<tr>
<td>Okamoto [13]</td>
<td>2013</td>
<td>Japan</td>
<td>I-IV</td>
<td>56.1</td>
<td>SCC</td>
<td>IHC</td>
<td>86</td>
<td>Esophagus or brain</td>
</tr>
<tr>
<td>Peng [14]</td>
<td>2012</td>
<td>China</td>
<td>III</td>
<td>58</td>
<td>SCC</td>
<td>IHC</td>
<td>136</td>
<td>Esophagus or liver</td>
</tr>
</tbody>
</table>

Figure 2. Forest plots of ORs for CD133 and lymph node metastasis.
[8-14] from 118 publications were finally included in our meta-analysis. The useable data and main characteristics of each article are summarized in Table 1. Included articles were published in the period 2010-2014. All the studies were conducted in Asian population, 6 from China, and 1 from Japan. A total of 538 patients were included.
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Correlation of CD133 with clinicopathological parameters

The association between CD133 and several clinicopathological parameters was illustrated in Figures 2-5. High expression of CD133 was also associated with lymph node metastasis, clinical stage and histopathological grade, leading to a risk difference of 1.75 (95% CI 1.17-2.61), 1.91 (95% CI 1.08-3.38) and 1.55 (95% CI 1.11-2.18), respectively. And there was no statistically significant association of CD133 with depth of invasion (OR=1.24, 95% CI: 0.53-2.92).

Sensitivity analyses

Sensitivity analysis was subsequently performed to detect the influence of individual study on the pooled estimate by omitting one study from the pooled analysis each time. The exclusion of each single study did not significantly change the pooled OR (Figures S1, S2, S3 and S4), suggesting that the results of the meta-analysis were robust and credible.

Publication bias

Begg's funnel plot was used to check the existence of publication bias. The plot was symmetric, suggesting that the publication bias was little. There was no evidence of publication bias for asymmetrical shapes existed in neither two groups analyses (data not showed).

Discussion

Esophageal cancer is the eighth most frequently diagnosed cancer worldwide, and because of its poor prognosis it is the sixth most common cause of cancer-related death [15]. It caused about 400,000 deaths in 2012, accounting for about 5% of all cancer deaths (about 456,000 new cases were diagnosed, representing about 3% of all cancers) [1]. In general, the prognosis of esophageal cancer is quite poor, because most patients present with advanced disease. By the time the first symptoms (such as difficulty swallowing) appear, the cancer has already well progressed.

Concerning the biological properties of CSCs, many research trials reported that level of CD133 expression in esophageal cancer may be useful as a novel predictive factor of prognosis. However, no consensus of results has been approached. So based on the previous literatures, this meta-analysis demonstrated that high expression of CD133 is significant associated with lymph node metastasis, clinical stage, and histopathological grade. Thus, these results suggested that level of CD133 expression is correlated with a number of parameters that are traditionally associated with poor prognosis.
To our knowledge, CD133 has been regarded as a promising molecular marker and therapeutic target in various solid tumors, such as brain tumors [16], colon cancer [17], lung cancer [18], liver cancer [19] and prostate cancer [20]. Additionally, CD133 may participate in tumor initiation, cellular migration, and vasculogenic mimicry [21]. Moreover, CD133 was associated with tumor differentiations in many cancers. For instance, Ying X, et al. [22] reported that CD133 expression was significantly correlated with tumor differentiation grade in stage II colorectal cancer. Next, Jiang Y, et al. [23] showed that CD133 was higher in the diffuse type than in the intestinal type of gastric cancers and was significantly increased in poorly differentiated gastric cancers. Next, Feng HL et al. [24] proposed that CD133 was negatively correlated with the cellular differentiation of colon cancer. In addition, Fan et al. [25] noted that CD133 expression was correlated with well differentiated or moderately differentiated cholangiocarcinoma. In term of esophageal cancer, Hang D, et al. found that height CD133 expression was linked with well and moderately differentiated tissue compared with poorly differentiated [26]. Our study found that there was a significant difference between the well- and moderately differentiated esophageal carcinoma group and the poorly differentiated esophageal carcinoma group (OR=1.55, 95% CI 1.11-2.18).

Recently, some other cell surface molecules such as CD44, CD24, CD166 and EpCAM have been verified as putative CSC markers in CRC. Undoubtedly, the combination of these markers could provide a better selection of CSCs. Horst D, et al. [27] proposed that CD133 is the best sole marker to predict low patient survival, while the combined analysis of CD133, CD44, and CD166 markers may be superior in identification of low-, intermediate-, and high-risk cases of colorectal cancer. In addition, besides immunohistochemical staining test, some studies have examined CD133 gene or mRNA expression using reverse transcriptase-polymerase chain reaction (RT-PCR) method. And elevated CD133 gene level may predict distant recurrence and poor prognosis of patients with CRC. Lin EH, et al. [28] revealed that increased levels of expression of CD133 messenger RNA (mRNA) in peripheral blood predicted disease recurrence in patients with colon cancer. And Artells R’ study [29], measuring CD133 mRNA expression levels by RT-PCR, observed longer relapse-free interval and overall survival in patients with lower levels of CD133, regardless of adjuvant treatment and other clinical characteristics. Similarly, Huh JW, et al. [30] verified that the 5-year disease-free survival rate of patients with a low CD133 mRNA expression was significantly higher than that of those patients with high levels of CD133 mRNA expression. Inuma H, et al. [31] suggested that OS and DFS of patients who were positive for CD133 (CEA/CK/CD133) mRNA were significantly worse than those of patients who were negative for these markers, further In patients with Dukes’ stage B and C CRC who require adjuvant chemotherapy, detection of CD133 (CEA/CK/CD133) mRNA in peripheral blood is a useful tool for determining which patients are at high risk for recurrence and poor prognosis.

Several restrictions of our study also need to be considered. First, the numbers of the studies and patients included in the current meta-analysis are relatively small. Secondly, all the studies are based on Asian population, none from western countries. Due to lack of statistics on other countries, further studies are needed to investigate the role of CSCs in other population. As is known, there are significant differences such as etiology, biology features, clinical types, and prognosis in the risk of CRC in different ethnic groups within a given geographical area. Although in the subgroup analysis, ethnicity, sample size, and research technique did not significantly influence the prognosis value of CD133. Finally, no attempt was made to identify unpublished work and grey literature, for example university theses or conference proceedings. As a result, publication bias may have influenced the results. And only English literatures were included in this study, it was possible that our findings were biased for many non-English literatures were not included.

In conclusion, this meta-analysis showed that a high level of CD133 was significantly correlated with lymph node metastasis, clinical stage and histopathological grade. Thus, CD133 may have a predictive role and be helpful tool in the management of patients with esophageal cancer. Large-scale, prospective clinical trials with advanced methodologies are still required to
verify the findings and provide a higher level of evidence.

Acknowledgements

We thank for long-fei xie his professional statistical help.

Disclosure of conflict of interest

None.

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Figure S1. Sensitivity analysis of CD133 and lymph node metastasis.

Figure S2. Sensitivity analysis of CD133 and clinical stage.
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Figure S3. Sensitivity analysis of CD133 and histopathological grade.

Figure S4. Sensitivity analysis of CD133 and depth of invasion.