Comparing the Efficacy and Safety of Cisplatin and other Platinum-based Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Cisplatin-based concurrent chemoradiotherapy has been identified as the primary and standard treatment for locally advanced nasopharyngeal carcinoma (NPC). The side effects of cisplatin affect the compliance to therapy. Thus, the search for a platinum-based substitute for NPC has always been a research focus. However, there is a variability in the efficacy of different platinum-based chemotherapy in the treatment of NPC. We performed a meta-analysis to compare between the efficacy and safety of the cisplatin-based regimens and the other platinum-based derivatives (carboplatin, nedaplatin, and lobaplatin) for locally advanced NPC.

Methods: PubMed, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov were systematically searched for all potentially eligible clinical trials as of February 15, 2022. The pooled hazard ratios, risk ratio, and 95% confidence interval were calculated using the Review Manager Software version 5.4.

Results: A total of 1,907 patients with locally advanced NPC were eligible from the 1,265 retrieved records. This systematic review included eight articles, six of which were randomized controlled clinical trials. There was no significant difference in the 3- and 5-years overall survival, progression-free survival, distant metastasis-free survival, and locoregional relapse-free survival between cisplatin-based chemotherapy and other platinum-based chemotherapy. Severe acute hematological side effects (≥ grade 3) during treatment, such as neutropenia, leukopenia, and thrombocytopenia, are equivalent in both groups. However, the incidence of anemia is higher in patients receiving other platinum-based chemotherapy. Moreover, the risks of nausea, vomiting and weight loss were higher in the cisplatin group but there was no significant difference in the other non-hematological and late side effects between the two groups.

Conclusion: Other types of platinum-based chemotherapy are as effective as cisplatin-based chemotherapy in the treatment of locally advanced NPC, thus acting as potential alternatives to cisplatin. Further studies providing high-level evidence are needed.

Background

The global geographical distribution of nasopharyngeal carcinoma (NPC) is extremely unbalanced, where > 70% of new NPC cases occur in China and Southeastern Asia. An age-standardized incidence rate between 3.0–10.2 per 100,000 population has been reported in China [1, 2]. More than 70% of newly diagnosed NPC cases are classified as locally advanced disease in stages II–IVB [3]. Cisplatin-based concurrent chemoradiotherapy (CCRT) has been identified as the primary and standard treatment for locally advanced NPC. Although cisplatin offers substantial survival benefits to patients [3–5], its limitations lie in the poor adherence to treatment and side effects, including nausea, vomiting, nephrotoxicity, ototoxicity, and neurotoxicity [6, 7]. Therefore, there is an emerging need for other chemotherapeutic agents having similar efficacy against NPC and fewer side effects. Other platinum-based derivatives such as nedaplatin, lobaplatin and carboplatin have similar efficacy and fewer side effects, thus they have been used to replace cisplatin in the treatment of NPC [8–10]. However, no statistically significant results have been obtained from these studies. Thus, the aim of this meta-analysis of published clinical trials, retrospective studies, and paired analyses, is to compare the efficacy and safety of cisplatin-based and other platinum-based regimens in the treatment of locally advanced NPC.

Methods

Search strategy

We conducted a thorough search of the databases of medical publications; PubMed trial, EMBASE, Cochrane Library, Web of Science, and ClinicalTrials.gov, searching for all available records until February 15, 2022. The search was conducted by "subject word" or "title or key word". The search terms included: “Nasopharyngeal carcinoma”, “Carcinoma, Nasopharyngeal”, “Carcinomas, Nasopharyngeal”, “Nasopharyngeal Carcinomas”, “Cisplatin”, “lobaplatin”, “Nedaplatin”, “carboplatin”, and “randomized controlled trial or Randomized or placebo or RCT”. We manually searched the references of relevant articles to retrieve more clinical studies. In addition, a search was conducted before the final analysis. Two researchers (ZL and CL) independently screened the literature from the above databases and selected articles that meet the inclusion criteria by reading the title or abstract. If published data overlap, only the most current information was included. In addition, a third researcher (DY) intervened to resolve any dispute(s).

Inclusion criteria

All the studies included in this meta-analysis followed the PICOS principles (Participants, Intervention, Comparison and Outcomes, Study design). The details are as follows: (1) P: patients with stage II–IVB locally advanced NPC diagnosed by pathology; (2) I: Patients in the experimental group received chemotherapy with the other platinum derivatives (carboplatin, nedaplatin, and lobaplatin), while the control groups received cisplatin chemotherapy. The specific combination of chemotherapy and radiotherapy techniques were ignored in both groups; (3) C: analysis of therapeutic efficacy and toxicity during and after radiotherapy and chemotherapy; (4) O: major positive outcomes include overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS), locoregional relapse-free survival (LRFS), while negative outcomes include hematologic and non-hematologic toxicities; (5) S: we not only included randomized controlled trials, but also observational studies (including cohort and case-control studies).

Exclusion criteria

Studies with any of the following criteria were excluded. The exclusion criteria were: (1) patients with multiple distant metastases before treatment; (2) patients with previous diagnosis of other malignant tumors; (3) patients were previously treated with or in combination with immunosuppressants or antiangiogenic drugs; (4) patients who had severe comorbidities; (5) patients whose detailed data or summary of the meeting were lacking; (6) the sample size was relatively small (< 50 cases in any group).

Data extraction and quality assessment

The following details were extracted from each eligible clinical trial: first author, publication year, inclusion period, registration number, study design, number of patients, tumor stage, mean age, median follow-up period, therapeutic regimens, OS, PFS, DMFS, LRFS, and adverse events. Two assessment scales were used to assess the methodological quality of each eligible trial, where the Newcastle-Ottawa Scale (NOS) was used for non-randomized controlled trials (non-RCTs) [11], while Cochrane bias risk tools were used for randomized controlled trials (RCTs) [12].

Statistical analysis

Summary statistics were compiled using the Review Manager Software 5.4 (Cochrane Collaboration RevMan, version 5.4, Oxford, UK). According to the methods published by Tierney *et al.*, survival outcomes (OS, PFS, DMFS, and LRFS) were assessed by hazard ratios (HR) and 95% confidence intervals (CI) [13]. If HR was not directly described in the paper, Engauge Digitalizer was used to extract the survival curve. The relative risk (RR) was to quantify and analyze efficacy. The inverse variance (IV) method was used to evaluate HR, and mantel Haenszel (MH) method was used to evaluate RR. The X^2 test and I^2 statistical and quantitative heterogeneity tests were used in each study, where $p < 0.10$ or $I^2 > 50\%$ indicated that there was heterogeneity in each study and the random effect model was used for analysis. However, $p > 0.10$ or $I^2 < 50\%$ indicated no statistical heterogeneity and the fixed effect model was used for analysis. Sensitivity analysis excluded any element from the study and observed its impact on the combined statistics and the heterogeneity test results.

Results

Study selection

A total of 1,265 articles were retrieved from the PubMed, EMBASE, Cochrane Library and Web of Science databases. About 252 duplicate records were deleted. After screening the title and abstract, there were 19 qualified articles left. After reading the full texts, 8 studies [14–22] were finally included in the meta-analysis. The specific process of research screening is shown in Fig. 1.

Eligible studies and characteristics

The 8 studies included in this review included a total of 1,907 patients. Six of the eight studies are RCTs, while the other two were retrospective studies. Through Cochrane bias risk tool analysis, four RCTs used random number method and the other two RCTs did not indicate specific random methods. All RCTs included in this study did not explain hidden groups and there was no indication that blinding was applied to patients and doctors. However, most of the outcome indicators for those RCTs were based on clinical data, and the blinding method has a relatively little impact on the clinical data. All the literature data were complete, where no missing information or incomplete data affected the analysis of the results, and no selective reports or other sources of bias were found in all the studies. The details about the risk bias are shown in Fig. 2. The NOS scale defined two retrospective studies as high-quality studies. Table 1 shows the basic characteristics of the eligible clinical trials, while Table 2 shows the details and outcome measures of the treatment regimens.

Table 1
Characteristics of the eligible studies

Study	Journal	Year	Inclusion period	Register	Type of study	Phase	chemoradiotherapy	No.Patients	No.male	Mean Age (Exp/con)	AJCC Stage
Lv et al.	Lancet Oncol	2021	2013–2015	ChiCTR-TRC-13003285	RCT	III	IC + CCRT	502	362	43.5/44	III–IVB
Tang et al.	American Journal of Cancer Research	2016	2011–2012	NCT 01479504	RCT	III	IC + CCRT	223	NR	45.1/45.3	III–IV
Linquan et al.	Lancet Oncol ogy	2018	2012–2014	NCT01540136	RCT	III	CCRT	402	302	44/45	II–IVB
Hu et al.	Journal of Cancer Research and Therapeutics	2016	2014–2015	NR	RCT	III	IC	62	45	50.2/49.8	III–IV
Liu et al.	Journal of Cancer	2018	2009–2011	NR	RE	FE	IC + CCRT	186	119	NR	II–IVB
Zhan et al.	Journal of Cancer	2020	2012–2017	NR	RE	FE	IC + CCRT	226	184	NR	III–IVA
Cao et al.	Zhonghua Zhong Liu Za Zhi	2011	2009–2010	NR	RCT	III	IC	100	NR	NR	III–IVA
Imjai et al.	European Journal of Cancer	2007	1999–2004	NR	RCT	III	CCRT + AC	206	126	50/46	III–IVB

RCT: randomized controlled trials; IC:Induction chemotherapy ;CCRT:Concurrent chemoradiotherapy;AC:Adjuvant chemotherapy;Con:control group (cisplatin-b group); Exp, experimental group (other platinum-based group). ; NA: not available; Re.: retrospetive study; NR:not reported. FE: fail to extract.

Table 2
Therapeutic regimens, survival outcomes in eligible studies

Study	Induction chemotherapy	Concurrent chemotherapy	Radiotherapy	OS	PFS	DMFS	LRFS
	Exp vs con	Exp vs con		Exp/con	Exp/con	Exp/con	Exp/con
Lv et al.	lobaplatin 30 mg/m² d1,22 + 5FU 800 mg/m²d1–5,every 21days for 2cycles vs cisplatin 100 mg/m²+ 5FU 800 mg/m²d1–5,every 21days for 2cycles	lobaplatin 30 mg/m² 2 cycles vs cisplatin 100 mg/m² 2 cycles	IMRT:GTVnx 68-70Gy GTVnd 62–68 Gy CTV1 60 Gy CTV2 54 Gy	5year: 88.2%/89%	75%/75.5%	86.6%/85%	87.7%/88.8%
Tang et al.	docetaxel 65 mg/m2 d1 + nedaplatin 80 mg/m2 d1, every 21days for 2cycles vs docetaxel 65 mg/m2 d1 + cisplatin 80 mg/m2 d1, every 21days for 2cycles	nedaplatin 40 mg/m2 every week for 3cycles vs cisplatin 40mg /m2 every week for 3cycles	IMRT:GTVnx 68–74 Gy, GTVnd 68-70Gy, CTV1 60–64 Gy, CTV2 50–56 Gy	3year: 87.5%/85.9%	3year: 77.5%/74.9%	3year: 86.7%/85.1%	3year: 91.9%/91.7%
Linquan et al.	NR	nedaplatin 100 mg/m²d1 every 21days for 3cycles or cisplatin 100 mg/m² every 21days for 3cycles	IMRT:GTVnx 66–70 Gy, GTVnd 64–70Gy, CTV1 60–62 Gy, CTV2 54–56 Gy	5year: 88.8%/89.4%	2year: 88.0%/89.9% 5year: 79.8%/81.4%	5year: 90.4%/85.9%	5year: 89.6%/92.6%
Liu et al.	cisplatin 75mg/m2 d1 + 5FU 800 mg/m²d1–5, every 21days for 2–3 cycles vs nedaplatin 75 mg/m²+5FU 800 mg/m²d1–5, every 21days for 2–3 cycles	nedaplatin 75 mg/m²d1 every 21days for 2cycles vs cisplatin 80 mg/m²d1 every 21days for 2cycles	IMRT:GTVnx 66–70 Gy, GTVnd 66–70 Gy, CTV1 60 Gy, CTV2 54 Gy	3year: 82.4%/79.4%	3year: 72.6%/68.7%	3year: 80.7%/77.0%	3year: 86.2%/92.6%
Zhan et al.	Docetaxel 60–75 mg/m2 d1 + cisplatin 60–75 mg/m2 d1 + 5FU 500–600 mg/m2, d1–5, every 21days for 1–4 cycles	nedaplatin 80 mg/m2 d1, every 21days or nedaplatin 30 mg/m2 d1 every week vs cisplatin 80 mg/m2 d1,every 21days or cisplatin 30 mg/m2 d1 every week	IMRT:GTVnx 68–70 Gy, GTVnd 68-70Gy, CTV1 60–62 Gy, CTV2 54–56 Gy	3year: 90.7%/92.3%	3year: 78.9%/79.4%	3year: 82.4%/85.1%	3year: 96.1%/93.3%
Imjai et al.	NR	carboplatin 100 mg/m2 every week vs cisplatin 100 mg/m²d1 every 21days for 3cycles	GTV 70 Gy CTVln 40–44 Gy	3year: 77.7%/79.2%	NR	3year: 63.4%/60.9%	NR

5FU:5-fluorouracil;OS overall survival; PFS Progressive-free survival; DMFS distant metastasis-free survival; LRFS locoregional relapse-free survival; FE: fail to extract.

OS

The 3-year OS data were obtained from three studies with a total of 655 patients (cisplatin group, 328 patients; and other platinumgroup, 327 patients). Forest plots showed that there was no significant difference in the 3-year OS between the two groups (HR, 0.88; 95% CI, [0.70–1.09]; $p = 0.24$; H:$I^2 = 0\%$, $p = 0.41$). The 5-year OS data were obtained from three studies with a total of 1,090 patients (cisplatin group, 534 patients; and other platinum group, 556 patients). There was no significant difference in the 5-year OS between the two groups (HR, 0.97; 95% CI, [0.70–1.35]; $p = 0.87$; H:$I^2 = 0\%$; $p = 0.76$)(Fig. 3).

PFS

The 3-year PFS data were obtained from 449 patients in two studies (cisplatin group, 223 patients; and other platinum group: 226 patients). There was no significant difference in the 3-year PFS between the two groups (HR, 1.12; 95% CI, [0.77–1.65]; $p = 0.55$; H:$I^2 = 0\%$; $p = 0.91$). The 5-year PFS data were obtained from three studies with a total of 1,090 patients (cisplatin group, 534 patients; and other platinum group, 556 patients). There was no significant difference in the 5-year PFS between the two groups (HR, 0.99; 95% CI, [0.78–1.27]; $p = 0.94$; H:$I^2 = 0\%$; $p = 0.64$) (Fig. 4).

DMFS

The 3-year DMFS data were obtained from a total of 655 patients in three studies (cisplatin group, 328 patients; and other platinum group, 327 patients). There was no significant difference in the 3-year DMFS between the two groups (HR, 0.95; 95% CI, [0.65–1.38]; $p = 0.79$; H:$I^2 = 56\%$; $p = 0.11$). The 5-year DMFS data were obtained from 1,090 patients in three studies (cisplatin group, 534 patients; and other platinum group, 556 patients). There was no significant difference in the 5-year DMFS between the two groups (HR, 0.78; 95% CI, [0.57–1.07]; $p = 0.12$; H:$I^2 = 0\%$; $p = 0.96$) (Fig. 5).

LRFS

The 3-year LRFS data were obtained from a total of 449 patients in two studies (cisplatin group, 223 patients; and other platinum group, 226 patients). There was no significant difference in the 3-year LRFS between the two groups (HR, 1.02; 95% CI, [0.97–1.07]; $p = 0.47$; H:$I^2 = 0\%$; $p = 0.51$). The 5-year LRFS data were obtained from three studies with a total of 1,090 patients (cisplatin group, 534 patients; and other platinum group, 556 patients). There was no significant difference in the 5-year LRFS between the two groups (HR, 1.13; 95% CI, [0.78–1.63]; $p = 0.51$; H:$I^2 = 26\%$; $p = 0.26$) (Fig. 6).

Grade ≥ 3 Acute Toxicities

Based on acute grade 3 or more acute toxicities during treatment in other platinum groups and cisplatin groups, the following risks were calculated. With regards to hematological toxicities, there was no significant difference in the risks of neutropenia (RR, 1.21; 95% CI, [0.94–1.57]; $p = 0.14$), leukopenia (RR, 0.97; 95% CI, [0.81–1.17]; $p = 0.78$) and thrombocytopenia (RR, 1.62; 95% CI, [0.98–2.69]; $p = 0.06$) between the other platinum group and the cisplatin group. However, the risk of anemia in other platinum group was significantly higher than that in the cisplatin group (RR, 0.30; 95% CI, [0.12–0.77]; $p = 0.01$).

With regards to non-hematological toxicities, there was no significant difference in the risks of xerostomia (RR, 0.83; 95% CI, [0.51–1.35]; $p = 0.46$), dermatitis (RR, 1.02; 95% CI, [0.58–1.81]; $p = 0.95$), mucositis (RR, 1.02; 95% CI, [0.58–1.81]; $p = 0.95$) and elevated levels of aminotransferase (RR, 0.71; 95% CI, [0.25–2.05], $p = 0.53$) between the other platinum group and the cisplatin group. However, the risks of nausea (RR, 0.12; 95% CI, [0.06–0.25]; $p < 0.0001$), vomiting (RR, 0.15; 95% CI, [0.06–0.40]; $p = 0.0001$) and weight loss (RR, 0.34; 95% CI, [0.12–0.98], $p = 0.04$) in the other platinum group were significantly lower than those in the cisplatin group (Table 3).

Table 3
Grade 3–4 acute toxicities during treatment

Advese event (grade3-4)	Availability			Effect		Heterogeneity		Analysis model
	Trials (N)	Other platinum (events/total)	Cisplatin (events/total)	RR (95% CI)	P value	I^2	P value	
Hematological								
neutropenia	5	210/781	169/753	1.21(0.94–1.57)	0.14	53%	0.07	Random effect
leucopenia	5	177/773	173/744	0.97(0.81–1.17)	0.78	45%	0.12	Fixed effect
thrombocytopenia	6	88/886	56/854	1.62(0.98–2.69)	0.06	51%	0.07	Random effect
anemia	5	26/783	77/771	0.30(0.12–0.77)	0.01	72%	0.007	Random effect
Nonhematologic								
xerostomia	5	28/773	33/741	0.83(0.51–1.35)	0.46	0%	0.48	Fixed effect
dermatitis	4	24/573	22/543	1.02(0.58–1.81)	0.95	0%	0.4	Fixed effect
mucositis	6	211/886	227/854	0.91(0.78–1.06)	0.23	27%	0.24	Fixed effect
nausea	3	8/555	62/530	0.12(0.06–0.25)	0.0001	0%	0.41	Fixed effect
vomiting	5	22/781	125/753	0.15(0.06–0.40)	0.0001	61%	0.04	Random effect
weight loss	3	4/468	12/445	0.34(0.12–0.98)	0.05	30%	0.24	Fixed effect
Elevation of aminotransferase	2	6/135	7/114	0.71(0.25–2.05)	0.53	0%	0.81	Fixed effect

Treatment-related late toxicities

Based on the late adverse events during the treatment of other platinum and cisplatin groups, there was no significant difference between the two groups in the risks of xerostomia (RR, 0.96; 95% CI, [0.88–1.05]; $p = 0.40$), subcutaneous fibrosis (RR, 0.95; 95% CI, [0.83–1.08]; $p = 0.42$), hearing impairment (RR, 0.91; 95% CI, [0.64–1.31]; $p = 0.62$), trismus (RR, 0.70; 95% CI, [0.45–1.07]; $p = 0.10$), cranial nerve palsy (RR, 0.83; 95% CI, [0.57–1.20], $p = 0.32$), and temporal lobe necrosis (RR, 0.80; 95% CI, [0.51–1.25]; $p = 0.32$) (Fig. 7).

Subgroup and Sensitivity Analyses

Two studies reported the efficacy and side effects of induction chemotherapy alone [18, 21], so these two outcomes were analyzed separately. After induction chemotherapy, there was no significant difference in complete response (CR) (RR, 1.24; 95% CI, [0.88–1.75.08]; $p = 0.21$) and partial response (PR) (RR, 1.25; 95% CI, [0.97–1.62]; $p = 0.09$) between the other platinum group and the cisplatin group. There was also no significant difference in the risk of leukocytopenia (RR, 1.06; 95% CI, [0.53–2.12]; $p = 0.86$) and thrombocytopenia (RR, 0.67; 95% CI, [0.22–2.09]; $p = 0.49$) between the two groups. However, the risk of anemia (RR, 0.47; 95% CI, [0.28–0.80]; $p = 0.005$) in other platinum group was significantly higher than that in the cisplatin group. Moreover, the incidence of vomiting (RR, 0.24; 95% CI, [0.12–0.49]; $p < 0.0001$) in the cisplatin group is significantly higher than that in the other platinum group. The sensitivity analysis showed that the aggregated results at all endpoints remained unchanged when any study was deleted, indicating that the results of this meta-analysis are reliable (Fig. 8).

Discussion

The study showed that the other platinum-based chemotherapy alternatives did not reduce survival and did not significantly increase the incidence of hematological and non-hematological side effects compared with cisplatin-based chemotherapy. To our knowledge, this is the first meta-analysis that examines of the efficacy and side effects of cisplatin versus other platinum chemotherapy in locally advanced NPC.

In the past 20 years, three major advances have significantly improved the prognosis of patients with NPC. First, intensity-modulated radiation therapy can cover the target area and the local expansion area with a good precision. Intensity-modulated radiation therapy can better protect the adjacent normal tissue especially for patients whose tumors extend backward to the cranial nerve [23, 24]. Secondly, the combination of cisplatin-based CCRT, induction chemotherapy, or adjuvant chemotherapy effectively improves the survival rate and disease control of NPC [5, 25–28]. Thirdly, the use of advanced imaging techniques, especially the application of MRI and PET-CT, can better evaluate the local and distant invasion of the tumor, which is very critical for the accurate application of intensity-modulated radiation therapy. However, cisplatin-based chemotherapy regimens are known to increase the acute and late toxicities of radiotherapy [16]. Long-term side effects such as nausea, vomiting, auditory function, renal function or effects on peripheral nerves caused by cisplatin may affect the quality of life of survivors. Moreover, cisplatin-based CCRT requires pretreatment and post-treatment hydration during cisplatin administration to protect the kidneys, which can prolong the hospital stay [14, 16, 17].

Carboplatin, nedaplatin and lobaplatin were successively included in the study as cisplatin substitutes to improve the compliance of patients, reduce the side effects of chemotherapy and meet the clinical needs. A randomized non-inferiority trial showed that there was no difference between carboplatin-based CCRT and cisplatin-based regimen in patients with locally advanced NPC. Moreover, carboplatin showed better tolerance in patients with locally advanced NPC [22]. Two other trials indicated that carboplatin induction chemotherapy combined with CCRT did not improve survival in patients with locally advanced NPC compared with carboplatin induction chemotherapy combined with radiotherapy alone [9]. In addition, carboplatin was less effective than cisplatin when given during CCRT in patients with borderline renal function [29].

Nedaplatin is a cisplatin analog whose antitumor mechanism and therapeutic effect are similar to that of cisplatin and does not require hydration to protect the kidneys. Two Phase 2 studies have shown that nedaplatin in combination with fluorouracil or docetaxel has an inductive effect on chemotherapy. In addition, nedaplatin-based CCRT is an effective and safe treatment for patients with stage II–IVB NPC, indicating that nedaplatin may be a promising alternative to cisplatin [30, 31]. In a randomized phase III trial, Mai HQ *et al.* [16] showed that for patients with stages II–IVB NPC, nedaplatin-based CCRT was not inferior to cisplatin-based CCRT with respect to the 2-year PFS. Subsequent comments [32] indicate that it is too early to conclude that nedaplatin will replace cisplatin. However, the newly published results of the 5-year follow-up still support the results of the initial report [17].

Lobaplatin is a third-generation platinum drug. In previous studies, lobaplatin was found to overcome some forms of multiple drug resistance caused by other platinum-based drugs, such as cisplatin or carboplatin [8]. A random non-inferiority trial showed that lobaplatin-based induction chemotherapy plus CCRT has similar survival outcomes and side effects' profile to cisplatin-based therapy and thus may act a promising alternative [14]. Clinical studies, such as Chictr1900021536, and ChiCTR-IIR-17013112, are still ongoing to further assess the benefits and risks of lobaplatin for NPC and to verify the value of these treatment strategies.

We conducted this meta-analysis to evaluate the efficacy and safety of other platinum-based chemotherapy versus cisplatin-based chemotherapy for locally advanced NPC. Yuan *et al.* [33] performed a network meta-analysis on the efficacy of different neoadjuvant chemotherapeutic strategies in the treatment of NPC. The results showed that some cisplatin-based neoadjuvant chemotherapy regimens improved the prognosis of patients with NPC and reduced the toxicity of chemotherapy. However, the optimal neoadjuvant chemotherapy protocol is not fully consistent in terms of survival and efficiency. Horace *et al.* [34] showed that the induction chemotherapy regimen, gemcitabine plus cisplatin, shows better performance in terms of survival outcomes. To date, there is no meta-analysis to adequately demonstrate differences in the efficacy of various platinum-based regimens in locally advanced NPC. To reduce bias, we selected RCTs that are clinically registered as eligible studies. Our meta-analysis revealed that there was no significant difference between other platinum-based and cisplatin-based chemotherapy in terms of OS, PFS, DMFS and LRFS. Severe acute hematological side effects (≥ grade 3) such as neutropenia, leukopenia and thrombocytopenia were observed after platinum-based induction chemotherapy or throughout the treatment period, however, such side effects were equivalent to those in the cisplatin treatment group. It is worth noting that risk of anemia was higher in patients receiving other platinum-based treatments. In contrast, the risk of non-hematological side effects such as nausea, vomiting, and weight loss after induction chemotherapy or during the whole treatment period was higher in the cisplatin treatment group. There was no difference in other non-hematological side effects such as xerostomia, dermatitis, mucositis, and elevated levels of aminotransferase between the two groups. Moreover, there was no significant difference in the late side effects such as xerostomia, subcutaneous fibrosis, hearing impairment, trismus, cranial nerve palsy and temporal lobe necrosis between the two groups. The studies included in this meta-analysis did not report any treatment-related disability or death.

The main limitation of this meta-analysis is that some of the studies included were not RCTs, which may affect our research outcomes. Secondly, most studies were conducted in China, which may be a source of potential bias. Third, there are differences in the specific study populations, combined treatment schemes and treatment durations, which may affect further data analyses. Finally, the DNA level of EB virus is a prognostic factor for NPC, however, the included studies could not be analyzed by subgroups.

Conclusion

Based on the systematic review and meta-analysis of the included studies, it was found that other platinum-based chemotherapy regimens were not inferior to cisplatin-based regimens and could be an effective alternative to cisplatin for the treatment of locally advanced NPC. Since most eligible studies were conducted in endemic areas, high-level evidence is needed to verify these findings in the future.

Abbreviations

NPC:nasopharyngeal carcinoma;RCT:randomized controlled trials;IC:Induction hemotherapy;CCRT:Concurrent chemoradiotherapy;AC:Adjuvant chemotherapy;Con:control group (cisplatin-based group); Exp, experimental group (other platinum-based group).; NA: not available; Re.: retrospetive study; NR:not reported. FE：fail to extract.5FU:5-fluorouracil;OS overall survival; PFS: Progressive-free survival; DMFS distant metastasis-free survival; LRFS locoregional relapse-free survival; FE：fail to extract.

Declarations

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Authors' contributions

Study design: Zhiru Li,Chao Li,and Dong Yang; Data extraction: Zhiru Li,Chao Li, and Junmei Song ; Data analysis: Zhiru Li,Chao Li, and Ting Liu; Manuscript writing: Zhiru Li,Chao Li,and Ziyan Zhou; Manuscript edition: Zhiru Li,Chao Li, and Min Kang. All authors have read and approved the manuscript.

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Availability of data and materials

All the published articles and data were available online.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F: Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021, 71(3):209-249.
2. Chen YP, Chan A, Le QT, Blanchard P, Sun Y, Ma J: Nasopharyngeal carcinoma. LANCET 2019, 394(10192):64-80.
3. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, Sun Y, Chen XZ, Li JG, Zhu XD et al: Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. LANCET ONCOL 2016, 17(11):1509-1520.

4. Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, Peng P, Wu X, Lin Q, Xi X et al: Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. LANCET 2016, 388(10054):1883-1892.
5. Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, Li WX, Chen YY, Xie FY, Liang SB et al: Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. LANCET ONCOL 2012, 13(2):163-171.
6. Rybak LP, Mukherjea D, Jajoo S, Ramkumar V: Cisplatin ototoxicity and protection: clinical and experimental studies. TOHOKU J EXP MED 2009, 219(3):177-186.
7. Fung C, Dinh PJ, Ardeshir-Rouhani-Fard S, Schaffer K, Fossa SD, Travis LB: Toxicities Associated with Cisplatin-Based Chemotherapy and Radiotherapy in Long-Term Testicular Cancer Survivors. Adv Urol 2018, 2018:8671832.
8. McKeage MJ: Lobaplatin: a new antitumour platinum drug. Expert Opin Investig Drugs 2001, 10(1):119-128.
9. Huang PY, Cao KJ, Guo X, Mo HY, Guo L, Xiang YQ, Deng MQ, Qiu F, Cao SM, Guo Y et al: A randomized trial of induction chemotherapy plus concurrent chemoradiotherapy versus induction chemotherapy plus radiotherapy for locoregionally advanced nasopharyngeal carcinoma. ORAL ONCOL 2012, 48(10):1038-1044.
10. Liao W, Huang J, Wu Q, Zhu G, Wang X, Wen F, Zhang P, Zhang N, Li Q: Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: A cost-effectiveness analysis. ORAL ONCOL 2019, 93:15-20.
11. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. EUR J EPIDEMIOL 2010, 25(9):603-605.
12. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011, 343:d5928.
13. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR: Practical methods for incorporating summary time-to-event data into meta-analysis. TRIALS 2007, 8:16.
14. Lv X, Cao X, Xia WX, Liu KY, Qiang MY, Guo L, Qian CN, Cao KJ, Mo HY, Li XM et al: Induction chemotherapy with lobaplatin and fluorouracil versus cisplatin and fluorouracil followed by chemoradiotherapy in patients with stage III-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised, controlled, phase 3 trial. LANCET ONCOL 2021, 22(5):716-726.
15. Tang C, Wu F, Wang R, Lu H, Li G, Liu M, Zhu H, Zhu J, Zhang Y, Hu K: Comparison between nedaplatin and cisplatin plus docetaxel combined with intensity-modulated radiotherapy for locoregionally advanced nasopharyngeal carcinoma: a multicenter randomized phase II clinical trial. AM J CANCER RES 2016, 6(9):2064-2075.
16. Tang LQ, Chen DP, Guo L, Mo HY, Huang Y, Guo SS, Qi B, Tang QN, Wang P, Li XY et al: Concurrent chemoradiotherapy with nedaplatin versus cisplatin in stage II-IVB nasopharyngeal carcinoma: an open-label, non-inferiority, randomised phase 3 trial. LANCET ONCOL 2018, 19(4):461-473.
17. Tang QN, Liu LT, Qi B, Guo SS, Luo DH, Sun R, Sun XS, Chen DP, Guo L, Mo HY et al: Effect of Concurrent Chemoradiotherapy With Nedaplatin vs Cisplatin on the Long-term Outcomes of Survival and Toxic Effects Among Patients With Stage II to IVB Nasopharyngeal Carcinoma: A 5-Year Follow-up Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open 2021, 4(12):e2138470.
18. Hu Y, Fu JT, Shi D, Feng B, Shi Z: Clinical efficacy and safety of gemcitabine plus nedaplatin in the treatment of advanced nasopharyngeal carcinoma. J CANCER RES THER 2016, 12(Supplement):C252-C255.
19. Liu T, Sun Q, Chen J, Li B, Qin W, Wang F, Ye Z, Hu F: Neoadjuvant Chemotherapy with Fluorouracil plus Nedaplatin or Cisplatin for Locally Advanced Nasopharyngeal Carcinoma: a Retrospective Study. J CANCER 2018, 9(20):3676-3682.
20. Zhan Z, Tao H, Qiu W, Liu Z, Zhang R, Liao K, Li G, Yuan Y, Yuan T, Zheng R: Clinical value of nedaplatin-based chemotherapy combined with radiotherapy for locoregional advanced nasopharyngeal carcinoma: a retrospective, propensity score-matched analysis. J CANCER 2020, 11(23):6782-6789.
21. Cao K, Zhang A, Ma W, Huang P, Luo D, Xia W: Nedaplatin or cisplatin combined with 5-fluorouracil for treatment of stage III-IVa nasopharyngeal carcinoma: a randomized controlled study. 2011, 33(1):50-52.
22. Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, Sumitsawan Y, Tharavichitkul E, Sukthomya V, Ford J: Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. EUR J CANCER 2007, 43(9):1399-1406.
23. Kam MK, Leung SF, Zee B, Chau RM, Suen JJ, Mo F, Lai M, Ho R, Cheung KY, Yu BK et al: Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J CLIN ONCOL 2007, 25(31):4873-4879.
24. Zhang MX, Li J, Shen GP, Zou X, Xu JJ, Jiang R, You R, Hua YJ, Sun Y, Ma J et al: Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: A 10-year experience with a large cohort and long follow-up. EUR J CANCER 2015, 51(17):2587-2595.
25. Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J, Chan AT, Huang PY, Benhamou E, Zhu G et al: Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. LANCET ONCOL 2015, 16(6):645-655.
26. Ribassin-Majed L, Marguet S, Lee A, Ng WT, Ma J, Chan A, Huang PY, Zhu G, Chua D, Chen Y et al: What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis. J CLIN ONCOL 2017, 35(5):498-505.
27. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, Sun Y, Chen XZ, Li JG, Zhu XD et al: Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. LANCET ONCOL 2016, 17(11):1509-1520.
28. Frikha M, Auperin A, Tao Y, Elloumi F, Toumi N, Blanchard P, Lang P, Sun S, Racadot S, Thariat J et al: A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02). ANN ONCOL 2018,

29(3):731-736.
29. Yau TK, Lee AW, Wong DH, Pang ES, Ng WT, Yeung RM, Soong IS: Treatment of Stage IV(A-B) nasopharyngeal carcinoma by induction-concurrent chemoradiotherapy and accelerated fractionation: impact of chemotherapy schemes. Int J Radiat Oncol Biol Phys 2006, 66(4):1004-1010.
30. Tang C, Wu F, Wang R, Lu H, Li G, Liu M, Zhu H, Zhu J, Zhang Y, Hu K: Comparison between nedaplatin and cisplatin plus docetaxel combined with intensity-modulated radiotherapy for locoregionally advanced nasopharyngeal carcinoma: a multicenter randomized phase II clinical trial. AM J CANCER RES 2016, 6(9):2064-2075.
31. Zheng J, Wang G, Yang GY, Wang D, Luo X, Chen C, Zhang Z, Li Q, Xu W, Li Z et al: Induction chemotherapy with nedaplatin with 5-FU followed by intensity-modulated radiotherapy concurrent with chemotherapy for locoregionally advanced nasopharyngeal carcinoma. JPN J CLIN ONCOL 2010, 40(5):425-431.
32. Blanchard P, Tao Y: Nedaplatin in nasopharyngeal cancer: the rebirth of platinum salts? LANCET ONCOL 2018, 19(4):429-431.
33. Choi HC, Chan SK, Lam KO, Chan SY, Chau SC, Kwong DL, Leung TW, Luk MY, Lee AW, Lee VH: The Most Efficacious Induction Chemotherapy Regimen for Locoregionally Advanced Nasopharyngeal Carcinoma: A Network Meta-Analysis. FRONT ONCOL 2021, 11:626145.
34. Yuan C, Xu XH, Luo SW, Wang L, Sun M, Ni LH, Xu L, Wang XL, Zeng G: Which neoadjuvant chemotherapy regimen should be recommended for patients with advanced nasopharyngeal carcinoma?: A network meta-analysis. Medicine (Baltimore) 2018, 97(34):e11978

Figures

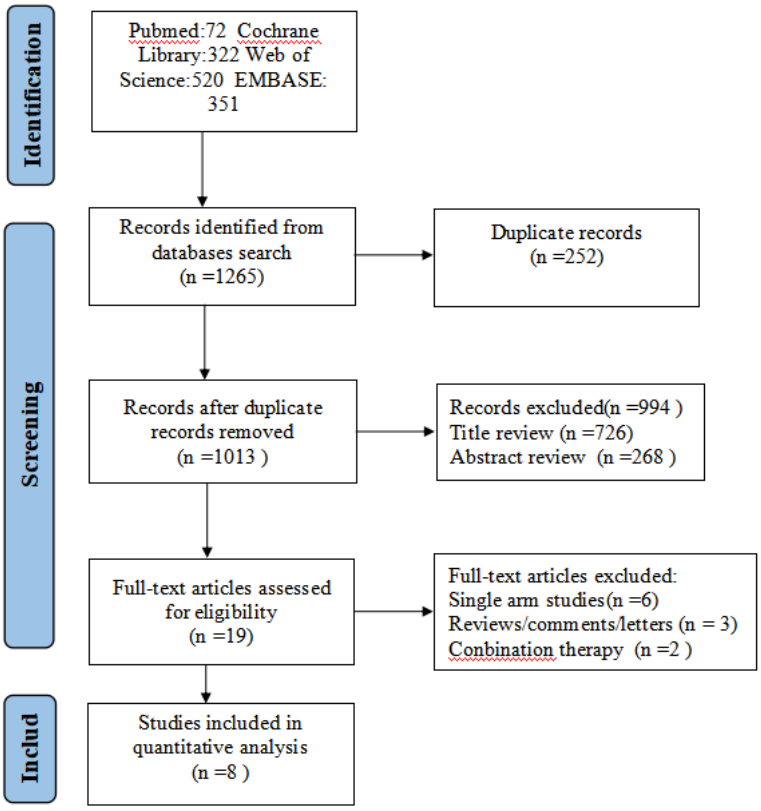

Figure 1

Flow chart of the selection process

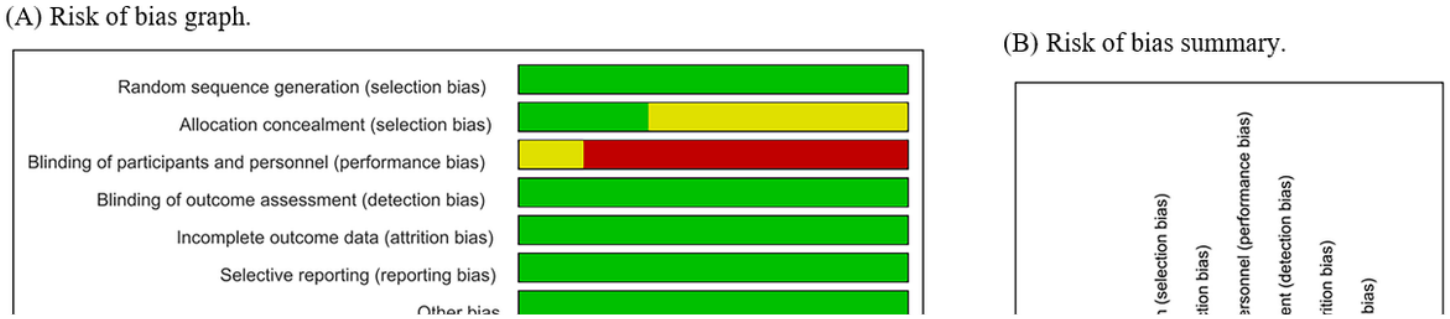

Figure 2

Risk of bias: review authors' judgments about each risk of bias item for each included RCTs.

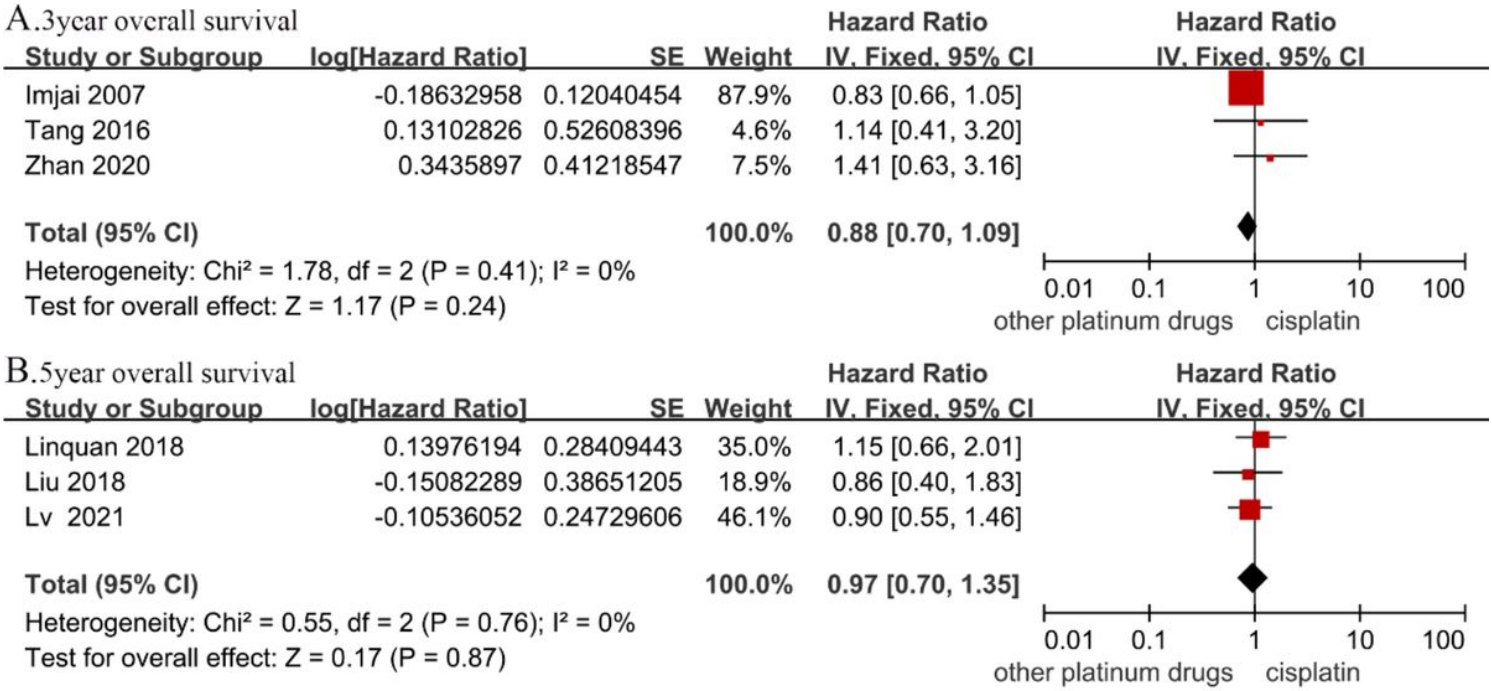

Figure 3

Forest plots of hazard ratios for (a) 3-year and (b) 5-year overall survival in nasopharyngeal carcinoma.

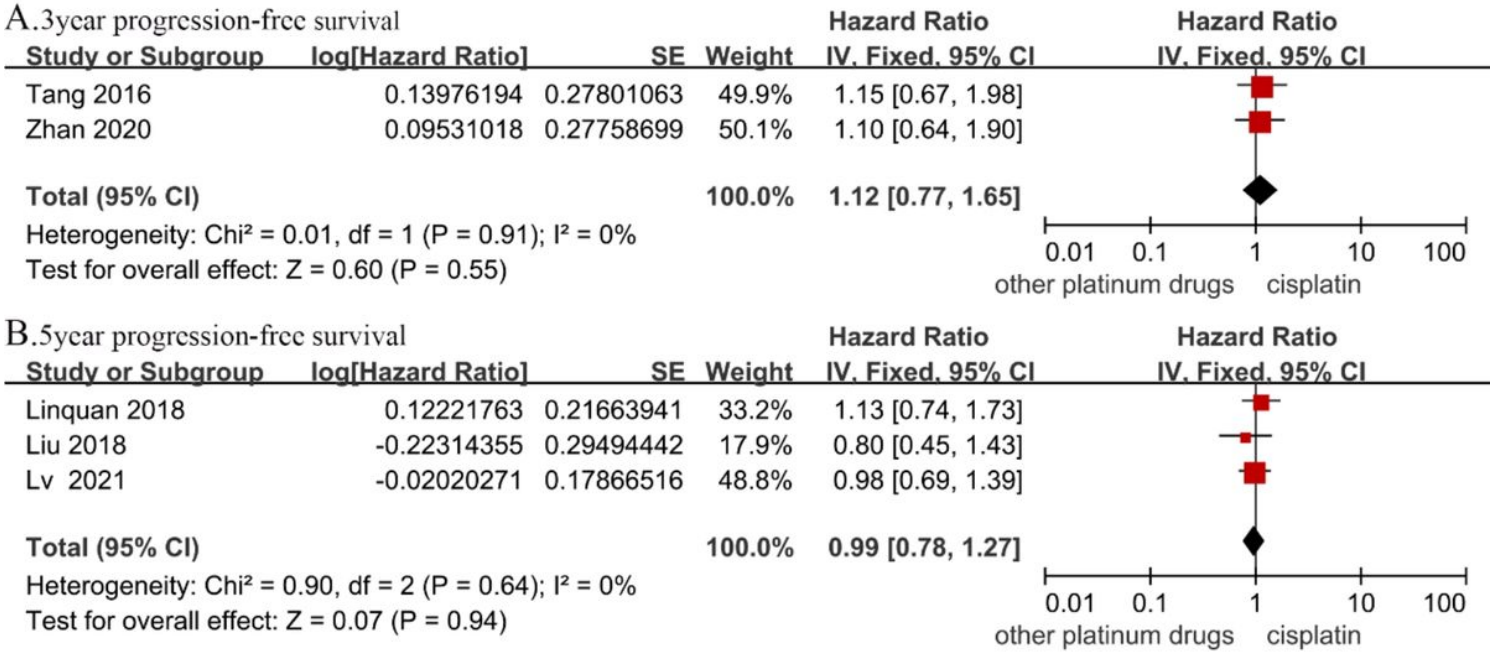

Figure 4

Forest plots of hazard ratios for (a) 3-year and (b) 5-year progression-free survival in nasopharyngeal carcinoma.

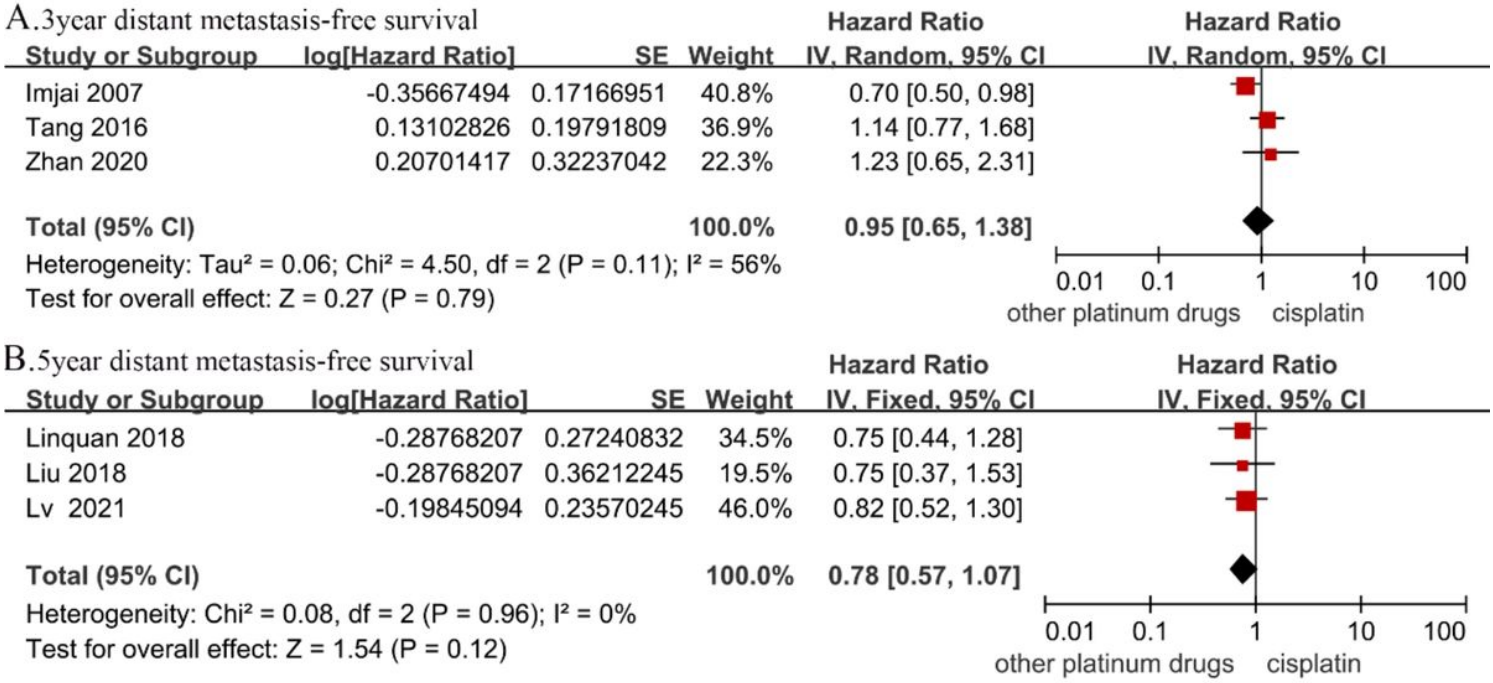

Figure 5

Forest plots of hazard ratios for (a) 3-year and (b) 5-year distant metastasis-free survival in nasopharyngeal carcinoma.

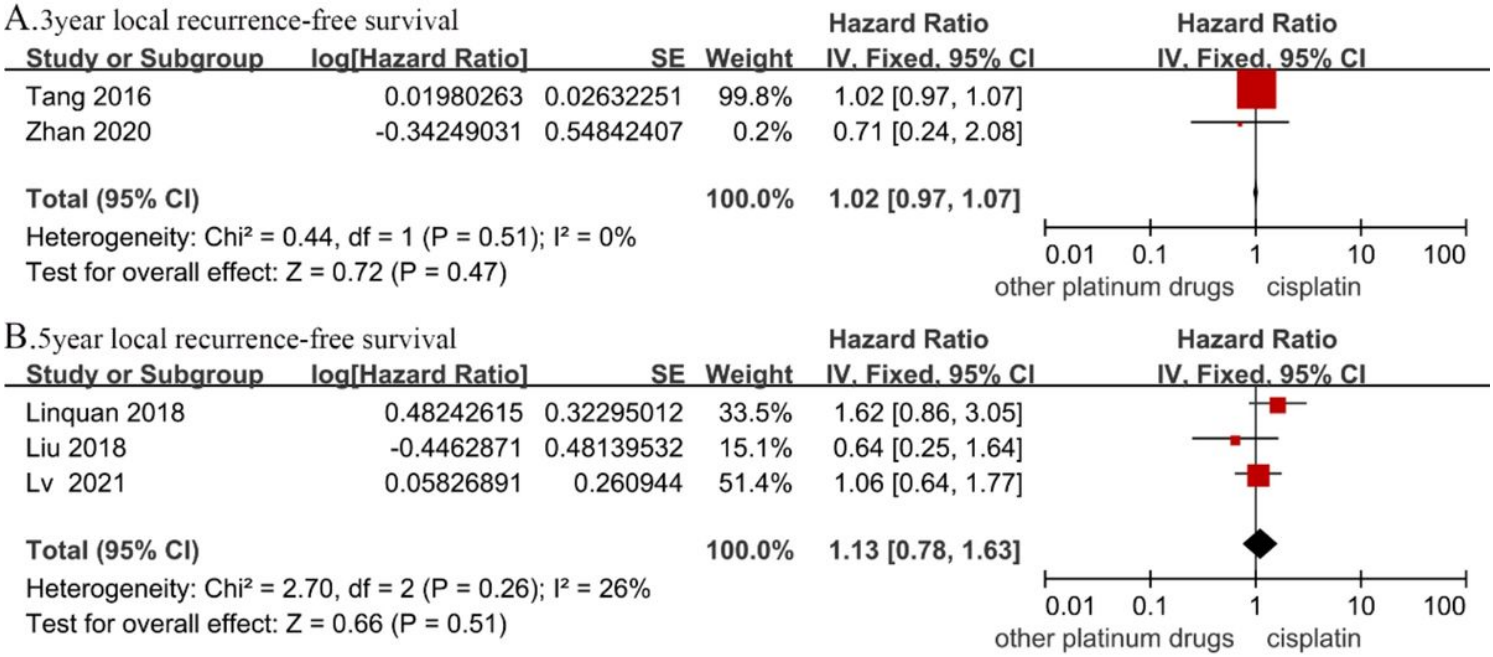

Figure 6

Forest plots of hazard ratios for (a) 3-year and (b) 5-year local recurrence-free survival in nasopharyngeal carcinoma.

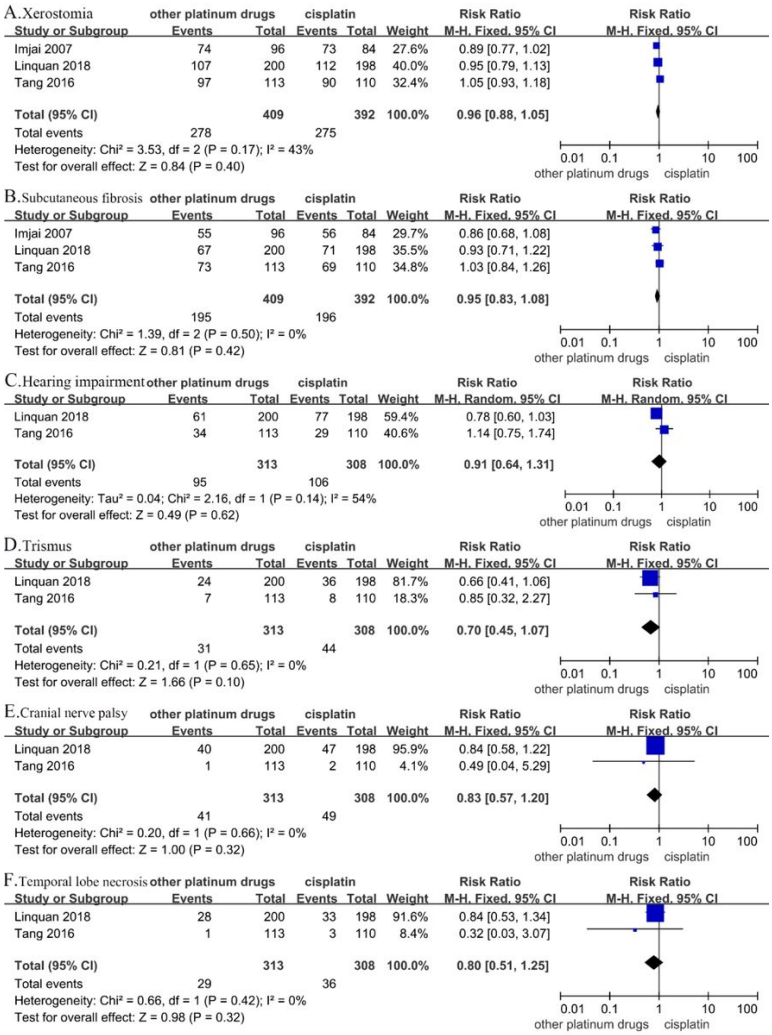

Figure 7

Forest plots of risk ratios for cumulative grade 1–2 late toxicities (a) xerostomia, (b) subcutaneous fibrosis, (c) hearing impairment, (d) trismus, (e) cranial nerve palsy, (f) temporal lobe necrosis.

Figure 8

Forest plots of risk ratios for cumulative response rates and toxicities in induced chemotherapy

Supplementary Files

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- PRISMA2020checklist.docx
- Supplementarymaterial.zip