Oral Oncology 51 (2015) 764–769

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Survival benefit of induction chemotherapy in treatment for locally advanced nasopharyngeal carcinoma – A time-to-event meta-analysis

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ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form 17 May 2015
Accepted 18 May 2015
Available online 3 June 2015

Keywords:
Induction chemotherapy
Concurrent chemoradiotherapy
Nasopharyngeal carcinoma
Time-to-event
Meta-analysis

SUMMARY

Objectives: This paper aims to compare the longtime efficacy of induction chemotherapy followed by concurrent chemoradiotherapy (IC + CCRT) and concurrent chemoradiotherapy (CCRT) alone in locally advanced nasopharyngeal carcinoma (LANPC) by using time-to-event data based on randomized controlled trials (RCTs).

Materials and methods: We searched all RCTs comparing the efficacy between IC + CCRT and CCRT of LANPC in major medical databases including Pubmed, web of science, cochrane, China National Knowledge Internet Web (CNKI), Wanfang, and VIP. The Hazard ratios (HR) of time-to-event data on overall survival (OS), progressive free survival (PFS), distant metastasis failure-free survival (D-FFS), and loco-regional failure-free survival (L-FFS) from the enrolled studies were calculated for this meta analysis. Our primary endpoints were OS, PFS, D-FFS, and L-FFS.

Results: Four studies with 798 patients were enrolled for this paper. Compared with in CCRT alone, HRs (95% confidence interval) of OS, PFS, D-FFS and L-FFS were 0.52 (0.21–1.29), 0.66 (0.49–0.90), 0.60 (0.39–0.98) and 0.66 (0.16–2.65) respectively in IC + CCRT.

Conclusions: Induction chemotherapy could significantly reduce the hazard of progression and distant metastasis in LANPC on the basis of concurrent chemoradiotherapy, but do less with the hazard of overall death and loco-regional failure.

Introduction

Nasopharyngeal cancer is common in southern China [1]. Being sensitive to X-rays and cytotoxic drugs, it is usually treated with radiation therapy or chemoradiotherapy. As for locally advanced nasopharyngeal carcinoma (LANPC), concurrent chemoradiotherapy (CCRT) is used as standard therapy [2,3]. At the same time, other chemotherapy regimens on the basis of CCRT are also continuously being researched for some additional benefit to LANPC [4–6]. Among these regimens, the benefit of adjuvant chemotherapy is doubted and its side effects appear to be intolerable [5,7]. Meanwhile, induction chemotherapy (IC) is believed to be potential for its ability to kill more local and possible distant metastasis tumour cells, decrease radiation side effects by reducing radiation targets, and being tolerable for patients [4,6,8]. All the characters above make IC an attractive growing focus in the past years. So far, several randomized controlled trials (RCTs) have been done in this area and achieved certain results, but a unified conclusion has not been formed for their small sample sizes, defective survival data or inappropriate statistical methods. Therefore, all eligible RCTs on the longtime efficacy of IC + CCRT (vs.) CCRT alone in patients with LANPC were gathered for this meta-analysis.

Materials and methods

Search strategy: we searched all relevant English and Chinese language literature until January 2015 in network databases including web of science, Pubmed, cochrane, China National Knowledge Internet Web (CNKI), Wanfang, and VIP. Reference lists of articles and the volumes of abstracts of scientific meetings were also scanned. The English search term was the *Medical Subject Headings* (MeSH) term: ("nasopharyngeal neoplasms") and ("induction therapy" or "neoadjuvant chemotherapy") and ("chemoradiotherapy") and ("randomized controlled trial" or "random allocation"). The Chinese search term was the *title or keyword* term: ("nasopharyngeal carcinoma") and ("induction chemotherapy" or "neoadjuvant chemotherapy") and ("chemoradiotherapy") (in Chinese).

Inclusion and exclusion criteria: search was limited in literature within the following series: 1. Patients confirmed as LANPC by

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http://dx.doi.org/10.1016/j.oraloncology.2015.05.006
1368-8375/

pathological and imaging examination, no early stage, no distant metastasis; 2. Research groups limited as IC + CCRT vs. CCRT, no adjuvant chemotherapy in either group; 3. RCTs; 4. Containing long-term survival data, including overall survival (OS), progressive free survival (PFS), distant metastasis failure-free survival (D-FFS), or loco-regional failure-free survival (L-FFS). Any study in one of the following circumstances was excluded: 1. Any review, case report, comment, retrospective study, nonrandomized study or uncontrolled study; 2. Repeated literature from the same research institution; 3. Unable to extract the hazard ratios (HR) with survival (time-to-event) data by Tierney's methods [9] (see appendix. 1 in detail).

Data extraction and impartial assessment: data containing basic information, intervention, long-term survival data was extracted by two partners independently from literature. Study quality was assessed by Jadad/Oxford quality scoring system [10]. When confronted with unclear information, telephone or email would be utilized to contact the authors. If there is disagreement, a third reviewer would join in to discuss a decision. Our primary endpoints were OS, PFS, D-FFS, and L-FFS.

Data analysis: the natural logarithm of HR (lnHR) and the Variance of the lnHR (V(lnHR)) in each study were firstly calculated from the survival data or survival curves of OS, PFS, L-FFS, D-FFS by Tierney's calculations spreadsheet [9]. And then HR and 95% confidence interval (CI) were analysed from lnHR and V(lnHR) of each study by using "metafor" package [11] in R v3.1.2. HR represented the hazard ratio of an event occurring in the IC + CCRT group vs. the CCRT group. HR less than 1 indicated the ascendancy of IC + CCRT group. When 95% CI did not include the value 1, the estimate of HR was of statistically significant ($P < 0.05$). I^2, H, and p-value of Q, with a critical point of 50%, 1.5, and 0.1 respectively, were used for heterogeneity analysis. The fixed-effect model would be used for pooled analysis when $I^2 < 50\%$, $H < 1.5$, $p < 0.1$, and the random-effect model would be used when $I^2 \geq 50\%$, $H \geq 1.5$, $p \geq 0.1$. Funnel plot, Begg's test, and Egger's test were utilized to observe the publication bias.

Results

A total of 653 documents were searched from the electronic databases, in which, 199 duplicate studies were removed firstly, and then 433 articles were discarded for failing to meet the criteria by reading their titles and (or) abstracts. After reviewed full texts of the left 21 studies, we excluded 17 documents inconsistent with the criteria. These 17 documents included one [12] of pseudorandom, three [13–15] being the same trials as other three ones, three [16–18] with some illegibility or mistakes, one [19] with early stage NPC, and nine [20–28] without adequate survival data for the calculation of lnHR and V(lnHR) by the eleven methods mentioned in Tierney's article [9]. Finally, a total of four RCTs [4,8,29,30] with 404 patients in the IC + CCRT group and 394 patients in the CCRT group were enrolled in this paper (selecting process was showed in Fig. 1). The baseline characteristics and bias analysis with Jadad scale of the four enrolled studies were listed in Tables 1 and 2. Among these four RCTs, lnHRs and V(lnHR)s were calculated by the third method of Tierney's calculations spreadsheet in Ma's

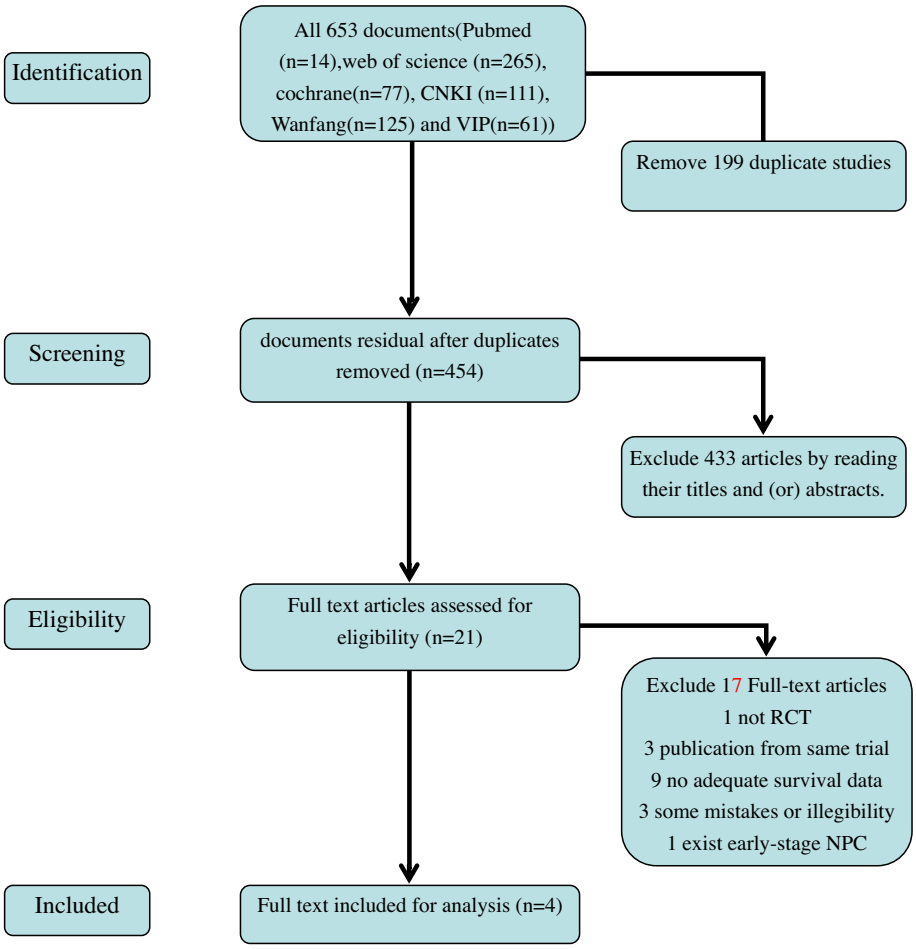

Fig. 1. Identification and selecting process of relevant articles in this paper.