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Over-expression of cyclo-oxygenase-2 predicts poor survival of patients with nasopharyngeal carcinoma: a meta-analysis

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Main Article

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Abstract

Objectives. The conclusive prognostic significance of cyclo-oxygenase-2 has been determined in various cancers but not in nasopharyngeal carcinoma. Therefore, this study aimed to evaluate the relationship of cyclo-oxygenase-2 expression with the survival outcome and treatment response of nasopharyngeal carcinoma patients via a systematic meta-analysis approach.
Methods. A meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') checklist. The primary clinical characteristics of patients, and hazard ratios with 95 per cent confidence intervals of overall survival data, were tabulated from eligible studies. The relationship of cyclo-oxygenase-2 expression with survival outcome (expressed as hazard ratio) and treatment response (expressed as odds ratio) in nasopharyngeal carcinoma patients was analysed, and explained with the aid of forest plot charts.
Results and conclusion. The pooled hazard ratio for overall survival was 2.02 (95 per cent confidence interval = 1.65–2.47). This indicates that the over-expression of cyclo-oxygenase-2 is significantly associated with the poor survival of nasopharyngeal carcinoma patients. The pooled odds ratio of 0.98 (95 per cent confidence interval = 0.27–3.49) reveals that over-expression of cyclo-oxygenase-2 was not significantly related to the treatment outcome.

Introduction

Nasopharyngeal carcinoma is a form of malignancy at the tissue of the upper section of the pharynx behind the nose – the nasopharynx region.[1] Globally, the disease accounts for 65 000 deaths yearly and has a regionally varied incidence rate.[2] In endemic regions, such as Southern China, Southeast Asia and the Middle East, there are over 20 cases of nasopharyngeal carcinoma per 100 000 people, although it is rare in North America and Europe.[3]

Based on the World Health Organization classification, nasopharyngeal carcinoma is histologically categorised into three subtypes: type I is characterised by keratinising differentiated squamous cell carcinoma (SCC); type II (or 2a) is distinguished by non-keratinising differentiated SCC; and type III (or 2b) is typified by non-keratinising undifferentiated basaloid SCC.[4] The latter, more chemosensitive type III/2b is predominant among Asian cases, whereas types I and II/2a are mostly found in Western countries.[5]

Risk factors for nasopharyngeal carcinoma include genetic factors, viral infection (Epstein–Barr virus), environmental factors, lifestyle influences (smoking) and the consumption of certain preserved foods.[6] The early stages of malignancy usually involve invasion of nasopharyngeal carcinoma cells to surrounding tissue and cervical lymph nodes.[7,8] Despite the radio-sensitivity of nasopharyngeal carcinoma tumours, patients with advanced disease stages show poor survival.[9–12] Improved therapeutic techniques, such as concurrent chemotherapy with or without neo-adjuvant or adjuvant intensity-modulated radiotherapy (RT), and high-resolution magnetic resonance image monitoring, have been the standard treatment protocol for locally advanced nasopharyngeal carcinoma.[13–15] Nevertheless, relapse and metastasis still occur in approximately 20–50 per cent of patients.[16]

Studies have shown that nasopharyngeal carcinoma patients with the same disease classification present with different prognoses.[17,18] This suggests that consideration of ethnicity[19] and biomolecular factors associated with survival outcome[20] may be necessary to accurately distinguish nasopharyngeal carcinoma patients for individualised and tailored treatment. Hence, it is important to identify prognostic factors (particularly molecular and genetic factors) that correspond closely to the actual clinical outcomes for the improvement of therapies, to yield a better treatment outcome.

One candidate biomarker of potential prognostic significance to nasopharyngeal carcinoma is the cyclo-oxygenase-2 gene. Expression of cyclo-oxygenase-2 has clinical and prognostic significance in cancers of the head and neck.[21] Its involvement in nasopharyngeal carcinoma carcinogenesis is most probably during the formation of the inflammatory microenvironment associated with tumorigenesis and malignancy. Cyclo-oxygenase-2

Table 1. Terms and search strategies used in electronic databases*

Search terms	Search strategy†
1. 'Nasopharyngeal neoplasm' or 'NPC' or 'nasopharyngeal carcinoma'	1 & 2
2. 'Cyclooxygenase-2' or 'COX-2' or 'prostaglandin-endoperoxide synthase'	

*The electronic databases searched were PubMed, Science Direct and Scopus. †The search strategy used for all databases.

over-expression is associated with metastasis to the lymph nodes in nasopharyngeal carcinoma patients,[22] and is thought to mediate this process by promoting interactions between cancer cells and myeloid-derived suppressor cells.[23]

Cyclo-oxygenase-2 is a key enzyme in the conversion of arachidonic acid to prostaglandins, and is poorly expressed (if detectable at all) in most normal tissues, but is rapidly induced by pro-inflammatory cytokines, growth factors, carcinogens and tumour promoters.[24–27] Over-expression of cyclo-oxygenase-2 in various cancers has been linked to angiogenesis, invasion and apoptotic resistance, suggesting an involvement in inflammation-induced tumorigenesis, and an influence on the outcome and survival of cancer cells.[23,25,28–32] Interestingly, the functional abrogation of cyclo-oxygenase-2, via cyclo-oxygenase inhibitor, reverses cancer progression. Actions of cyclo-oxygenase inhibitor and non-steroidal anti-inflammatory drugs have been reported to reduce the incidence and progression of tumours in animal models.[33–35]

To date, there has been no comprehensive review of cyclo-oxygenase-2 in terms of its prognostic value for nasopharyngeal carcinoma. It is difficult to make inferences based on existing literature linking the expression of cyclo-oxygenase-2 to nasopharyngeal carcinoma tissues because of differences in experimental study methodology and relatively small sample sizes, which have resulted in inconsistent findings. Herein, we report a systematic review and meta-analysis study conducted (in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') checklist) to establish the relationship of cyclo-oxygenase-2 expression with the survival outcome and treatment response of nasopharyngeal carcinoma patients.

Materials and methods

Literature search

A literature search was conducted via electronic and manual search strategies. Electronic sources included PubMed, Science Direct and Scopus. Manual searches were performed using the reference lists of relevant articles. The keywords used to retrieve related articles and abstracts were: 'nasopharyngeal carcinoma', 'NPC' or 'nasopharyngeal neoplasm', and 'cyclooxygenase-2', 'COX-2' or 'prostaglandin-endoperoxide synthase' (Table 1). The last date of the literature search was 7 March 2019.

Selection criteria

The titles and abstracts of all articles retrieved from the literature search were scrutinised for relevancy based on specific inclusion and exclusion criteria. The inclusion criteria were: (1) studies containing nasopharyngeal carcinoma patients; (2) articles evaluating the expression of cyclo-oxygenase-2; (3) studies with data related to hazard ratio and/or odds ratio with a 95 per cent confidence interval (CI); (4) papers reported in English; and (5) investigations conducted on humans.

The exclusion criteria were: (1) review articles or letters; (2) papers written in Chinese; (3) studies with duplicated data; (4) articles containing insufficient information to calculate the log hazard ratio, standard error of log hazard ratio and/or odds ratio for analysis; (5) meta-analysis articles; and (6) single nucleotide polymorphism related reports.

Following article selection, the full texts of the potential eligible studies were downloaded to procure the required data. In order to avoid duplication, only the newest article with biggest sample size was included when more than one trial was carried out within the same patient population.

Data retrieval

Data extracted from each eligible study included: the first author's surname, publication year, region of publication, ethnicity, number of female patients, number of patients with high or low cyclo-oxygenase-2 expression, cyclo-oxygenase-2 expression assay (method and cut-off level), clinicopathological data (number of patients with different tumour stages), therapy regimen used, and survival data (hazard ratio for overall survival, and odds ratio for treatment response, with 95 per cent CIs).

Statistical analysis

The primary result of interest in this meta-analysis was overall survival rate, which was expressed as a hazard ratio with a 95 per cent CI. Overall survival is a direct estimate of the clinical benefit to a patient, and is defined as the time from random assignment to death.[36] Log hazard ratio and standard error of log hazard ratio data available in the eligible studies were extracted for our meta-analysis. In instances where these data were not shown, methods developed by Parmar and colleagues[37] were used to obtain the relevant data. Appropriate methods were used to determine the pooled hazard ratio, CI and weight. A hazard ratio of more than 1 reflects a poor prognosis in cyclo-oxygenase-2 over-expression. Significance of the outcome was proven at $p < 0.05$. Significant heterogeneity exists in pooled hazard ratios when $p < 0.10$ or $I^2 > 50$ per cent. The results for each individual study and the pooled results for the eligible studies were displayed as forest plots.

The odds ratio was used to determine the impact of cyclo-oxygenase-2 expression on treatment response. MedCalc (version 18.11) statistical software was used to determine the odds ratio with a 95 per cent CI. The odds ratio for included studies were also displayed using forest plots. The same software was employed to determine the publication bias, represented by I^2 and p-values. Heterogeneity was considered significant for pooled odds ratios where $p < 0.10$ or $I^2 > 50$ per cent; this was graphically represented using a funnel plot. Publication bias was considered significant when $p > 0.10$; this can be visually evaluated by funnel plot asymmetry.

Results

Eligible studies

In the initial search, 46, 24 and 37 potential studies were obtained from Scopus, Science Direct and PubMed,

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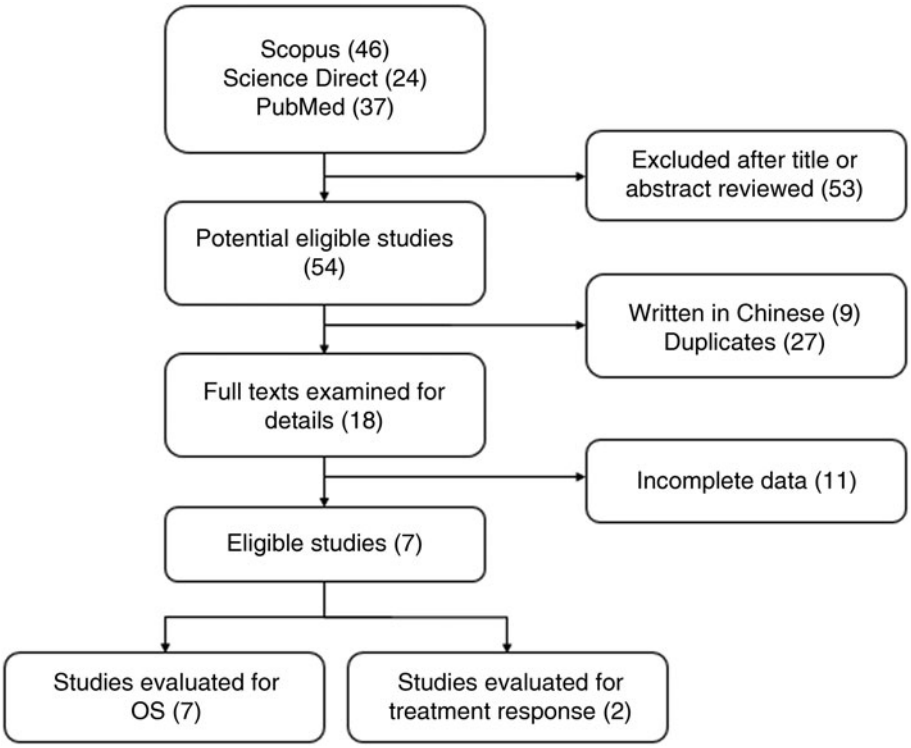

Fig. 1. Flowchart for the selection of eligible studies. OS = overall survival

respectively, yielding a total of 107 studies (Figure 1). From these, 53 studies were excluded after their titles and abstracts were reviewed and deemed irrelevant. The full texts of the remaining 54 potentially relevant studies were downloaded and reviewed in detail. Subsequently, another 36 studies were excluded because 9 were written in Chinese and 27 were duplicates. Eleven of the remaining 18 articles had incomplete data, preventing inclusion in the meta-analysis, leaving a final total of 7 eligible studies (Figure 1).

The publication years for these 7 eligible studies,[38–44] which include a total of 495 patients (range of 38–148 per study), are between 2009 and 2018. Retrieved clinical information from these patients is shown in Table 2. All the studies involved cases in Asia, and hence only Asian patients. Except for one study, female patients represented a minority group among the total number of patients included. In six of the studies, most patients had advanced disease (stage III and IV) upon diagnosis. Although a variety of chemotherapy strategies were employed, the dominant treatment method reported in six of the studies was RT. With the exception of one study, the detection method for cyclo-oxygenase-2 expression was immunohistochemistry assay. Four of the studies had more patients in the high expression group. All seven articles provided data (overall survival) for survival analysis, whereas only two articles provided data (odds ratios) for the analysis of treatment response.

Correlation with survival outcome

Correlation of cyclo-oxygenase-2 expression with nasopharyngeal carcinoma patients' survival outcome was determined by the hazard ratio value of overall survival. The pooled hazard ratio of overall survival from the seven studies was 2.02 (95 per cent CI = 1.65–2.47) (I^2 = 84 per cent, $p < 0.001$) in a random model (Figure 2). The patient group with higher cyclo-oxygenase-2 expression showed a higher risk of death compared to the control groups, as the hazard ratio obtained was greater than 1. The hazard ratio value of 2.02 implies that at any time during the follow up, the patient group with cyclo-oxygenase-2 over-expression had a 102 per cent higher risk of death. Overall survival was statistically significant because the 95 per cent CI did not include 1. However, the results showed significant heterogeneity, suggesting that our findings may be improved further by a greater sample size.

Correlation with treatment response

Two of the seven studies that had sufficient data on treatment response were analysed to determine the correlation between cyclo-oxygenase-2 expression and treatment response in nasopharyngeal carcinoma patients. The odds ratio results were evaluated for this purpose. The pooled odds ratio was 0.98 (95 per cent CI = 0.27–3.49) (I^2 = 46.7 per cent, $p = 0.171$) in a random model (Figure 3). As the odds ratio was less than 1, the treatment response among patients with high cyclo-oxygenase-2 expression was better than for the control group. Nonetheless, this result is not statistically significant because the 95 per cent CI included 1.

Publication bias

Based on the funnel plot (odds ratio *vs* standard error; Figure 4), no publication bias is evident. Hence, our result is significant, and closely relevant to the true scenario.

Discussion

The main finding of our meta-analysis is that over-expression of cyclo-oxygenase-2 is associated with a poor prognosis of nasopharyngeal carcinoma patients with respect to survival outcome. In fact, patients with high cyclo-oxygenase-2 level

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Table 2. Patient characteristics and clinical information from relevant studies

First author	Year	Region	Ethnicity	Females (*n* (%))	High/low COX-2 (*n* (%))	COX-2 detection method	Cut-off value	Stage of NPC patients (*n*)	Chemotherapy regimen	Survival outcome
Li YJ[38]	2018	China	Asian	28 (24.3)	53/62 (46.1/53.9)	RNA ISH	NR	– I & II = 31 – III & IV = 84	RT, concurrent CRT (platinum)	OS
Xu L[39]	2013	China	Asian	93 (62.8)	107/41 (72.3/27.7)	IHC	Score	– I & II = 95 – III & IV = 53	NR	OS
Pan J[40]	2012	China	Asian	27 (24.3)	59/52 (53.2/46.8)	IHC	NR	– I & II = 30 – III & IV = 81	RT, combined CRT (5-FU)	OS
Kim YJ[41]	2011	Korea	Asian	19 (27.5)	43/26 (62.3/37.7)	IHC	Score	– I & II = 17 – III & IV = 52	RT, induction CRT, concurrent CRT	OS
Huang TL[42]	2010	Taiwan	Asian	61 (36)	NR	IHC	H-score	– I & II = 71 – III & IV = 99	RT	OS
Kim TJ[43]	2010	Korea	Asian	8 (21)	31/7 (82/18)	IHC	NR	– I & II = 6 – III & IV = 32	Induction CT, RT, concurrent CRT	OS
Loong SL[44]	2009	Singapore	Asian	9 (15.5)	24/34 (41.4/58.6)	IHC	Score	– I & II = 0 – III & IV = 58	RT, CRT	OS

COX-2 = cyclo-oxygenase-2; NPC = nasopharyngeal carcinoma; ISH = in situ hybridisation; NR = not related; RT = radiotherapy; CRT = chemoradiotherapy; OS = overall survival; IHC = immunohistochemistry; 5-FU = 5-fluorouracil; H-score = histological score

were 2.02 times more likely to die post-treatment relative to those in the low expression group.

This observed correlation between poor prognosis and up-regulation of cyclo-oxygenase-2 has also been reported in previous studies of different cancers. Its over-expression has been linked to angiogenesis and lymph node metastasis in breast carcinoma,[45] and tumour progression in head and neck SCC[46] and in oral SCC.[47] There has only been one study that contradicts this observation. Loong and colleagues[44] reported that weak or low (rather than high) cyclo-oxygenase-2 expression was associated with a worse survival rate in nasopharyngeal carcinoma patients. Nevertheless, our analysis, which involved pooled data from multiple nasopharyngeal carcinoma studies, validates our conclusion, and affirms the reliability of cyclo-oxygenase-2 as a prognostic marker for nasopharyngeal carcinoma.

In nasopharyngeal carcinoma carcinogenesis, the up-regulation of cyclo-oxygenase-2 most probably plays essential roles in angiogenesis, invasion, metastasis and apoptosis inhibition, demanding a persistent presence in a wide range of pre-neoplastic and malignant conditions.[33–35] The induction of cyclo-oxygenase-2 by inflammatory cytokines, tumour promoters and growth factors in cancer cells and tissues[48] maintains its level in cancer progression, where it acts in concert with vascular endothelial growth factor and epidermal growth factor receptor, which are similarly activated.[49,50]

Incidentally, the tumourigenic effects of cyclo-oxygenase-2 are inhibited by specific cyclo-oxygenase-2 inhibitors.[23,45,51] One such inhibitor is celecoxib, which has anti-proliferative, anti-invasive and anti-angiogenic effects on nasopharyngeal carcinoma cell lines in a dose-dependent manner.[52] Celecoxib could potentially be used in combination with current chemotherapy and RT strategies in the treatment of nasopharyngeal carcinoma; this is a prospect that warrants clinical trial studies.

- Previous studies have investigated the association between cyclo-oxygenase-2 expression and nasopharyngeal carcinoma
- These studies lacked systematic evaluation of expression patterns correlated with survival outcome and treatment response
- This study is the first to evaluate cyclo-oxygenase-2 expression associated with survival outcome and treatment response in nasopharyngeal carcinoma patients via systematic meta-analysis
- Cyclo-oxygenase-2 over-expression was associated with poor survival among nasopharyngeal carcinoma patients
- Cyclo-oxygenase-2 over-expression was not significantly related to treatment outcome in these patients

Our treatment response analysis indicated that patients with high cyclo-oxygenase-2 expression responded better compared to those with low expression or control groups. However, our result was statistically insignificant and hence inconclusive. This could be partly because of the very limited number of studies (only two) available for meta-analysis. The responsiveness of chemotherapy and/or RT among nasopharyngeal carcinoma patients with high cyclo-oxygenase-2 levels requires further exploration; additional clinical and experimental studies are needed to verify this.

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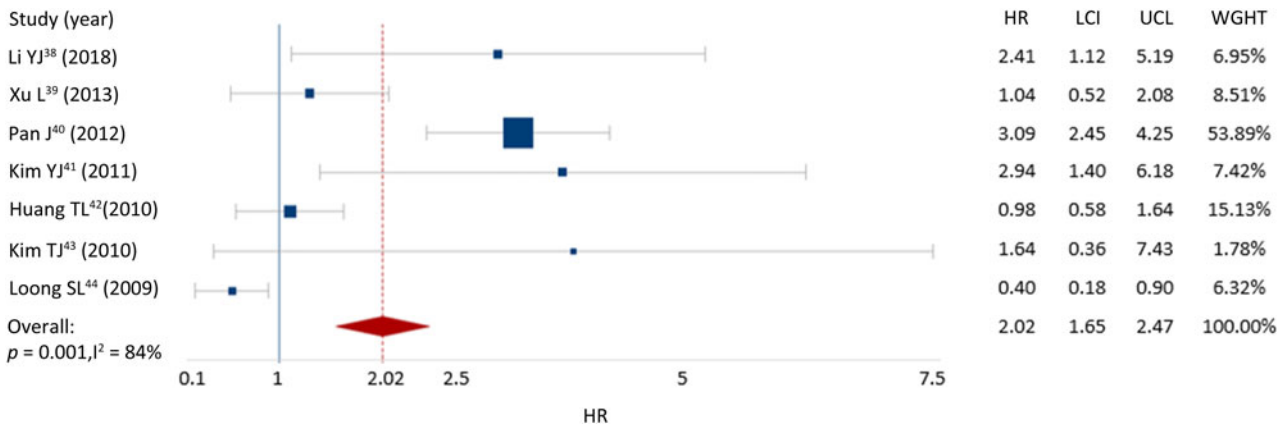

Fig. 2. A forest plot showing the meta-analysis estimate of cyclo-oxygenase-2 expression with overall survival (hazard ratio (HR) estimated in random model).
LCI = lower confidence interval; UCL = upper confidence limit; WGHT = weight

Fig. 3. A forest plot showing the meta-analysis estimate of cyclo-oxygenase-2 expression with treatment response (odds ratio (OR) estimated in random model).
LCI = lower confidence interval; UCL = upper confidence limit; WGHT = weight

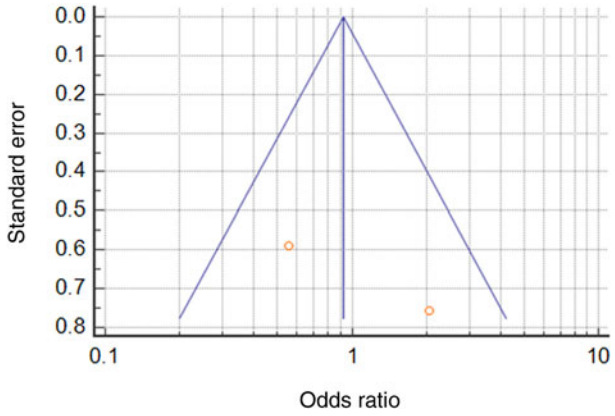

Fig. 4. A funnel plot to detect publication bias and systemic heterogeneity in the meta-analysis.

Conclusion

Our study showed a low survival rate among nasopharyngeal carcinoma patients with high cyclo-oxygenase-2 expression. This is the first study to scientifically establish the relevance of cyclo-oxygenase-2 as a prognostic biomarker for nasopharyngeal carcinoma in terms of post-treatment survival outcome. The development of a standard protocol for evaluating cyclo-oxygenase-2 expression in nasopharyngeal carcinoma patients following chemotherapy and RT should now have direct applicability in the management and treatment of nasopharyngeal cancer.

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Competing interests. None declared

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