Long-term follow-up of a phase III study comparing radiotherapy with or without weekly oxaliplatin for locoregionally advanced nasopharyngeal carcinoma

X. Wu1,2,†, P. Y. Huang1,3,†, P. J. Peng1,2,‡‡, L. X. Lu1,4, F. Han1,4, S. X. Wu1,4, X. Hou1,2, H. Y. Zhao1,2, Y. Huang1,2, W. F. Fang1,2, Y. Y. Zhao1,2, C. Xue1,2, Z. H. Hu1,2, J. Zhang1,2, J. W. Zhang1,3, Y. X. Ma1,2, W. H. Liang1,2, C. Zhao1,3,§ & L. Zhang1,2,§*

1State Key Laboratory of Oncology in South China; Departments of 2Medical Oncology; 3Nasopharyngeal Carcinoma; 4Radiation Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, People’s Republic of China

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Background: Previous results from our trial showed that adding oxaliplatin to radiotherapy (RT) increased survival in patients with locoregionally advanced nasopharyngeal carcinoma (NPC) at 2 years. Here, we present the data of long-term efficacy and late toxic effects.

Patients and methods: Between January 2001 and January 2003, 115 Patients with nonkeratinizing/undifferentiated locoregionally advanced NPC were randomly to receive either RT alone (n = 56) or plus concurrent oxaliplatin 70 mg/m2 weekly for six cycles (n = 59).

Results: After a median follow-up of 114 months (range 18–139 months), the 5-year overall survival (OS) and metastasis-free survival (MFS) rates in the concurrent chemoradiotherapy (CCRT) group were significantly higher than those observed in the RT-alone group (OS, 73.2% versus 60.2%, P = 0.028; MFS, 74.7% versus 63.0%, P = 0.027). However, CCRT did not improve locoregional failure-free survival significantly. Subgroup analyses showed that the superiorities of CCRT mainly existed in the T3-4N0-1 stage subgroup (OS: HR = 0.394, P = 0.034). The grade 3/4 late toxic effects were similar in the two groups.

Conclusion(s): The long-term follow-up data confirms the role of CCRT as a treatment of locoregionally advanced NPC. Oxaliplatin can be considered as an alternative optional therapeutic regimen for these patients due to its high efficiency and low toxic effect.

Key words: nasopharyngeal carcinoma, concurrent chemotherapy, oxaliplatin, radiotherapy

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introduction

Nasopharyngeal carcinoma (NPC) is highly sensitive to both radiotherapy (RT) and chemotherapy (CT). RT plays a key role in the treatment of all stages of NPC without distant metastases. Although RT is effective in the control of patients with early-stage diseases, the outcome of locoregionally advanced NPC remains unsatisfactory. Five-year survival rate ranges from ~56%–85% due to high rates of local and distant failure [1–3].

Chemotherapy, neoadjuvant, adjuvant, or concomitant has been added to the treatment regimen for NPC in numerous randomized studies in an attempt to improve the outcome of this patient population [2–6]. It is widely accepted that the concurrent chemoradiotherapy (CCRT) is most effective among different combination of chemotherapy and RT. Cisplatin is considered as a standard chemotherapy regimen of concurrent CCRT, providing benefit in relapse-free and overall survival (OS) [4–7]. However, a significant increase in toxic effects was also found using this aggressive regimen. Furthermore, the treatment compliances are generally poor, ranging from 44% to 94% [2, 4–8]. New agents with more effective antineoplastic activities and less toxic effect profile need to be explored.

Oxaliplatin, an analogue of cisplatin, has been shown to be a good radiosensitizer and less toxic effect agent [9, 10]. In a multicenter phase II study, Ma et al. [10] showed that oxaliplatin is active in the treatment of recurrent NPC. Accordingly, we previously conducted a phase III trial (Guangzhou-01) to compare the efficiency and safety profile of conventional RT plus weekly oxaliplatin in patients with locoregionally advanced NPC. The OS, the metastasis-free survival (MFS), and relapse-free survival were significantly longer in CCRT arm at a median follow-up time of 24 months [11].

In the present study, we updated the data of Guangzhou-01 trial after a long-term follow-up to compare the survival and adverse events between CCRT and RT arms.

patients and methods

eligibility criteria

This trial focused on patients with histological confirmed World Health Organization (WHO) subtype II, or III NPC according to the WHO classification system, and all cases were classified as stage T3/T4 (any N) and (or) N2/N3 (any T) without evidence of distant metastases (M0) according to the 1997 American Joint Committee on Cancer /International Union Against Cancer staging system [12]. Details of eligibility criteria have been previously reported [11]. All patients provided written informed consent.

randomization and treatment

All patients were divided randomly into the CCRT or RT-alone arm based on a 1 : 1 treatment allocation. Dosage and fractionation of RT were similar in both arms. The accumulated radiation doses to the primary tumor were 70–74 Gy. The accumulated doses were 60–64 Gy to the involved areas of the neck.

Patients assigned to the CCRT group were scheduled to receive a total of six cycles of chemotherapy. The regimen using oxaliplatin 70 mg/m² were delivered via intravenous infusion 1 h on days 1 every week. The details of RT techniques, dose modifications for both CT and RT, patient assessment, and follow-up had been previously reported [11].

statistical analysis

All events were measured from the date of random assignment. The current analyses focus on the following end points: objective response rate, OS (the time to death due to any cause or last follow-up), locoregional failure-free survival (LR-FFS, time to recurrence in the nasopharyngeal and/or cervical region), and MFS (time-to-distant metastasis) rates, safety profile of the combination Safety profile included events of acute toxic effects and late toxic effects.

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS, Chicago, IL) version 16.0 software. The Kaplan–Meier product-limit method was used in the calculation of OS, LR-FFS, and MFS rates. Toxic effect and response rates were compared using the χ² test. Fisher’s exact test was used when a small sample size existed. The statistical significance of differences among survival curves was analyzed using the log-rank test. The Cox regression method was used to calculate the hazard ratios and determine the interaction between treatments with covariates. P < 0.05 were considered statistically significant. Statistical tests were based on the two-sided significance level.

result

From January 2001 to January 2003, a total of 115 patients were recruited. Of these patients, 56 were randomized to the RT arm, and 59 were randomized to the CCRT arm. As described previously, all patient characteristics were well balanced in both arms (P > 0.05). The median follow-up time for the whole trial was 114 months (range from 18 to 139 months, 115 months for CCRT arm and 114 months for RT arm). Ninety-two percent of cancer survivors followed up for more than 60 months. Compliance with the protocol treatment was excellent, with 97% of patients completing all planned doses of oxaliplatin and RT (supplementary Figure S1, available at Annals of Oncology online). All the patients in both group completed the planned dose of RT without any interrupt. Three patients (3%) only received five cycles of oxaliplatin because of hematotoxic effect. The mean dose intensity of oxaliplatin received was 69.60 mg/m²/week (range 58.3–81.6 mg/m²/week).

treatment response

Clinical responses of the primary tumor site and of metastatic neck adenopathy were coded separately. All patients were assessable for response at the primary site. The complete response rate reached 83% (95% CI 74%–92%) in CCRT arm compared with 66% (95% CI 54%–78%) in the RT arm (P = 0.032). Ninety-one patients were assessable for neck response. Complete response rates were 88% (95% CI 79%–97%) in the CCRT arm and 95% (95% CI 88%–100%) in the RT arm (P = 0.233) in cervical lymph nodes. In the RT arm, three patients with neck recurrence received neck dissection. Eight patients with nasopharynx recurrence received reirradiation (three received CCRT with cisplatin, and five received intensity-modulated RT). In the CCRT arm, one patient with neck recurrence received neck dissection. Five patients with nasopharynx recurrence received reirradiation...
(three received intensity-modulated RT). One patient received salvage surgery for primary recurrence.

**survival**

In this trial, significantly improved OS, MFS rates were obtained in the CCRT arm compared with RT arm. The 3, 5, and 7-year OS rates were, respectively, 89.6%, 73.2%, and 71.3% in the CCRT arm versus 67.6%, 60.2%, and 56.3% in the RT arm; (HR = 0.54, 95% CI 0.31–0.94, P = 0.028; Figure 1A). The 5-year MFS rates in the CCRT arm and RT arm were 74.7% and 63.0%, respectively (HR = 0.52, 95% CI 0.29–0.94, P = 0.027; Figure 1B). However, the improvement in LR-FFS rates was not significant (HR = 0.61, 95% CI 0.29–1.29, P = 0.190). (supplementary Table S1, available at *Annals of Oncology* online).

In a post hoc exploratory subgroup analysis, the survival benefit from CCRT was observed mainly in the T3-4N0-1 stage subgroup. (5-year OS, CCRT versus RT: 84.2% versus 55.3%; HR = 0.39, 95% CI 0.16–0.96, P = 0.034, Figure 1C). However, there was no difference between OS in the arms for another two subgroups (T3-4N2-3 and T1-2N2-3 stage) (Table 1). There was no significant interaction between treatment and the three different risk subgroups with respect to OS (P = 0.789).

**toxic effect**

All patients were evaluated for safety. No fatal toxic effect or grade 4 toxic effect was observed in either arm. Acute Toxic effect was been reported before [26] (supplementary Table S2, available at *Annals of Oncology* online).

The most common late toxic effects in both groups were neuropathy, mucosal damage, soft-tissue damage, xerostomia, auditory toxic effect (supplementary Table S2, available at *Annals of Oncology* online). The CCRT arm showed higher late toxic effect rate than the RT group (66.1% versus 48.2%, P = 0.040) when total types of late toxic effects were calculated. And this difference was mainly attributed to xerostomia (CRT versus RT: 13.6% versus 1.8%, P = 0.002). In CCRT group, there was a numerical increase in grade 3 late toxic effects but this was not statistically significant (CRT versus RT: 28.8% versus 19.6%, P = 0.102).

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**Figure 1** (A) Comparison between concurrent chemoradiotherapy (CCRT) and radiotherapy (RT) arm on overall survival. (B) Comparison between CCRT and RT arm on metastasis-free survival. (C) Comparison between CCRT and RT arm on overall survival for T3-4N0-1M0 NPC patients.
Table 1. Subgroup analysis of adding oxaliplatin on survival

<table>
<thead>
<tr>
<th>End point</th>
<th>HR (95% CI)</th>
<th>T3-4 N0-1 (n = 58)</th>
<th>T2-3 N2-3 (n = 44)</th>
<th>T1-2 N2-3 (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.394 (0.162–0.960)</td>
<td>0.945 (0.429–2.085)</td>
<td>0.243 (0.022–2.739)</td>
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</tr>
<tr>
<td>P-value</td>
<td>0.034</td>
<td>0.889</td>
<td>0.252</td>
<td></td>
</tr>
<tr>
<td>LR-FFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.370 (0.098–1.397)</td>
<td>0.876 (0.316–2.426)</td>
<td>0.535 (0.033–8.559)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.127</td>
<td>0.798</td>
<td>0.658</td>
<td></td>
</tr>
<tr>
<td>MFS</td>
<td></td>
<td></td>
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<tr>
<td>HR (95% CI)</td>
<td>0.383 (0.149–0.983)</td>
<td>0.839 (0.366–1.923)</td>
<td>0.296 (0.027–3.274)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.038</td>
<td>0.677</td>
<td>0.321</td>
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</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; LR-FFS, locoregional failure-free survival; MFS, metastasis-free survival; OS, overall survival.

Discussion

Approximately 75% of NPC patients were locoregionally advanced at diagnosis. Recent progressions highlight the need of adjunct chemotherapy to RT for these patients. Results of randomized trials and meta-analyses had shown that CCRT was superior to RT alone and could be defined as the standard treatment of locoregionally advanced NPC [4–8].

The Intergroup-0099 trial [INT-0099] is the first phase III randomized trial comparing CRT versus RT alone in patients with locally advanced NPC [5]. The 5-year results showed a statistically significant difference in OS: 37% in the RT-alone arm, compared with 67% in the CRT arm. However, this trial had been argued for the poor result in RT group and doubted whether the results were applicable in endemic areas. Since then, there have been two other randomized trials, Taiwan-93 trial and PWHQEH-94 trial [6, 7], confirming the efficacy of this strategy. And in the present trial, even though the OS in RT group was substantially superior to the INT-0099 trial, the CCRT group also gained a significant survival benefit when compared with RT alone, suggesting the oxaliplatin-based CCRT is effective and applicable to endemic patients.

Concurrent chemotherapy has many potential advantages, including eliminating subclinical metastasis, lowering locoregional tumor load and a possible additive or synergistic effect with RT. Since results of randomized trials and meta-analyses had shown that CCRT was superior to RT alone in terms of OS, but the role of chemotherapy in CCRT, whether reducing the locoregional relapse or distant metastasis, was not clear. In Taiwan-93 trial [6], CCRT showed significantly better local control rates and a trend of reducing the distant metastasis (P = 0.0577). In contrast, no statistically significant difference in occurrence of distant metastases was observed in PWHQEH-94 trial [7]. In 9901 trial [8], which focus on the role of RT plus concurrent-adjuvant chemotherapy in staged T1–4N2–3M0 NPC patients, the CRT arm achieved significantly higher LR-FFR (92% versus 82%, P < 0.005). However, the improvement in D-FFS was not significant (76% versus 73%, P = 0.47). In our study, the data showed that the addition of CT to RT increased MFS by 11.7% at 5 years but failed to increase the locoregional control. It is now widely accepted that local and spatial cooperation between chemotherapy and radiation is important in NPC. Previous studies have indicated sequential treatments reduce local failure and concomitant treatments reduce distant metastasis [13]. Our results also agreed with this opinion. Further, phase II trials have showed that the neoadjuvant chemotherapy followed by chemoradiotherapy seem to be a logical strategy to maximize the benefit from both approaches [14]. But it needs to be validated in a phase III trial.

As we know, node-positive patients (N+) have a high risk of distant metastasis. Since the 9901 trial focused on patients with N2-3 disease, they failed to find the improvement of distant control when CT was added to RT. However, in Taiwan-93 trial [15], CCRT was superior to RT alone in distant control for low-risk patients (more patients were stage N0-1, 59%). In contrast, for the high-risk group (which included more N2-3 patients), CCRT was failed to decrease the distant metastasis rate. Besides, in PWHQEH-94 trial Subgroup analysis demonstrated that CRT arm had an OS benefit in T3/T4 subgroup (P = 0.013) [7]. In this trial, we carried out exploratory subgroup analysis of survival in three different risk cohorts: advanced T and early N (T3-4N0-1), advanced T and advanced N (T3-4N2-3), early T and advanced N (T1-2N2-3). The results showed that the patients with T3-4N0-1 stage significantly benefit from the addition of CT. But there was no clear benefit from concurrent CT in patients with T3-4N2-3 or T1-2N2-3 disease. Consistent with this, the NPC-9902 trial of patients with T3-4N0-1 disease also showed that combining the Intergroup-0099 regimen with accelerated fractionation could achieve a significantly higher distant failed free rate compared with RT alone [4].

Given these finding, it is indicated that concurrent chemotherapy, at least oxaliplatin chemotherapy regimens, is more effective in eradicating distant micrometastases in relative early N-stage patients, but inadequate for advanced N patients (N2–3 stage). More potent strategy, such as concurrent/induction-adjuvant CRT or even more aggressive adjuvantive agents like combined modality regimens might be needed for the high-risk groups. However, given the post hoc nature of these analyses and no significant interaction between treatment and the different risk groups, the results should be interpreted cautiously.
While it is indisputable that CRT is the standard approach, different regimens have been adopted in clinical trials and also in clinical practice. Cisplatin-based combination chemotherapy had resulted in favorable outcome for locally advanced NPC, but was associated with increased acute and late toxic effects. The proportion of patients who could complete all scheduled cycles ranged from 39%–71% during the concurrent phase, and 39%–76% during the adjuvant phase [2–3, 16]. Recently, a meta-analysis included 2829 NPC patients from 13 RCTs indicated that RT plus cisplatin-based chemotherapy significantly increased the risk of treatment-related mortality (1.7% versus 0.8%). [16] These evidences may partly explain the failure to observing the survival benefit of cisplatin-based CCRT in previous studies.

The aim of CCRT is to achieve a significant improvement in therapeutic outcome with minimal and acceptable additional toxic effects. Perhaps this issue can be overcome by the use of other anticancer agents. Promising results have been reported for other noncisplatin modalities in concurrent chemotherapy regimes, as the outcome of NPC patients receiving taxanes or carboplatin was encouraging [17, 18]. In the present study, we found that the regimen of oxaliplatin combined concomitantly with conventional RT was better than RT alone. Compliance with the protocol treatment was excellent, with 95% of patients completing all planned doses of oxaliplatin. We surmised that the positive result in this trial may partly attribute to the relatively high-dose intensity of concurrent chemotherapy. And it is possible that the lower dose intensity of cisplatin regimen in previous trials due to the poor compliance could narrow the actual magnitude of survival gain [2, 3, 15]. The information of late toxic effects after concomitant chemoradiotherapy comparing with radiation alone is scarce. In this trial, we also focused on the late toxic effects. The incidence of late radiation toxic effects were slightly increased in CCRT groups, but none of the patients experience the late radiation-induced morbidity. In comparison with NPC-9901/9902 trials [4, 8], the grade 3/4 late toxic effects in our CRT group was similar with the NPC-9901 trial but lower than the NPC-9902 trial. Especially, the soft-tissue toxic effect in CCRT group was lower than that of NPC-9902 trial. It might be due to the reduced radiation dose to the neck and conventional fractionation RT applied in our trial. And notably, the auditory toxic effect in our CRT group was less common than another two trials (supplementary Table S3, available at Annals of Oncology online). Thus, it is shown that oxaliplatin-based CCRT is feasible and tolerable for most patients with locally advanced NPC.

However, it should be kept in mind that our study had some limitations. First, when we initiated this trial, RT is still the standard treatment of locoregionally advanced NPC, and CCRT was now the widely accepted as the most effective strategy. Hence, the result achieved in the current trial is insufficient and a randomized trial comparing cisplatin-based CCRT and oxaliplatin-based CCRT would be necessary. Secondly, during the past decade, contemporary RT technique (e.g. 3D-CRT and IMRT) has gained increasing popularity in the treatment of NPC [18, 19]. However, distant metastasis remained the predominant pattern of failure. The pattern of chemoradiotherapy in our trial remains the potentially effective strategy and need to be confirmed. Finally, our trial recruited cases of WHO II/III NPC in endemic areas of NPC. It still remained unclear whether the conclusion of our study could be extrapolated to nonendemic areas in which the well-differentiated WHO I NPCs were more common.

In conclusion, the data of this long-term update confirms the role of concurrent chemoradiotherapy as a treatment of locoregionally advanced NPC. And Oxaliplatin can be considered as an alternative optional therapeutic regimen for this group of patients on account of its high efficiency and low toxic effect.

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disclosure

LZ has received research support from Sanofi-Synthelabo. All other authors have declared that they have no conflicts of interest. Sanofi-Synthelabo Corporation had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article; or the decision to submit the article for publication.

references

Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials

P. Y. OuYang1,†, C. Xie2,†, Y. P. Mao1, Y. Zhang1, X. X. Liang1, Z. Su1, Q. Liu3 & F. Y. Xie1*

1Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou; 2Department of Neurology, Medical School, Nanchang University, Nanchang; 3Department of Epidemiology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China

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Background: We carried out this meta-analysis to demonstrate efficacies of neoadjuvant chemotherapy (NACT) and adjuvant chemotherapy (AC) for nasopharyngeal carcinoma (NPC) patients based on randomized, controlled trials (RCTs). Patients and methods: We comprehensively searched electronic databases and manuscripts for RCTs and extracted data from eligible studies for meta-analysis. Overall survival (OS) with hazard ratios (HRs), locoregional recurrence rate (LRR) and distant metastasis rate (DMR) with relative risks (RRs) were concerned using random and/or fixed-effects models. Subgroup and sensitivity analyses were also carried out.

Results: Six trials in NACT group (n = 1418) and five in AC group (n = 1187) were eligible. HR of death for NACT was 0.82 [95% confidence interval (CI) 0.69–0.98, P = 0.03], corresponding to an absolute survival gain of 5.13% after 3 years. Significant reduction of DMR (P = 0.0002; RR 0.69, 95% CI 0.56–0.84) was also found from NACT. But no decrease in LRR (P = 0.49; RR 0.90, 95% CI 0.66–1.22) was observed. Patients receiving additional AC had lower LRR (P = 0.03; RR 0.71, 95% CI 0.53–0.96). But no benefit of OS and DMR were seen in AC.

*Correspondence to: Prof Fang-Yun Xie, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, NO. 651 Dongfeng Road East, Guangzhou 510060, China. Tel: +86-020-87343484, Fax: +86-020-87343484; E-mail: xiefy@sysucc.org.cn
†P.Y.O.Y. and C.X. contributed equally to this work.

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