

Clinicopathological and prognostic significance of chemokine receptor CXCR4 overexpression in patients with esophageal cancer: a meta-analysis

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Received: 31 October 2013 / Accepted: 28 November 2013 / Published online: 11 December 2013
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Abstract The prognostic significance of CXC chemokine receptor type 4 (CXCR4) for survival of patients with esophageal cancer remains controversial. To investigate its expression impact on clinicopathological features and survival outcome, a meta-analysis was performed. A comprehensive search in the PubMed, Embase, and Web of Science (up to October 8, 2013) was performed for relevant studies using multiple search strategies. Correlation between CXCR4 expression and clinicopathological features and overall survival (OS) was analyzed. A total of 1,055 patients with esophageal cancer from seven studies were included. The pooled odds ratios (ORs) which indicated CXCR4 expression was associated with tumor depth (OR=0.35, confidence interval (CI)=0.27–0.47, $P<0.00001$), status of lymph node (OR=0.36, CI=0.21–0.61, $P<0.0002$), TNM (tumor, node, metastasis) stage (OR=0.38, CI=0.25–0.56, $P<0.00001$), and histological type (OR=1.81, CI=1.07–3.05, $P=0.03$). Poor overall survival of esophageal cancer was found to be significantly related to CXCR4 overexpression (hazard ratio (HR) 1.49, 95 % CI=1.24–1.80, $P<0.0001$), whereas combined ORs exhibited that CXCR4 expression has no correlation with gender or tumor differentiation. Based on the published studies, CXCR4 overexpression in patients with esophageal

cancer indicated worse survival outcome and was associated with common clinicopathological poor prognostic factors.

Keywords Meta-analysis · Esophageal cancer · CXCR4 · Prognosis

Introduction

Esophageal cancer is the eighth most common cancer worldwide [1]. Owing to a highly malignant potential for lymph node metastasis and vascular invasion, long-term prognosis of esophageal cancer is poor, and reported 5-year survival rates are only 20 to 36 % after curative surgery [2]. Investigating the mechanism of invasion and metastasis and finding out the therapeutic molecular target have become the focus in the treatment of esophageal cancer.

Chemokines, or chemotactic cytokines, are a group of related small soluble peptides that play a predominant role in regulating the homing and trafficking of various leukocyte subpopulations, particularly during inflammation, tissue damage, and infection [3, 4]. According to the number and spacing of their N-terminal cysteine residues, they are classified into four groups (CXC, CX3C, CC, and C) [5]. To mediate their chemical effects on target cells, chemokines use G protein-coupled receptors that are characterized structurally by seven transmembrane-spanning domains and are involved in the attraction of leukocytes to different organs [6]. CXC chemokine receptor type 4 (CXCR4) is one of these receptors, which is the only natural receptor for stromal cell-derived factor 1 (SDF-1, also called CXCL12) [7]. The binding of CXCL12 to CXCR4 induces intracellular signaling, which related to chemotaxis, cell survival and/or proliferation, increase in intracellular calcium, and gene transcription. The CXCL12/CXCR4 axis is involved in tumor progression, angiogenesis, metastasis, and survival of cancer patients [8, 9]. Recent

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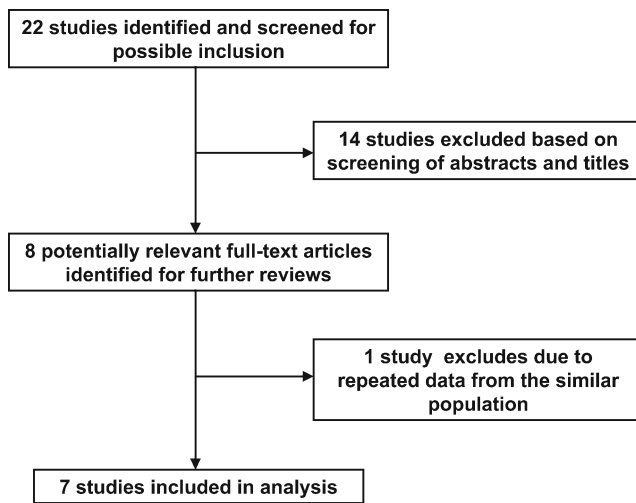


Fig. 1 Flow chart for selection of studies

researches have shown that the expression of CXCR4 plays a key role in migration and metastasis with associated tumor progression and poor prognosis in several malignancies [10–13].

Although evidence exists that CXCR4 is an important factor implicated in clinicopathologic features and prognosis of esophageal cancer [14–21], some conflicting results were also present. Whether discrepancy in these data has been due to limited sample size or to genuine heterogeneity is still confused. A meta-analysis was carried out to clarify this issue.

Materials and methods

Search strategy

A comprehensive literature search of the electronic databases PubMed, Embase, and Web of Science was performed up to

October 8, 2013. Studies were selected using the following search terms: “esophageal or oesophageal” and “cancer or neoplasm or carcinoma” and “CXCR4 or C-X-C chemokine receptor type 4.” The references of articles and reviews were also manually searched for additional studies. The eligible reports were identified by two reviewers (J.W. and X.W.). Controversial studies were adjudicated by the third reviewer (H.A.).

Selection criteria

We collected all eligible articles about relationship between CXCR4 and clinicopathological features and clinic outcome in esophageal cancer in this meta-analysis. Studies meeting the following inclusion criteria were included: (1) CXCR4 expression evaluated in the primary esophageal cancer tissues, (2) researches revealed the relationship between CXCR4 expression and esophageal cancer clinicopathological parameters and prognosis, (3) CXCR4 expression examined by immunohistochemistry (IHC), (4) articles published as a full paper in English, (5) studies provided sufficient information to estimate hazard ratio (HR) about overall survival (OS) and 95 % confidence interval (CI), and (6) if there were multiple articles based on similar patients, only the largest or the most recently article was included. The exclusion criteria included the following: (1) letters, reviews, case reports, conference abstracts, editorials, expert opinion, and non-English language papers; (2) articles that had no information of OS or that could not calculate the HR about OS from the given information; and (3) patients had received previous chemotherapy or radiotherapy.

Data extraction

Two investigators (J.W. and H.A.) independently extracted data from eligible studies. Disagreements were resolved by discussion and consensus. Two investigators reviewed all of

Table 1 Characteristics of eligible studies

First author	Year	Origin	Cases	Method	Antibody source	Dilution	CXCR4 distribution	Counting method	Definition of CXCR4 positive
Kaifi [15]	2005	Germany	136	IHC	R&D	1:100	–	Percentage of positive cells	>20 %
Gockel [14]	2006	Germany	102	IHC	Capr	1:200	Membrane, cytoplasm	Staining intensity score and percentage of positive cells	≥2.0
Wang [20]	2009	China	186	IHC	R&D	1:100	Membrane, cytoplasm	Staining intensity score and percentage of positive cells	≥2.0
Sasaki [18]	2009	Japan	219	IHC	R&D	1:200	Membrane, cytoplasm	Staining intensity	≥1.0
Lu [17]	2011	China	127	IHC	R&D	–	Nuclear, cytoplasm	Staining intensity score and percentage of positive cells	≥2.0
Zhang [21]	2013	China	136	IHC	R&D	–	Nuclear, membrane, cytoplasm	Staining intensity score and percentage of positive cells	–
Lu [16]	2013	China	154	IHC	R&D	–	Nuclear, membrane, cytoplasm	Staining intensity score and percentage of positive cells	≥2.0

IHC immunohistochemistry

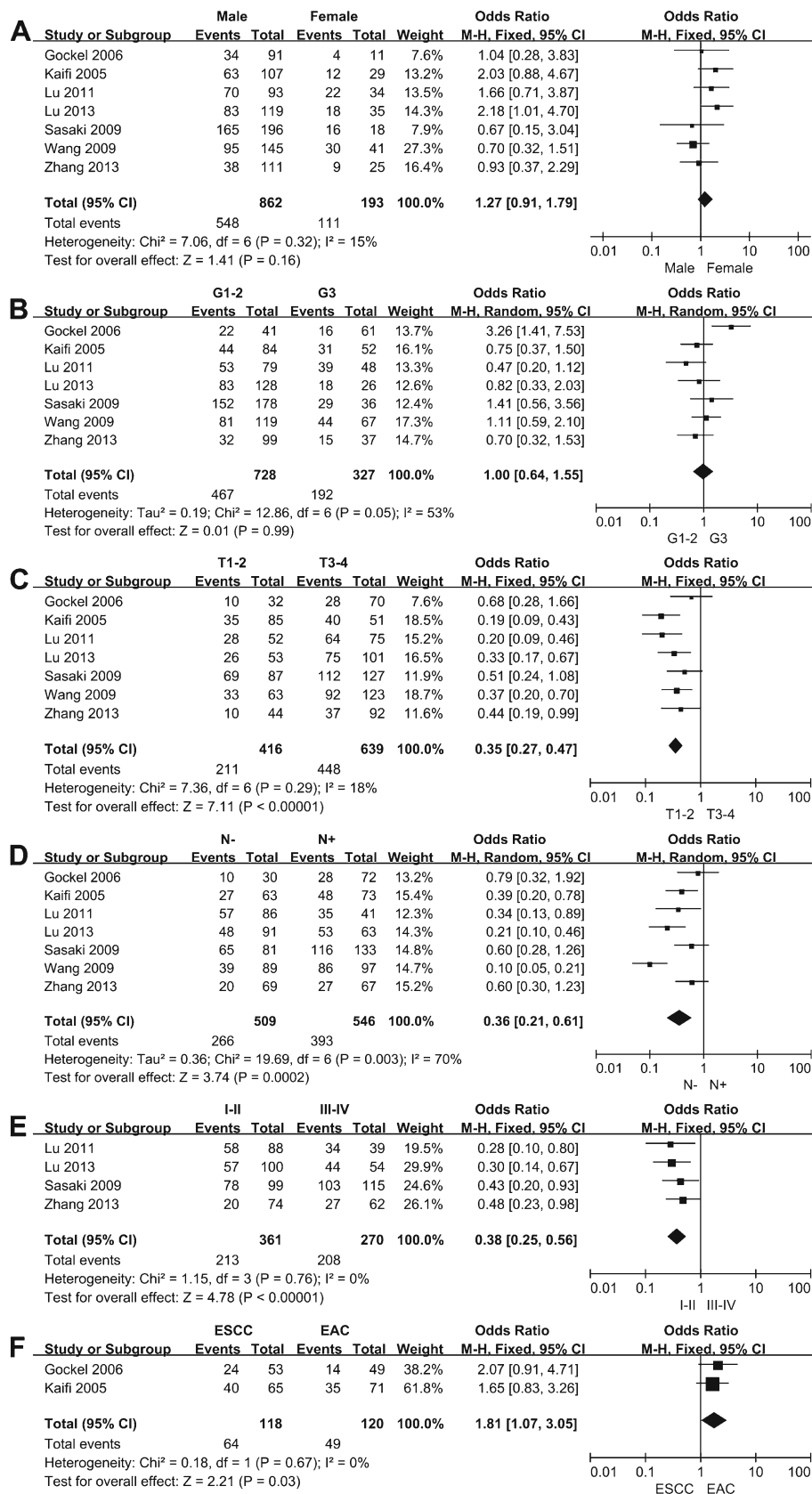


Fig. 2 Forest plots of CXCR4 expression and the clinicopathological features of patients with esophageal cancer. **a** Gender. **b** Differentiation. **c** Tumor depth. **d** Status of lymph node. **e** TNM staging. **f** Histological

type. *G* grade, *T* tumor, *N* node, *ESCC* esophageal squamous cell carcinoma, *EAC* esophageal adenocarcinoma

researches that met inclusion and exclusion criteria. The following information was recorded for each study: the first author name, year of publication, sample source, number of cases, clinicopathological parameters, cancer TNM (tumor node metastasis) stage, immunohistochemical technique, CXCR4-positive expression, and patient survival. If the HR or standard errors (SEs) were not reported in included studies, we calculate or estimate the HR from available data or Kaplan–Meier curves using the methods reported by Tierney et al. [22].

Statistical analysis

Analysis was performed using the Stata 12.0 (Stata Corporation, TX, USA) and Review Manager 5.2 (Cochrane Collaboration, Oxford, UK). Comparisons of dichotomous measures were performed by pooled estimates of odds ratios (ORs) as well as their 95 % CIs. *P* value of <0.05 was considered to be statistically significant. Heterogeneity was tested using a chi-square test with significance being set at *P*<0.10; the total variation among studies was estimated by *I* square. If there was heterogeneity among studies, we used a random effect model to pool the ORs; otherwise, a fixed effect model was selected.

Results

Identification of relevant studies

Twenty-two articles were identified using the search strategy above. Fourteen of those were excluded due to laboratory studies, non-original articles (review), research of patients that received preoperative chemoradiotherapy, or studies irrelevant to the current analysis. After excluding one repeated data from the similar population [19], eventually, there were seven studies included in final meta-analysis [14–18, 20, 21] (Fig. 1).

Study characteristics

Seven studies published from 2005 to 2013 were eligible for meta-analysis. Their characteristics were summarized in Table 1.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio	
				IV, Fixed, 95% CI	IV, Fixed, 95% CI
Gockel 2006	0.39	0.29	10.8%	1.48	[0.84, 2.61]
Kaifi 2005	0.85	0.27	12.5%	2.34	[1.38, 3.97]
Lu 2011	0	0.53	3.2%	1.00	[0.35, 2.83]
Lu 2013	0.56	0.35	7.4%	1.75	[0.88, 3.48]
Sasaki 2009	0.16	0.24	15.8%	1.17	[0.73, 1.88]
Wang 2009	0.32	0.17	31.5%	1.38	[0.99, 1.92]
Zhang 2013	0.45	0.22	18.8%	1.57	[1.02, 2.41]
Total (95% CI)			100.0%	1.49	[1.24, 1.80]
Heterogeneity: Chi ² = 4.83, df = 6 (<i>P</i> = 0.57); <i>I</i> ² = 0%					
Test for overall effect: Z = 4.20 (<i>P</i> < 0.0001)					

A total of 1,055 patients from China, Germany, and Japan were enrolled, including 862 male, 193 female, 935 esophageal squamous cell carcinomas (ESCCs), and 120 esophageal adenocarcinomas (EACs). Regarding the histological grading of tumor, 31.0 % of patients were poorly differentiated. Around 39.4 % of patients were identified to be T1 or T2 after operation, and 51.8 % of patients were diagnosed with lymphatic metastasis. TNM stage was reported in four studies, among which 57.2 % were stage I or II, while the other 42.8 % were stage III or IV. IHC was the only method used to evaluate the expression of CXCR4 in esophageal cancer specimens. The most commonly used antibody was a R&D Systems antibody against CXCR4. The definition of overexpressed CXCR4 staining varied among the studies.

CXCR4 expression and clinicopathological features

All the included studies evaluated the correlation of CXCR4 expression with gender, histological differentiation, tumor depth, and status of lymph node metastasis. The pooled OR indicated that CXCR4 expression had no clear correlation with gender (OR=1.27, CI=0.91–1.79, *P*=0.16, Fig. 2a) or differentiation (OR=1.00, CI=0.64–1.55, *P*=0.99, Fig. 2b). However, CXCR4 expression was likely to be associated with tumor depth (OR=0.35, CI=0.27–0.47, *P*<0.00001, Fig. 2c) and status of lymph node (OR=0.36, CI=0.21–0.61, *P*<0.0002, Fig. 2d).

Four out of seven studies examined the relation between CXCR4 expression and TNM stage. The combined OR for stages I and II group versus stages III and IV group was 0.38 (CI=0.25–0.56, *P*<0.00001, Fig. 2e).

In two studies, the association of CXCR4 with a histological type of esophageal cancer was also investigated. It is found that CXCR4 expression was different in ESCC and EAC (pooled OR=1.81, CI=1.07–3.05, *P*=0.03, Fig. 2f).

The heterogeneity was observed in the analysis of CXCR4 expression with histological differentiation (*P*=0.05; *I*²=53 %) and status of lymph node (*P*=0.003; *I*²=70 %), so a random effect model was used. The other analyses above were carried out by the fixed effect model.

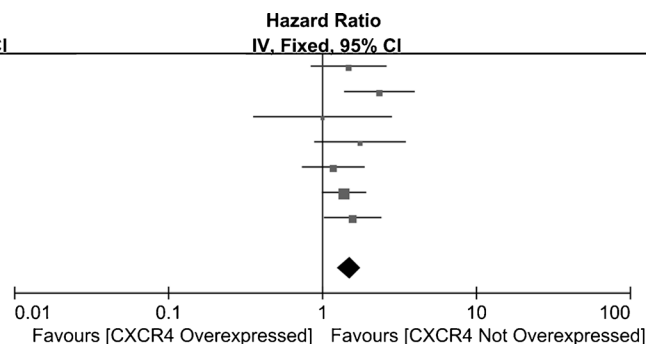


Fig. 3 Forest plot of hazard ratio for overall survival of patients with esophageal cancer

CXCR4 as a prognostic factor for esophageal cancer

All seven included studies estimated the relationship between OS and CXCR4 expression. The pooled HR for OS showed that overexpression of CXCR4 reduced OS in esophageal cancer (HR=1.49, 95 % CI=1.24–1.80, $P<0.0001$, Fig. 3).

Sensitivity analyses and publication bias

A sensitivity analysis, in which one study was removed at a time, was performed to evaluate result stability. The corresponding pooled ORs and HRs were not significantly altered, suggesting stability of our results.

Egger's and Begg's test indicated no publication bias among these studies regarding hazard ratio about overall survival with P values of 0.926 and 0.881, respectively. The funnel plots were largely symmetric (Fig. 4). There were also no publication biases in the meta-analysis of CXCR4 expression and clinicopathological features (Fig. 5).

Discussion

Chemokines are chemotactic factors regulating the development and migration of various types of cell. CXCR4 is the natural receptor for CXCL12 which is a member of the CXC chemokine family. Activation of chemokine receptor can lead to growth, adhesion, and directional migration of cell. CXCR4 overexpression, which was considered to play an important role in tumor growth, invasion, and metastasis, was found in many malignant tumors [23].

The correlation between CXCR4 expression and esophageal cancer has also been studied by many researches, and most of them showed that overexpression of CXCR4 is

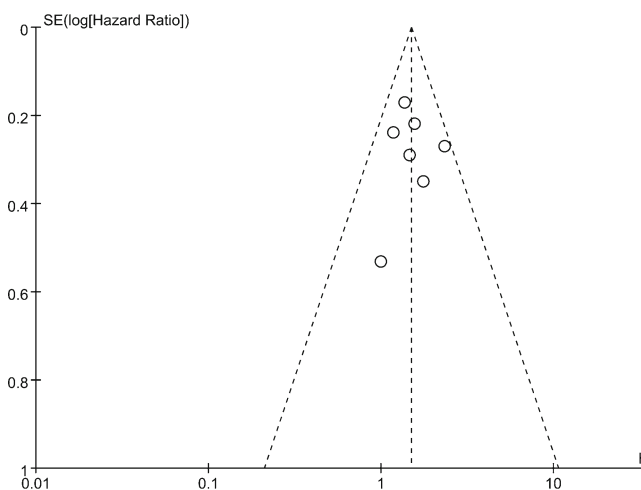


Fig. 4 Funnel plot of publication bias of hazard ratio for overall survival in the meta-analysis

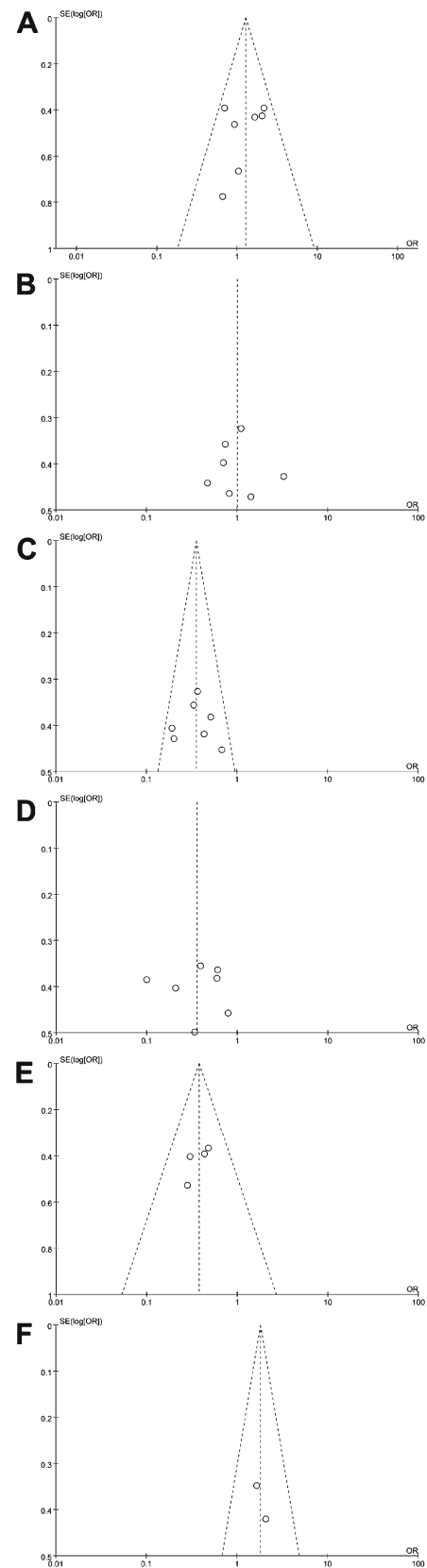


Fig. 5 Funnel plots of publication biases in the meta-analysis of CXCR4 expression and clinicopathological features. **a** Gender. **b** Differentiation. **c** Tumor depth. **d** Status of lymph node. **e** TNM staging. **f** Histological type

associated with some clinicopathologic features and a poor prognosis, but the results were not confirmed by other studies [14–21]. For procuring a reasonable conclusion, we combined seven eligible studies including 1,055 cases to perform this meta-analysis.

Exterior expansion and lymph node metastasis of esophageal cancer are the major reasons for incomplete incision of the tumor and postoperative failure which are associated with poorer survival [24, 25]. Uchida et al. and Almofti et al. discovered that overexpression of CXCR4 could apparently increase the metastatic potential of tumor cells to migrate to regional lymph nodes [26, 27]. Kaifi et al. reported that CXCR4 was expressed in 55 % of esophageal cancer, and its expression was associated with tumor cell dissemination into lymph nodes as an indicator for local disease and bone marrow as an indicator for systemic spread [15]. In present meta-analysis, we found that CXCR4 expression was related to tumor depth, status of lymph node, and TNM staging. In line with previous studies, the results of our meta-analysis supported that the function of the CXCL12/CXCR4 axis might be dependent on CXCR4. With the development of ESCC, CXCL12 selectively binds to cells with expression of CXCR4 to promote the growth of tumor cells [20]. On the other hand, previous studies showed that CXCL12 is secreted locally in high amounts by the lung, bone, and liver. The attraction of CXCL12 and CXCR4 causes breast cancer cells to metastasize into these organs [28, 29], which may lead to the reduction of survival, because metastasis is the leading cause of tumor-related death. The complex pathophysiologic pathways and processes of metastatic spread were still unclear. In a research of HER2-positive esophageal cancer, Gros et al. [30] revealed that a blockage of the CXCR4 pathway activates HER2 overexpression. Besides, under inhibition of the HER2 receptor, no metastases occur, whereas solitary inhibition of CXCR4 still leads to metastases. These suggested an involvement of CXCR4 in the HER2-mediated response, but further functional investigation was needed.

In our research, only two out of seven studies [15, 21] suggested statistically significant HRs for OS of elevated CXCR4 expression, and the remaining five studies just have shown the trend of reduced survival outcome. Sample size plays an important role in this controversy, because it serves as a strong predictor for epidemiological studies. When we pooled the data from these studies together, a remarkable association was found.

There are two main histological types of esophageal cancer: ESCC and EAC [31]. ESCC is most common in the endemic regions of the world (Asia, Southern Africa, and Eastern Africa), and EAC is most common in nonendemic areas (North America and many Western European countries). ESCC had a higher incidence rate of locoregional spread, as the development of distant metastasis was more frequently found in EAC [32]. Though the tumor-biologic behaviors of

these two esophageal cancers were different, only two studies had investigated the expression of CXCR4 in both squamous cell and adenocarcinoma up to now. The remaining five studies were all concerning about ESCC. Among pooled patients (935 ESCCs and 120 EACs), overexpression of CXCR4 was associated with ESCC, proposing that CXCR4 might be responsible for different patterns of tumor spread.

Efforts were made to conduct a comprehensive analysis, but some limitations still should be acknowledged. Firstly, two types of esophageal cancer might have different biological behaviors. It is better to perform a subgroup analysis stratified by histological types. However, having limitation to the inadequacy of studies about EAC (only two studies [14, 15]) and insufficient information to estimate the hazard ratio of OS for different histological types in one study [15], we pooled together 935 ESCCs and 120 EACs to investigate the association between CXCR4 expression and survival outcome. In the future, more efforts should be addressed in the research of EAC. Secondly, the number of included studies is relatively small. Thirdly, the survival analysis was not performed by multivariate analyses in most studies reported; we calculated or estimated the HR from available data or Kaplan–Meier curves. Fourthly, the different concentrations of antibody and the variable cut of definition of CXCR4 expression used in these studies might influence the result of our meta-analysis.

Conclusions

Overexpression of CXCR4 in esophageal cancer was not only associated with tumor exterior expansion, lymph node metastasis, and advanced TNM stage but also was a poor prognostic biomarker in our meta-analysis. Further large-scale clinical researches should be performed to investigate the precise prognostic significance of CXCR4 in esophageal cancer, especially in different histological types.

Conflicts of interest None

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