A meta-analysis of c-Met expression in head and neck cancer

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ABSTRACT

The prognostic role of c-Met expression in head and neck cancer patients were controversial among different studies. Thus, we performed a meta-analysis to evaluate the relationships between c-Met expression and survival and clinical parameters of head and neck cancer patients. The databases PubMed and Embase were searched. Summary hazard ratio (HR) and 95% confidence intervals (CIs) were calculated to analyze the correlations between c-Met expression and overall survival (OS), and disease-free survival (DFS). Furthermore odds ratios (ORs) and 95% CIs were used to describe the relationships between c-Met expression and different clinicopathological parameters. A total of 2,417 patients from 19 studies were enrolled in the final analysis. The results showed that c-Met expression was significantly associated with OS (HR: 1.65; 95% CI: 1.20–2.27, $P = 0.002$) while not DFS (HR: 1.48, 95% CI: 0.99–2.20, $P = 0.055$). And c-Met expression was associated with the N stage of head and neck cancer patients (OR: 2.11; 95% CI: 1.12–3.96, $P = 0.02$). These results suggested that c-Met expression was a risk factor for head and neck cancer; increased c-Met expression could be a predictor of a poorer prognosis for the patients.

INTRODUCTION

Head and neck cancer (HNC) are cancers that arise in the tissues of the head and neck, which includes cancers occurred in oral cavity, pharynx and larynx. Worldwide, approximately 550,000 individuals develop head and neck cancer and about 380,000 die from this disease every year [1]. In the United States, there would be more than 63,000 new cases of HNC and 13,000 deaths in 2017 [2]. Despite the incidence and mortality rate of head and neck cancer declined in the past two decades, there were no standard or routine screening tests for head and neck cancers. It is necessary to find new biomarkers that could help to screen high-risk individuals and predict the prognosis of the patients.

c-Met is a member of receptor tyrosine kinase family, it also known as hepatocyte growth factor receptor (MET). It is overexpressed in multiple human cancers, activation of c-Met could mediate the migration, invasion, and angiogenesis of tumor cells [3]. By immunohistochemistry, Knowles et al found that c-Met and /or its ligand (hepatocyte growth factor, HGF) overexpressed in nearly 80% of primary HNC tumors [4]. The prognostic role of overexpression of c-Met had been investigated in head and neck cancer [5–7], but the results were inconsistent among different studies. Thus, we carried out a system review to evaluate the prognostic role of overexpression of c-Met in head and neck cancer patients.

MATERIALS AND METHODS

Literature searching

A comprehensive literature retrieve was carried out in PubMed and Embase for the eligible studies published up to June 2017. The following keywords were used in the literature searching: “c-Met” and “head and neck cancer” or “oral cancer” or “pharyngeal cancer” or “laryngeal cancer” or “nasopharyngeal cancer” and “prognosis” or “survival”. Furthermore, we manually searched the reference lists of relevant articles to identify the possible missing publications. Studies were included unless they met the following inclusion criteria: provided survival data in head and neck cancer patients stratified by c-Met expression and sufficient data to calculate an estimate of hazard ratio (HR) and a 95% confidence interval (CI); the expression of c-Met was measured in the head and neck cancer specimens; and all selected patients were pathologically confirmed. All publications were reviewed to avoid the duplicate data. If there were overlapping between studies, only the most recent or most complete data was included.

Data extraction and quality assessment

Five investigators were divided into two groups and they conducted the literature review and extracted data from each included publication separately. For each article, the following information was extracted: author's name, publication year, sample size, research country, tumor types, clinicopathological data (number of patients with different gender, T stage, N stage and clinical stage), c-Met expression detection methods, cut-off level of high expression, and survival data (HR and its 95% CIs for OS and DFS). If the survival data were not reported in the publications, we extracted it from the Kaplan-Meier curves by the methods of Jayne et al. [8]. The extracted data were crosschecked and any disagreements were resolved by discussion.

Statistical analysis

Overall survival (OS) and disease free survival (DFS) were the main outcomes to evaluate the prognostic value of c-Met expression, hazard ratios (HRs) and 95% confidence intervals (CIs) were used to combine as the effective value. For clinicopathological data, odds ratios (ORs) and 95% CIs were used to describe the relationships between c-Met expression and different clinicopathological parameters. Pooled HRs or ORs with 95% CIs were calculated using random-effects model due to the potential substantial heterogeneity among studies [9]. I^2 statistic was used to detect the heterogeneity, it indicated the presence of significant heterogeneity if $I^2 \geq 50\%$ [10]. For survival datasets, we

further investigated potential heterogeneity by subgroup analyses stratified by tumor types, region of the study, and calculation methods of HR. We used sensitivity analysis to assess the stability of the results. Potential publication bias was evaluated by the shape of funnel plots, an asymmetric plot indicates a possible publication bias [11]. The publication bias was further assessed by Egger's test, $P < 0.05$ was considered indicative of significant publication bias [12]. The “trim and fill” method was used to examine the potential impact of the publication bias on the interpretation of the data if publication bias was found [11]. All statistical analyses were performed by Stata statistical software (version 11.0; Stata Corporation, College Station, TX, USA).

RESULTS

Literature searching and study characteristics

A total of 348 publications were found by the databases searching. After title and abstract checking, 36 studies remained for the further evaluating in details, in which 15 articles were excluded for there were no enough data to calculate the survival rate [13–27], one article was removed because of duplication [28]. So, a total of 20 publications were fulfilled the eligibility criteria [5–7, 29–45]. Among them, one study was excluded by the poor data quality [45], so 19 publications were included in the final analysis. The details of the procedures of literature screening were shown in Figure 1. Among the 19 studies, 5 studies reported head and neck cancer without site information [7, 33, 36, 39, 43], 4 studies focused on oral and oropharyngeal cancer [30, 32, 40, 44], 3 for tongue cancer [6, 29, 34], 3 for nasopharyngeal cancer [5, 35, 42], 2 for salivary gland cancer [37, 38], 1 for hypopharyngeal cancer [41] and another one for tonsillar cancer [31]. The total number of patients included in the meta-analysis was 2,417, the mean sample size was 127 (ranges from 33 to 396). Among them, 16 studies reported the overall survival (OS) and 8 for disease-free survival (DFS). We extracted hazard ratio (HR) and a 95% confidence interval (CI) from the Kaplan-Meier curves in 8 articles. The main characteristics of the included studies were listed in Table 1.

c-Met expression and the survival of head and neck cancer

We used OS and DFS as the main outcomes to evaluate the impact of c-Met expression on the survival of head and neck cancer patients. In the collected dataset, there were 16 studies reported overall survival (OS) and 8 studies reported disease-free survival (DFS). Firstly, we analyzed the relationships between c-Met expression and OS in 16 studies. The results showed that the patients with higher c-Met expression had a poor prognosis than those

with lower expression (HR: 1.65; 95% CI: 1.20–2.27, $P = 0.002$). Subgroup analysis was carried out based on tumor types, regions of the study and calculation methods of HR. Based on the region of study, we found significant association between c-Met expression and survival rate in Asian studies. In the subgroup analysis by statistical methodology, there was significant difference in the group of multivariable analysis. For different tumor types, we found c-Met expression was significant associated with the survival rate of HNC and NPC (Figure 2).

Then HR and 95% CI were calculated to test the relationship between c-Met expression and disease-free survival (DFS). The results revealed that there was no significant association between c-Met expression and DFS rate (HR: 1.48; 95% CI: 0.99–2.20, $P = 0.055$). In the subgroup analysis, the significant association was just found in “Asia” and “Multivariate” (Figure 3). All the details were listed in Table 2.

To evaluate the reliability of the results, sensitivity analysis was carried out by deleted single study each time. There was no significant change on the results of OS by removing any of the studies. As for DFS, the association changed into significant when we delete the study of “Lo Muzio”, Figure 4. The results shown single study basically did not have any influence on the results. Begg’s funnel plots were constructed to evaluate the publication bias; we did find the sign of publication bias by the shapes of

the plots in OS while not in DFS (Figure 5). The results of Egger’s test were consistent with the plot ($P = 0.006$ for OS; $P = 0.335$ for DFS). The “trim and fill” method was used to adjust for the publication bias and to find the possible influence of the bias on the results. By this method, we estimated there would be one missing study, the filled dataset is much more symmetric than the original data (Figure 6). Compared with the original results (HR: 1.65; 95% CI: 1.20–2.27, $P = 0.002$), the association between c-Met expression and the prognosis did not change when the missing study were added (HR: 1.56; 95% CI: 1.16–2.89, $P = 0.004$).

c-Met expression and clinical parameters

ORs and 95% CI were calculated to evaluate the associations between c-Met expression and different clinical parameters such as gender (male vs. female), T stage (T1/T2 vs. T3/T4), N stage (N0 vs. N+) and clinical stage (I/II vs. III/IV). Pooled ORs showed that c-Met expression was association with gender, T stage, N stage and clinical stage. But the association was not significant except between c-Met expression and N stage (OR: 2.11; 95% CI: 1.12–3.96, $P = 0.02$). Sensitivity analysis and publication bias were carried out too. The results did not change after we deleted any single study (data not show). No publication bias was found in all of these analyses. The details were showed in Table 3.

Figure 1: Flow chart of the literature searching.

Table 1: Main characteristics of the studies included in this meta-analysis

Study ID	Publication date	Country	Sample size	Median or mean age/ range(year)	Tumor type	Follow-up time/months	Cut-off	Outcome (OS/DFS)	Source of HR
Kwon	2014	South Korea	79	NA	HNC	NA	Staining intensity and the proportion of positively stained cells were summed up and the scores ≥ 4	OS/DFS	I
Baschnagel	2014	U.S.A	107	62	HNC	35(1–93)	Staining intensity value of 2.5 or higher	OS/DFS	D
MadozGúrpide	2015	Spain	33	61	HNC	NA	H-score >120	OS	D
Chau	2011	Canada	49	56	HNC	NA	Semi-quantitative score > 2	OS	D
Lo Muzio	2005	Italy	84	65	HNC	NA	Stained cells accounted more than 30%	DFS	D
Cho	2016	South Korea	396	58	HNC	37.1 (0.8–99.6)	Presence of strong and diffuse nuclear and cytoplasmic staining in $> 70\%$ of the HNSCC cells	OS	D
Kim	2006	South Korea	40	60	HPC	NA	Tumor samples were scored as positive of they were + or ++ and stained more than 30% of the cancer cells.	OS	I
Qian	2002	China	66	46.4	NPC	79 (1–163)	Fluorescent intensity > 94	OS	I
Li	2015	China	376	NA	NPC	62.4 (2.6–97.3)	$\geq 50\%$ of tumor cells with moderate or higher staining intensity	OS/DFS	D
Kim	2011	South Korea	38	48	NPC	30 (11–83)	Stained cells accounted more than 50%	OS	D
Zhao	2011	China	76	NA	OOC	41(4–80)	$> 30\%$ tumor cells were scored + or ++	OS/DFS	I
Perisanidis	2013	Austria	113	NA	OOC	4.6 years	IHC score	OS/RFS	D
Freudlsperger	2010	Germany	211	58	OOC	42 (1–172)	Specimens with $\geq 50\%$ of cancer cells	OS	I
Aebersold	2001	Switzerland	97	57	OOC	2.6 years	Moderate (++) or strong (+++) staining	OS/DFS	D
Bell	2015	U.S.A	200	52	SGC	NA	Strong staining in $>50\%$ of the neoplastic cells	OS	I
Ach	2013	Germany	221	60.2	SGC	4.85 years (0.1–21.2)	Immunoreactivity score (IRS) > 10	DFS	I
Endo	2006	Japan	99	61.7	TC	NA	Positive cells $\geq 45\%$	DFS	D
Lim	2012	South Korea	71	NA	TC	6.1 years	Tumor samples were scored as positive of they were + or ++ and stained more than 30% of the cancer cells.	OS	I
Kim	2010	South Korea	61	53.5	TC	NA	Tumor samples were scored as positive of they were + or ++ and stained more than 30% of the cancer cells.	OS	D

Abbreviate: NA: not available; HNC: head and neck cancer; NPC: nasopharyngeal cancer; OOC: oral and oropharyngeal cancer; SGC: salivary gland cancer; TC: tongue cancer; HPC: Hypopharyngeal cancer; OS: overall survival; DFS: disease-free survival; RFS: recurrence-free survival; D: directly extracted from the articles; I: estimated from Kaplan-Meier plots.

DISCUSSION

c-Met was first identified in the 1980s as an oncogene [46]. It is overexpressed in a variety of tumors and plays an important role in malignant transformation, activated c-Met could mediate tumor growth, metastasis and angiogenesis [47]. It had been reported that c-Met could activate a lots of downstream signal factors, such as MAPK, PI3K/AKT and STAT3 [48, 49]. Given its critical role in tumor malignant transformation, c-Met could be considered as a prognosis marker for cancer. But the prognosis role of c-Met in human head and neck cancer is unclear, the results is inconsistent among different studies, so we carry out this meta-analysis to combine these studies and get a more reliable result.

To our knowledge, the present meta-analysis is the first one to consider the relationships between c-Met expression and clinical pathological parameters and prognosis of human head and neck cancer. In this study, 2,417 patients from 19 studies were collected. For all kinds of head and neck cancer, the results showed that patients with higher c-Met expression had a bad overall survival rate ($P = 0.002$), but for the disease-free survival rate, the association was not significant ($P = 0.055$). Even though oral cavity and pharynx were the most common sites of the head and neck cancer, we did not find significant associations between c-Met expression and survival in oral and oropharyngeal cancer (OOC) and tongue cancer (TC), which could be the result of small sample size. So more studies with large number of patients were needed to

Figure 2: Forest plots of hazard ratios (HRs) for the association between c-Met expression and overall survival (OS) in head and neck cancer patients. Plots for all datasets (A) and subgroup analysis based on region (B), analysis type (C) and tumor type (D). The 95% confidence intervals (CI) for individual studies are represented by a horizontal line and by a diamond for pooled effect. CI denotes confidence interval.

Table 2: Main results of the meta-analysis

Categories	Number of studies	HR	95%CI	P*	Degree of heterogeneity (I ² statistics; %)
OS	16	1.65	1.20–2.27	0.002	76.20%
Region					
Europe	4	1.35	0.62–2.95	0.451	85.20%
North America	3	2.02	0.86–4.75	0.106	79.30%
Asia	9	1.85	1.42–2.40	< 0.001	0%
Analysis type					
Multivariate	5	2.12	1.61–2.78	< 0.001	0%
Univariate	11	1.4	0.97–2.01	0.072	66.40%
Tumor types					
HNC	5	2.32	1.47–3.66	< 0.001	22.00%
NPC	3	2.02	1.36–2.99	< 0.001	6.90%
OOC	4	1.21	0.60–2.41	0.596	83.80%
TC	2	1.69	0.68–4.21	0.256	0%
DFS	8	1.48	0.99–2.20	0.055	56.00%
Region					
Europe	3	1.23	0.44–3.44	0.7	84.10%
Asia	4	1.7	1.26–2.28	< 0.001	0%
Analysis type					
Multivariate	4	1.35	0.62–2.94	0.44	0.00%
Univariate	4	1.59	1.06–2.36	0.02	56.00%
Tumor types					
OOC	2	1.98	0.86–4.55	0.11	54.30%
HNC	3	1	0.30–3.34	0.995	79.70%

Abbreviations: OS: overall survival; HNC: head and neck cancer; NPC: nasopharyngeal cancer; OOC: oral and oropharyngeal cancer; TC: tongue cancer; OS: overall survival; DFS: disease-free survival; HR: hazard ratio; CI: confidence interval.

**P value for HR.

Table 3: Association of c-Met expression with clinical features in head and neck cancer

Clinical parameter	Number of studies	OR	95%CI	P*	Degree of heterogeneity (I ² statistics; %)
Gender (male vs. female)	9	1.14	0.89–1.49	0.293	0%
T stage (T1/T2 vs. T3/T4)	9	1.37	0.96–1.96	0.08	34.40%
N stage (N0 vs. N+)	7	2.11	1.12–3.96	0.02	66.80%
Clinical stage (I/II vs. III/IV)	7	1.97	0.86–4.51	0.108	74.30%

Abbreviations: OR: odds ratio; CI: confidence interval; *P value for OR.

clarify the relationships between c-Met expression and the survival rate of OOC and TC.

Furthermore, we found the results were different between subgroup of univariable analysis and multivariable analysis. For overall survival (OS), we found there was significant association in the subgroup of “multivariate analysis”, but for disease-free survival (DFS), the results showed there was significant

association in the subgroup of “univariate analysis”. In survival analysis, the “univariate” was used to evaluate the relations of the single factor to the survival rate, but the single factor was seldom informative due to relations among different factors and the potential interaction among the other factors to the survival rate. These issues could be handled by multivariate analysis, which could evaluate the effect of single factor without

Figure 3: Forest plots of hazard ratios (HRs) for the association between c-Met expression and disease-free survival (DFS) in head and neck cancer patients. Plots for all datasets (A) and subgroup analysis based on region (B), analysis type (C) and tumor type (D). The 95% confidence intervals (CI) for individual studies are represented by a horizontal line and by a diamond for pooled effect. CI denotes confidence interval.

Figure 4: Sensitive analysis of the pooled hazard ratio for OS (A) and DFS (B). Meta-analysis random effects estimates were used. Results were computed by omitting each study (on the left) in turn. The two ends of every broken line represented the 95% confidence interval.

Figure 5: Funnel plot for the assessment of publication bias of the included literature for OS (A) and DFS (B).

Figure 6: Funnel plot with 'filled' studies for analysis of overall survival. The circle represents the literatures enrolled in the analysis; the square represents the filled one.

the interaction of others. So the results of multivariate analysis were much more reliable than the results of univariate analysis.

As for the relationships between c-Met expression and clinical parameters of head and neck cancer, we found the expression of c-Met was associated with the N stage (N0 vs. N+). Patients with higher c-Met expression had a significant higher probability to occur lymph node metastasis. Based on these results, c-Met expression could act as a valuable prognosis marker for head and neck cancer patients.

Heterogeneity is an important indication to evaluate a meta-analysis. The heterogeneity test showed that there was obvious heterogeneity among different studies. In this study, we used random-effect model to calculate the pooled OR and HR to reduce the effect of the heterogeneity to the results. As for the source of heterogeneity, it may mainly come from different tumor types, studies regions and analysis types. So, we carry out the subgroup analysis to reduce the heterogeneity. The results showed the heterogeneity reduce or disappear in most subgroups. The results showed that Asian studies were quite homogeneous, while there was obvious heterogeneity in the Europe and North American studies. The possible reason of the high heterogeneity in these subgroups was that the number of the studies in these two groups is relatively small and these studies focused on different tumor types.

Sensitivity analysis and publication bias are the other two important ways to test the liability of the results of meta-analysis. These results showed our study were accurate and trustiness. But there are still some limitations in the present study. First, the number of the enrolled studies is relatively small, especially for each kind of cancer. Second, the sample size was small, most of the included studies just had limited patients (< 100).

In conclusion, c-Met expression was a risk factor for head and neck cancer patients, the patients with higher c-Met expression had a significant poorer survival rate. It would be helpful to define the high-risk patients by determination of the expression of c-Met. But more studies with larger sample size were needed to expound the relationships between c-Met expression and prognosis of head and neck cancer patients.

Author contributions

H.S., L.M. and G.L. designed the research. L.L., Z.S., X. H., X. L., and L.S. collected articles and extracted data. L.L., Z.S., L.Z., X.Z. L.Y., and J.Y. performed the statistical analysis. L.L. and H.S. wrote the manuscript. All of the authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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