Chomoradiotherapy of NPC

Concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: Treatment outcomes of a prospective, multicentric clinical study

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A B S T R A C T

Background and purpose: To evaluate long-term outcome in locoregionally advanced nasopharyngeal carcinoma (NPC) treated with intensity-modulated radiation therapy (IMRT) and concurrent chemotherapy.

Material and methods: Between January 2006 and August 2008, 249 patients with stage III–IVb NPC were treated by IMRT plus concurrent chemotherapy in this multicenter prospective study.

Results: With a mean follow-up of 54.1 months, the 5-year actuarial rates of overall survival (OS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS) were 78.4%, 86.8%, 88.4%, 78.0%, respectively. There were 29 local recurrences, 25 regional recurrences and 52 distant metastases, respectively. Distant metastasis is the main cause of treatment failure. N-stage was an independent prognostic factor for LRFS, RRFS, DMFS and OS. Acute toxicity grade III mainly consisted of mucositis (34.9%), neutropenia (11.2%), xerostomia (5.6%), and dermatitis (5.2%).

Conclusions: IMRT with concurrent cisplatin chemotherapy resulted in encouraging rates of local and distant control and overall survival with acceptable rates of acute and limited rates of late toxicity in patients with locoregionally advanced NPC. Distant metastasis remained the main cause of failure. More effective systemic therapy should be explored for patients with advanced N-stage.

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Nasopharyngeal carcinoma (NPC) is endemic in Southern China and Southeast Asia, with an annual incidence of 15–50 cases per 100,000 [1]. Radiation therapy (RT) is a paramount approach as the initial treatment option for NPC. Intensity modulated radiotherapy (IMRT), which delivers a high dose of radiation to the tumor while keeping a reduced dose to normal tissues surrounding the NPC region and excellent tumor coverage, has become widely accepted for the treatment of NPC, and has been shown to be more advanced than the conventional two-dimensional technique and three-dimensional conformal radiation in local or regional control [2]. However, patients with locoregionally advanced NPC remain to be shown a relatively poor prognosis when treated with IMRT alone [3]. Based on multiple phase III studies and meta-analyses, concurrent cisplatin-based chemoradiotherapy is the current standard of care for locoregionally advanced NPC (American Joint Committee on Cancer manual [7th edition] stages II–IVb). Here, we report our experience of a prospective, multicentric clinical study in 249 patients with locoregionally advanced NPC who were treated by IMRT combined with simultaneous chemotherapy.

Materials and methods

Patient characteristics

We identified a total of 249 patients with primary histopathologically-confirmed NPC at six centers in Guangxi Zhuang Autonomous Region who participated between January 2006 and
August 2008. Patients with a Karnofsky performance status of 70 or more, who met criteria for blood counts and other tests (i.e., serum creatinine <1.6 mg/dl and serum bilirubin <1.5 mg/dl; white blood cell > 3600/mm^3, platelet > 100,000/mm^3, and hemoglobin > 12.0 g/dl for male, > 11.0 g/dl for female) were eligible. Patients younger than 18 years old or those with a prior (i.e., within 5 years) or synchronous malignancy were excluded. Initial work-up included clinical and laboratory examinations, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck region, endoscopy with histological confirmation, chest X-ray or CT, abdominal ultrasound or CT and bone scan for exclusion of distant metastases. Patients were staged in III–IVb according to the 2002 AJCC Staging System. NPC was classified into three categories according to the World Health Organization (WHO) criteria: type I, squamous cell carcinoma; type II, non-keratinizing carcinoma; and type III, undifferentiated carcinoma. All patients signed written informed consents, and the study was approved by participating centers’ institutional review boards.

Radiation therapy

External beam radiotherapy (EBRT) was performed in intensity-modulated technique in all patients. The technique of IMRT has been previously described [4]. Briefly, all patients were fixed in an individually manufactured precision mask from head to shoulders, with the head in a neutral position. Contrast-enhanced CT was performed for planning. CT data were imported to the treatment planning system for treatment design. The primary gross volume (GTVnx) and the involved lymph nodes (GTVnd) included the entire macroscopic tumor defined after correlative analysis of CT- and MRI-scans. For the clinical target volume 1 (CTV1) a margin of 0.5–1 cm was added manually to the GTV. CTV2 was defined as CTV1 plus 0.5–1 cm margin, including the bilateral uninvolved regional nodes (retro- and parapharyngeal nodes, cervical nodes level II, III, and upper portion of level V limited to inferior body of the cricoid bone). PTVnx, PTVnd, PTV1, and PTV2 were generated by adding 5-mm margins to GTVnx, GTVnd, CTV1, and CTV2, respectively. The total doses were prescribed to the median of the target volume and usually the 95% isodose surrounded the target volume and usually the 95% isodose surrounded the target volume. The average maximum dose, minimum dose, mean dose, and the dose statistics of PTVnx, PTVnd, PTV1, and PTV2 are listed in Table 2. The Dose–Volume Histogram Statistics for critical structures are listed in Table 3. Follow up

Patients underwent weekly examinations during treatment. Follow-up evaluations occurred every 2 months during the first 2 years, every 3 months for the third year, and every 6 months thereafter. Acute and late morbidities were assessed according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Statistical analysis

Actuarial rates of overall survival (OS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS) were calculated by the Kaplan–Meier method. The primary endpoint for OS, LRFS, RRFS, and DMFS was death, local recurrence, regional recurrence and distant metastasis occurrence, respectively. The time-to-event was calculated from the date of treatment completion to the date-of-event occurrence. Univariate analysis was performed using the log-rank test to identify parameters associated with treatment outcome, and multivariate analyses using Cox regression. A P value of <0.05 was considered statistically significant.

Results

Patient characteristics

Between January 2006 and August 2008, a total of 249 patients were included in the trial. The mean age at the time of diagnosis of NPC was 44.5 ± 8.8 years. There were 198 males and 51 females. WHO type I, II, and III were in 8, 16, and 225 patients, respectively. Stage distributions were as follows: stage III, 141; stage IVa and IVb, 108. Table 1 lists the pretreatment patient demographic and clinical tumor characteristics.

Dose statistics

The median overall treatment time was 44.3 days, ranging from 40 to 51 days. The mean total radiation dose and mean radiation dose per fraction for PTVnx, PTVnd, PTV1, and PTV2 were 73.3 and 2.36 Gy, 69.6 and 2.25 Gy, 70.2 and 2.26 Gy, and 64.7 and 2.09 Gy, respectively. The average maximum dose, minimum dose, mean dose, and the percentage target volume covered by the 100% prescribed dose line of PTVnx, PTVnd, PTV1, and PTV2 are listed in Table 2. The Dose–Volume Histogram Statistics for critical structures are listed in Table 3.

Survival analysis

The median follow-up time was 54.1 months (range 11–85 months). Fifty-one patients died: 39 from distant metastasis, 7 from locoregional recurrence, 1 from hemorrhage in nasopharynx, 1 from second primary malignance, 1 from unknown cause, and 2 died during reirradiation course. The median time of death of the 51 patients was 33.7 months (range 11–62 months). For all patients, the 5-year OS was 78.4%.

Patterns of treatment failures

There were 80 patients who experienced treatment failures. Local recurrence was observed in 29 patients after a median time...
of 26.9 months (range 6–57 months), 10 of them presented with T3 disease, and 19 presented with T4 disease. No patients presented with T1 or T2 disease. All local recurrences were located inside the boost areas. 25 patients suffered from regional recurrence after a median time of 25.8 months (range 6–59 months), 12 of them occurred inside GTVnd, 11 inside CTV2 and 2 outside the boost areas. Distant metastasis was found in 52 patients after a median time of 21.7 months (range 6–61 months), 2 of them suffered from local recurrence too, 8 had regional recurrence, and 7 had locoregional recurrence. Of all the patients who developed distant metastasis, 39 had single organ metastasis, and 13 had multiple organ metastasis. The most frequently involved metastatic sites were bone (26 patients), lung (22 patients), and liver (18 patients). The most common acute toxicities were mucositis, dermatitis, and xerostomia. Grade 0–2 mucositis, dermatitis, and xerostomia were seen in 87 patients (34.9%), 13 patients (5.2%), and 14 patients (5.6%), respectively. No grade 4 acute toxicities were observed. Neutropenia was another major acute toxicity observed during treatment, 15.3% of patients had grade 1, 72.7% had grade 2, and 87% had grade 3 in 20 patients (8.0%), and grade 4 in 8 patients (3.2%).

The main documented late toxicity for 227 patients who survived for more than 2 years was xerostomia. At 3 months after treatment, 15.3% of patients had grade 1, 72.7% had grade 2, and 11.6% had grade 3 xerostomia. However, the severity of xerostomia decreased over time. At 24 months, only 13.2% of patients had grade 2 xerostomia, and none had grade 3 or 4 xerostomia. Other late toxicities observed included subcutaneous fibrosis, hearing impairment, trismus, cranial nerve palsy, temporal lobe necrosis, vision loss, dysphagia and subclinical hypothyroidism. Table 5 shows the frequency of the late toxicities by type and grade.

### Discussion

NPC is characterized by poorly or undifferentiated carcinoma. The proximity of the nasopharynx to critical normal tissues, such as the brainstem, spinal cord, parotid, and optic pathways, presents unique challenges in the delivery of radiation therapy. The use of concurrent chemoradiotherapy has shown promising results in improving local control and overall survival compared to chemotherapy alone. However, this approach also increases the risk of acute and late toxicities, which need to be carefully monitored and managed to ensure the best possible outcomes for patients.
diotherapy had a significantly better DFS (HR = 2.64; 95% CI, 0.62–4.3; 95% CI, with the IMRT alone arm, patients treated by concurrent chemoradiotherapy (CCRT) group were significantly higher than those observed in the RT-alone group (OS, 73.2% vs. 60.2%; 5-year OS and MFS in the concurrent chemoradiotherapy (CCRT) arm of patients with NPC demonstrated that this radiation technique could improve tumor control [10,11]. However, patients with locoregionally advanced NPC remain to be shown to have a relatively poor prognosis when treated with IMRT alone [3]. The addition of chemotherapy to IMRT has been suggested in an attempt to reduce failures and prolong survival. Ji et al. [12] reported that 276 patients with locoregionally advanced NPC were treated by IMRT alone or IMRT plus chemotherapy. After a mean follow-up of 33.8 months, the 3-year OS, MFS, RFS, and DFS were 90.3%, 84.2%, 72.2%, 61.9%, and 78.1%, respectively. Concurrent chemoradiotherapy. The rates of 5-year LC, DFS, PFS, and OS were 90.3%, 84.2%, 88.4%, 78.0%, and 78.4%, respectively. This was consistent with other reports.

Dosimetrically, IMRT has the ability to deliver the prescription dose to the delineated target volume with precision, while sparing the adjacent normal tissue structures. Numerous dosimetry studies on linear accelerator based IMRT treatments of nasopharyngeal carcinoma have been reported, and all of them show that IMRT can have definite dosimetry advantages over 2-dimensional (2D) and conventional 3-dimensional conformal radiotherapy (3DCRT) treatments [18–22]. In comparison with conventional IMRT, the image-guided IMRT has demonstrated better dosimetry coverage and highly conformal dose distributions to the targets and the impressive ability to simultaneously spare critical organs [23]. NPC is a cancer disease that can benefit from the treatment because of the recognized radio-curability and the evidence of a relationship between dose and response for the disease. IMRT’s high conformity makes it possible to facilitate the delivery of high radiation doses to the target, reduce the probability of in-field recurrence and consequently improve locoregionally control. Saleh et al. [17] reported their experience in 49 consecutive patients with NPC who were treated by IMRT combined with simultaneous chemotherapy. The median follow-up for the entire cohort was 48 months. They observed 4 local recurrences after 7, 14, 20 and 34 months of follow up, all of which were located inside the boost areas. The resulting estimated 1-, 3- and 5-year local control (LC) rates were 98%, 90% and 90%, respectively. One additional patient suffered from an isolated nodal recurrence in the neck after 12 months, which was located inside the radiation fields. The resulting estimated 1-, 3- and 5-year regional control rates were 98%. In Xiao et al.’ study [24], eighty-one patients with pathologically diagnosed locally advanced NPC were treated with IMRT and concurrent chemotherapy. The median duration of observation was 54 months (range, 6–87 months). At the time of the analysis, four patients experienced local recurrence, 2 had regional

as the brain stem/optic structures, makes it difficult to treat the tumor with two-dimensional techniques while the dose to surrounding organs is kept within an acceptable range [5–7]. IMRT has been shown to result in remarkable advances compared to conventional radiotherapy in target conformity, increased radiation dose in the target volume, and sparing of surrounding normal organs at risk [8,9]. The clinical applications of IMRT in patients with NPC has been shown to result in remarkable advances compared to conventional IMRT, and sparing of surrounding normal organs is kept within an acceptable range[5–7]. IMRT tumor with two-dimensional techniques while the dose to surrounding organs is kept within an acceptable range.
The IMRT group had recovered at least 25% of preradiotherapy xerostomia than patients in the 2DRT arm (39.3% vs. 82.1%; P = 0.001). Pow et al. [23] retrospectively analysed 28 patients with pathological proven locally advanced NPC who were treated with concurrent image-guided IMRT and chemotherapy following neoadjuvant chemotherapy. With a median follow-up after 33 months (range, 13–53 months), there have been 2 primary and 1 nodal relapse after completion of radiotherapy. No patients failed at the field margins or out of RT fields. The estimated 3-year LRFS and RRFS were 92.4% and 95.7%, respectively. In the present study, we similarly observed that most LR and RR occurred in the high dose areas. All the 29 LR were located inside the boost areas. The resulting estimated 5-year LRFS 86.8%. 25 patients suffered from RR, 12 of whom occurred inside GTVnd, 11 inside CTV2 and 2 outside the boost areas. The resulting estimated 5-year RRFS 88.4%.

Although locoregional control has been improved with IMRT, distant metastasis is the main cause of treatment failure and death [25]. In a pilot study conducted by Wang et al. [18], 138 NPC patients were treated with IMRT, 81.5% of whom had stage III/IV disease. Overall disease failure developed in 36 patients, 99% belonged to stage III/IV disease. Among these, there were 26 distant metastases, 6 local recurrences, and 4 regional recurrences. The 3-year LC and MFPS were 93.9% and 79.5%, respectively. The inferior outcome of DMFS over LC and RC was also reflected by other series [2,26–29], in which the 2-year distant relapse rate ranged from 6% to 15%, and the 5-year distant relapse rate was as high as 32%. In our study, there were 52 distant metastases, resulting in a 5-year DMFS of 78.0%, which was inferior to LRFS (86.8%) and RRFS (88.4%). The treatment outcome is comparable to the above results. Given that the predominant pattern of failure in locoregionally advanced NPC treated with IMRT and chemotherapy is distant metastases, and given that patients with NPC who have elevated vascular endothelial growth factor have a higher likelihood of recurrence, distant metastases, and decreased survival, we have embarked on finding novel chemotherapeutic agents, and testing the role of antiangiogenic agents.

We explored the prognostic value of some factors, including gender, age, T stage, N stage, and stage grouping, and found that the N-stage was an independent prognostic factor for RRFS, DMFS and OS. The results hint that effective systemic therapy for patients with advanced N-stage is demanding. Although at 3 months after treatment, there were 34.9%, 5.2%, and 5.6% of the patients who underwent grade 3 mucositis, dermatis, and xerostomia, respectively, all the patients could well tolerate and finish the complete treatment. Moreover, we observed a few significant late toxicities. The most common late toxicity was xerostomia. However, the severity of xerostomia decreased over time. At 24 months, only 13.2% of patients had grade 2 xerostomia, and none had grade 3 or 4 xerostomia in our analysis. The degree of xerostomia is dependent largely on the dose and volume of salivary gland in the radiation field. Studies have shown that salivary flows are markedly reduced after 10–15 Gy of RT [30–31]. High doses to most of the gland will result in permanent xerostomia [32], which compromises patient quality of life. Lee et al. [28] suggested that 50% of one parotid gland should receive <34 Gy if substantial sparing of the gland function was desired. Furthermore, the severity of xerostomia decreased over time. In Kam et al.’s [9] report, 60 patients with early-stage NPC were randomly assigned to receive either IMRT or 2DRT. At 1 year after treatment, patients in the IMRT arm had a lower incidence of observer-rated severe xerostomia than patients in the 2DRT arm (39.3% vs. 82.1%; P = 0.001). Pow et al. [33] reported that fifty-one patients with NPC took part in a randomized controlled clinical study and received IMRT or CRT. At 12 months postradiotherapy, 12 (50.0%) and 20 patients (83.3%) in the IMRT group had recovered at least 25% of preradiotherapy stimulated whole (SWS) and parotid (SPS) flow respectively, compared with 1 (4.8%) and 2 patients (9.5%), respectively, in the CRT group, and consequently improved QoL for patients with NPC. Beyond xerostomia, we also discovered a low incidence of subcutaneous fibrosis, hearing impairment, trismus, cranial nerve palsy, temporal lobe necrosis, vision loss, dysphagia and subclinical hypothyroidism in our current cohort. The low incidence of late toxicities more likely due to IMRT planning’s dosimetric advantages compared to other radiation techniques in NPC [18–22], which theoretically should lead to reduced late toxicity.

In conclusion, IMRT with concurrent cisplatin chemotherapy resulted in encouraging rates of local and distant control and overall survival with acceptable rates of acute and limited rates of late toxicity in patients with locoregionally advanced NPC. Distant metastasis remained the main cause of failure. More effective systemic therapy should be explored for patients with advanced N-stage.

References


