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Original article

Surrogate endpoints for overall survival in combined chemotherapy and radiotherapy trials in nasopharyngeal carcinoma: Meta-analysis of randomised controlled trials

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ABSTRACT

Background and purpose: We used a literature-based meta-analysis to assess whether failure-free survival (FFS) or progression-free survival (PFS) could be reliable surrogate endpoints for overall survival (OS) in trials of combined chemotherapy and radiotherapy for nasopharyngeal carcinoma (NPC).

Methods and materials: We identified randomised trials that evaluated combined chemoradiotherapy strategies, and reported FFS or PFS and OS in NPC. We analysed the treatment effects on FFS or PFS, and OS. We used the coefficient of determination (R^2), and the surrogate threshold effect (STE) to assess the trial-level correlation.

Results: Twenty-one trials (5212 patients), with sixteen treatment-control comparisons for FFS, and nine for PFS, were analysed. FFS was strongly correlated with OS (R^2 = 0.88, STE = 0.84), as was PFS (R^2 = 0.90, STE = 0.88). Moreover, FFS and PFS at 3 years were still strongly correlated with 5-year OS (R^2 = 0.80, STE = 0.83; R^2 = 0.85, STE = 0.84).

Conclusions: Both FFS and PFS could be valid surrogate endpoints for OS in trials of combined chemotherapy and radiotherapy for NPC; PFS may be a more acceptable surrogate endpoint compared with FFS.

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Nasopharyngeal carcinoma (NPC) is a unique head and neck cancer with an extremely unbalanced distribution: the age-standardised incidence rate ranges from 20 to 50 per 100,000 males in south China to 0.5 per 100 000 in mainly white populations [1]. Worldwide, around 84 400 new cases of NPC are diagnosed annually, with 51,600 deaths in 2008 [1]. Radiotherapy is the primary treatment for non-disseminated NPC because of its anatomical location and radiosensitivity. Using intensity-modulated radiotherapy, the local control rates have been further improved, and distant metastasis is now the predominant cause of treatment failure [2].

NPC is also highly chemosensitive; therefore, many randomised trials have investigated the efficacy of combining chemotherapy with primary radiotherapy in the past two decades [3]. Concurrent chemoradiotherapy, with or without adjuvant chemotherapy, is the most efficacious [4–6], and is now the standard treatment for stages IIB and advanced disease. The addition of neoadjuvant chemotherapy is promising, and the results of phase III trials are awaited [7].

The gold standard endpoint in randomised trials of NPC is overall survival (OS), because of its simple and reliable measurement, and its easy interpretation; OS at 5 years is commonly used to assess the long-term benefits of a particular treatment. However, this endpoint has disadvantages: it requires a large number of patients and an extended follow-up period to detect statistically significant differences. Besides, its measurement is potentially diluted by non-cancer deaths and subsequent therapies after progression.

Present in various definitions in the trials of NPC, the main potential surrogate endpoints for OS are failure-free survival (FFS), and progression-free survival (PFS). Whether improved FFS or PFS is a predictor of improved OS needs to be understood. Therefore, we aimed to analyse the literature to determine whether FFS or PFS could be used as surrogate endpoints to assess the effect of combined chemotherapy and radiotherapy in NPC.

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Such surrogates would shorten the duration of trials, thereby reducing the development cost of effective therapies for NPC.

Materials and methods

Search strategy and data collection

In January 2015, we searched Medline systematically using the key words "nasopharyngeal neoplasm", "radiotherapy" and "chemotherapy". The results were limited to "clinical trial," "controlled clinical trial," or "randomized controlled trial." The Embase and Central Registry of Controlled Trials of the Cochrane Library, and conference reports presented at the annual meetings of American Society of Clinical Oncology, European Society for Medical Oncology, and European Cancer Organisation Congress were also searched. There was no language restriction in the search, and any studies that met the inclusion criteria would be included in this meta-analysis.

Inclusion criteria were randomised controlled trials of combined chemotherapy and radiotherapy for non-metastatic NPC, reporting OS, and FFS and/or PFS in full-text publications. Patients should have received definitive radiation with conventional fraction to the primary lesion. For each trial, intention-to-treat data on study design, trial conduct period, sample size, staging information, treatment protocol, FFS and/or PFS, OS results, and follow-up duration were collected. Our analysis primarily used the treatment effects on FFS and/or PFS, and OS at 5 years, while censoring all events taking place after this time-point. Unadjusted hazard ratios (HRs) for the endpoints that were available directly in an individual trial were used. Otherwise, FFS and/or PFS, and OS were determined for treatment arms using published data or survival curves, according to methods detailed by Parmar et al. [8].

Endpoints definitions

OS was defined as the time from randomisation to death from any cause. FFS was defined as the time from randomisation to disease progression (first failure at any site). PFS was defined as the time from randomisation to disease progression or death from any cause. Patients with no documented evidence of events were censored at the date of last follow-up. As the surrogate endpoints were usually defined differently in the trials, two investigators (YPC and YS) labelled an endpoint of a trial as FFS or PFS according to our established definitions, regardless of the terminology used by the original authors.

Statistical analysis

Our quantitative evaluation used a correlation approach to assess trial-level statistical surrogacy, as previously described [9,10]. The analysis is at the trial-level throughout, with no patient-level data being incorporated. To quantify the trial-level correlations between the treatment effects (log hazard ratios) on FFS/PFS and OS, we applied an errors-in-variables linear regression model, which accounted for measurement error of the estimated effects [11]. For the errors-in-variables regression, we used a conservative reliability coefficient of 0.9 [12]. The regression was weighted by trial size. We down-weighted comparisons from trials with more than two arms after A'Hern et al. [13], because they are not independent. We calculated the coefficient of determination, R^2 (or the explained variation), to assess the strength of association. A squared correlation value >0.75 was deemed to be a strong correlation between OS and the surrogate endpoints at the trial level.

On the basis of a linear regression model adjusted for estimation error, we calculated the surrogate threshold effect (STE), defined as the minimum treatment effect on the surrogate necessary to predict an OS benefit [14]. The upper limit of the confidence interval for the estimated surrogate treatment effect should be below the STE to predict a non-zero effect on OS.

For each meta-analysis, we used a leave-one-out cross-validation strategy to evaluate the prediction accuracy of the surrogate model. Each trial was left out once at each step, and the surrogate model was rebuilt with the other trials. This model was then applied to the left-out trial, with a calculated 95% prediction interval, to compare the predicted and observed treatment effects on OS [15].

To reflect typical conditions, correlations between treatment effects on 1, 2, and 3-year surrogate endpoints, and 3 and 5-year OS were assessed, while censoring all events taking place after these respective time-points. Statistical analyses were done with Stata 12.

Results

After the screening procedure, 28 articles reporting 21 trials were included (Supplementary Fig. S1, Table 1) [16–43]. We excluded the trial by Zhang et al. [44,45] as no FFS or PFS was reported; the trial by Lee et al. [46] was excluded because the data for OS could not be extracted. The trial by Chan et al. was first published in 2002 [25] and updated in 2005 [26] with the long-term outcome. The same updates were made to the trials by Lee et al. [29,30,32,33], Chen et al. [34,35], Huang et al. [36,37], and Xu et al. [42,43]. The preliminary report of the trial by Chua et al. was published in 1998 [20], and the long-term outcome of the majority of patients was reported in 2001 [21]; thus we included the latter publication in our study. Note that only the 4-year FFS and OS could be extracted from the trial by Rossi et al. [16], and FFS was calculated from the date of documented complete response in the trials by Chan et al. [17] and Hareyama et al. [23]. The trial by Kwong et al. [28] had a 2×2 design. It tested the efficacy of concurrent chemoradiotherapy, and adjuvant chemotherapy independently, with patients divided into four treatment groups: Group A (radiotherapy alone), Group B (Concurrent chemoradiotherapy), Group C (radiotherapy and adjuvant chemotherapy), and Group D (concurrent chemoradiotherapy and adjuvant chemotherapy). Two comparisons were included in our analysis: additional concurrent chemoradiotherapy (Group B + D versus Group A + C), and additional adjuvant chemotherapy (Group C + D versus Group A + B). The two trials by Lee et al. [29,30,32,33] and the trial by Chen et al. [34,35] reported both FFS and PFS. Overall, the 21 qualifying trials (5212 patients) yielded 25 comparisons, with 16 comparisons for FFS, and nine for PFS (Table 2); the 1- to 5-year FFS/PFS of each trial are shown in Supplementary Table S1, while the 3- and 5-year OS of each trial are shown in Supplementary Table S2.

FFS was strongly correlated with OS ($R^2 = 0.88$) with normality of error (no heteroskedasticity). The estimated HRs on the endpoints and the linear regression lines are depicted in Fig. 1. The linear regression model adjusted for estimation errors was: log (HR OS) = 0.07 + 1.42 × log (HR FFS). The slope of the regression was 1.42 (95% CI 1.10–1.74), and the intercept was significantly different from 0 (0.07; 95% CI 0.02–0.12). The 95% prediction limits indicated the range of treatment effects on OS expected for certain treatment effects on FFS. The STE, defined as the intersection of the upper prediction limit and the horizontal line representing a hazard ratio of 1 for OS, was 0.84 for FFS. Therefore, in a future trial, the upper limit of the confidence interval of an HR for FFS less than 0.84 would predict an OS benefit with 95% probability. The

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