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Long-term results of concurrent chemoradiotherapy for T3/T4 locally advanced nasopharyngeal carcinoma

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Abstract. Nasopharyngeal carcinoma (NPC) is one of the most commonly diagnosed head and neck malignancies. This study investigated the outcome of locally advanced NPC patients on concurrent intensity-modulated radiation therapy (IMRT) and chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF). A total of 226 patients with locally advanced NPC received IMRT, with a total dose of 65-70 Gy and concurrent chemotherapy, with 2 cycles of TPF administered during radiotherapy, between March, 2005 and March, 2007. An additional 2 to 4 cycles of chemotherapy were administered every 21 days following radiotherapy. With a median follow-up time of 35 months (range, 7-60), the 5-year overall survival (OS) rate was 81.4%, with 93.6 and 75.0% for T3 and T4 lesions, respectively, (P=0.001). The 5-year progression-free survival (PFS) was 50.4%, with 66.7 and 46.9% for T3 and T4 lesions, respectively (P<0.001). T-classification was a significant prognostic factor for PFS and OS. The subgroup analysis revealed that pterygopalatine fossa invasion was associated with a significantly lower 5-year PFS (P=0.001) and OS (P=0.002), foramen rotundum invasion was associated with a significantly lower 5-year PFS (P<0.001) and OS (P=0.004), foramen ovale invasion was associated with a significantly lower 5-year PFS (P=0.013) and OS (P=0.024) and foramen lacerum and cavernous sinus invasion were associated with a significantly lower 5-year PFS (P<0.001 and P<0.001, respectively). Concurrent chemoradiotherapy is an advocated regimen for patients with locally advanced NPC, since it exhibits satisfactory 5-year PFS and OS rates. Our results suggest that the estimation of invasive range may identify a subgroup of patients with a higher risk of locoregional failure who may be better candidates for this treatment strategy.

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Abbreviations: NPC, nasopharyngeal carcinoma; IMRT, intensity-modulated radiation therapy; OS, overall survival; PFS, progression-free survival; OAR, organs at risk; CT, computed tomography; GTV, gross tumor volume; CTV, clinical tumor volume; RTOG, radiation therapy oncology group

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Key words: nasopharyngeal carcinoma, intensity-modulated radiation therapy, chemotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is the most commonly diagnosed head and neck malignancy in Southeast Asia and 70% of patients present with locally advanced-stage cancer at the time of diagnosis (1-3). Moreover, NPC demonstrates the highest incidence rates of distant metastasis among all head and neck cancers. Due to anatomical restrictions, the standard treatment for NPC is definitive radiotherapy. The benefits of chemotherapy administered concurrently with radiation are supported by the present data, demonstrating significant increases in progression-free survival (PFS), as well as overall survival (OS) (4,5).

Although considered essential for patients with locally advanced NPC, the therapeutic value of chemotherapy administered concurrently with intensity-modulated radiation therapy (IMRT) and the optimal strategy of combining the two, has not yet been sufficiently addressed. The rationale of concurrent chemotherapy and IMRT in the treatment of NPC is mostly derived from experience with conventional radiotherapy. Concurrent chemoradiotherapy has shown significant benefits following treatment; however, whether it offers equal therapeutic benefits to all the patient subgroups with locally advanced NPC remains to be determined. The objective of this study was to assess treatment outcomes and elucidate the efficacy of concurrent chemoradiotherapy, by analyzing results obtained from a relatively large group of patients with locally advanced NPC, uniformly treated with IMRT and concurrent chemotherapy.

Materials and methods

Patients and pretreatment evaluation. A total of 226 patients with histologically diagnosed non-metastatic NPC were treated with concurrent chemoradiotherapy at the First Affiliated Hospital of Soochow University (Suzhou, China),

between March, 2005 and March, 2007. The pretreatment evaluation consisted of a complete history and physical examination, flexible fiberoptic endoscopic examination, blood chemistry tests, urinalysis, chest X-ray, electrocardiogram, computed tomography (CT) scans of the nasopharynx and neck, magnetic resonance imaging (MRI) scans of the head and neck, bone emission computed tomography scans, liver and abdominal lymph node ultrasounds and dental evaluation. Positron emission tomography scans and CT scans of the chest and abdomen were optional and performed when clinically indicated. Tumors were staged according to the Guangzhou staging system (2008). Patients who presented with evidence of distant metastasis were not eligible for this treatment protocol. The characteristics of the 226 patients are listed in Table I.

IMRT techniques. IMRT was performed using a commercial stereotactic radiotherapy system (Varian Eclipse; Varian Medical Systems, Inc., Palo Alto, CA, USA), in order to deliver revolving conformal radiation based on multileaf collimator to the target, using a 6-MV linear accelerator (Varian 23EX; Varian Medical Systems, Inc.). The patients were immobilized in the supine position with thermoplastic masks. CT planning scans with intravenous contrast material were performed, using 3-mm slices from the head to 2 cm below the level of the sternoclavicular joints. The primary and nodal gross tumor volumes (GTV-nx) and the cervical lymph node gross tumor volumes (GTV-nd) included the gross diseases visualized on CT and MRI. The high-risk clinical tumor volume (CTV-1) included GTV and a 5- to 10-mm margin, encompassing the entire nasopharyngeal mucosa, as well as a 5-mm submucosal volume. CTV-2 was designed for potentially involved regions, including the nasopharyngeal cavity, maxillary sinus, pterygopalatine fossa, posterior ethmoid sinus, parapharyngeal space, skull base, anterior third of the clivus and cervical vertebrae, inferior sphenoid sinus and cavernous sinus, as well as the retropharyngeal lymph nodal regions, from the base of skull to the cranial edge of the second cervical vertebra. The planning target volume was created based on each volume, with an additional 2- to 3-mm margin, which allowed for setup variability. Critical normal structures, including brainstem, spinal cord, parotid glands, optic nerves, optic chiasm, lens, eyeballs, temporal lobes, temporomandibular joints, mandible and hypophysis, were contoured and set as organs at risk (OAR) during optimization. The radiation doses prescribed in the protocol were as follows: a total dose of 65-70 Gy in 32 fractions to the GTV-nx and GTV-nd, 56-60 Gy in 32 fractions to the CTV-1 and 50-52 Gy in 28 fractions to the CTV-2. The patients were treated with one fraction daily for five days per week. The dose received by each OAR should be less than its tolerance limit, according to the radiation therapy oncology group (RTOG) 0225 protocol.

Chemotherapy. Concurrent chemotherapy was administered to all patients, in order to prevent disease progression during IMRT treatment planning. Concurrent chemotherapy consisted of 6 cycles of TPF regimen (cisplatin 80-100 mg/m^2 i.v. on Day 1, 5-fluorouracil 500-600 mg/m^2 i.v. on Days 1-5 and docetaxel 135-175 mg/m^2 i.v. on Day 1). The patients received 2 courses of chemotherapy every 28 days during radiotherapy, followed by an additional 2-4 cycles of chemotherapy every 21 days after radiotherapy.

Table I. Patient characteristics in the study population of 226 nasopharyngeal carcinoma patients, according to the Guangzhou staging system (2008).

Characteristics	No.	Percentage (%)
Patients	226	100
Age (years)		
>60	71	31.4
≤60	155	68.6
Gender		
Male	154	68.1
Female	72	31.9
T-classification		
T3	78	34.5
T4	148	65.5
N-classification		
N0	36	15.9
N1	72	31.9
N2	112	49.6
N3	6	2.7
Clinical classification		
III	78	34.5
IV	148	65.5

Follow-up. The patients were evaluated weekly during radiation therapy and were required to be followed-up by their attending radiation oncologist following the completion of their treatment, every 3 months for the first 2 years, every 6 months from the second through the fifth year and annually thereafter. Each follow-up included a complete examination, basic serum chemistry tests, chest X-ray and ultrasound of the liver and abdomen. Flexible fiberoptic endoscopy was performed at every visit after the treatment. MRI of the head and neck areas was performed every 6 months. Treatment-induced toxicities were assessed and scored according to the RTOG radiation morbidity scoring criteria at each follow-up.

Statistical analysis. The PFS and OS rates were calculated using the Kaplan-Meier method. The duration of time to local failure and distant metastasis was measured from the date of completion of the radiation therapy (including boost irradiation) until documented treatment failure. The OS duration was calculated from diagnosis until death or until the date of the last follow-up visit for the surviving patients. The statistical tests were performed using SPSS version 17.0. $P \leq 0.05$ among the groups was considered to indicate a statistically significant difference.

Results

Patients and treatment evaluation. A total of 226 patients diagnosed with locally advanced NPC were included in this study. The patients received concurrent chemoradiotherapy (IMRT and TPF). The mean age of the patients was 43 years (range, 17-72). The majority of the patients were male (68.1%)

Table II. Kaplan-Meier estimate of progression-free survival (PFS) and overall survival (OS), according to pterygopalatine fossa, foramen rotundum, foramen ovale, foramen lacerum and cavernous sinus invasion, or lack thereof.

Characteristic	No.	5-year PFS (%)	χ^2	P-value	No.	5-year OS (%)	χ^2	P-value
Pterygopalatine fossa								
+	120	43.3	11.74		71	74.2	9.68	
-	106	58.5		0.001	155	89.6		0.002
Foramen rotundum								
+	38	7.9	47.73		154	65.8	8.08	
-	188	59.9		0.000	72	84.6		0.004
Foramen ovale								
+	102	43.1	6.12		78	74.5	5.11	
-	124	53.5		0.013	148	85.1		0.024
Foramen lacerum								
+	111	39.6	23.27		36	77.5	2.10	
-	115	60.9		0.000	72	85.2		0.148
Cavernous sinus								
+	112	38.4	18.91		78	77.7	1.92	
-	114	62.3		0.000	148	85.1		0.166

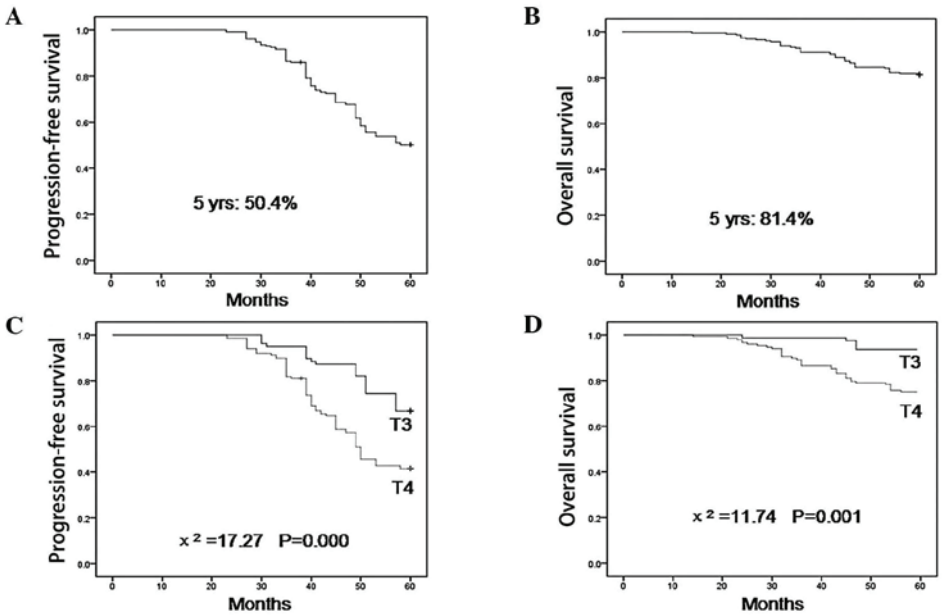

Figure 1. (A and B) Five-year progression-free survival and overall survival rates were 50.4 and 80.4%, respectively. (C and D) Kaplan-Meier estimate of progression-free survival and overall survival, according to T-classification.

and Guangzhou stage III (34.5%) and IV (65.5%). The patients received 4-6 planned cycles of chemotherapy.

Both the primary site and neck nodes achieved an objective response rate of 98% for the response evaluation. The primary site showed an 87% complete response and the partial response was 11%.

PFS and OS. With a median follow-up time of 35 months (range, 7-60), the 5-year OS rate was 81.4%, with 93.6 and 75.0% for T3 and T4 lesions, respectively (P=0.001, Fig. 1). The 5-year PFS was 50.4%, with 66.7 and 46.9% for T3 and T4 lesions, respectively (P<0.001, Fig. 1). T-classification was a significant prognostic factor for PFS and OS. The subgroup analysis revealed that pterygopalatine fossa invasion was associated with a significantly lower 5-year PFS (P=0.001, Table II) and OS (P=0.002, Table II), foramen rotundum invasion was associated with a significantly lower 5-year PFS (P<0.001) and OS (P=0.004), foramen ovale invasion was associated with a significantly lower 5-year PFS (P=0.013, Table II) and OS (P=0.024, Table II) and foramen lacerum and cavernous sinus invasion were associated with a significantly lower 5-year PFS (P<0.001 and P<0.001, respectively; Table II). By contrast,

foramen lacerum and cavernous sinus invasion had no impact on the 5-year OS (P=0.148 and P=0.166, respectively; Table II). None of the patients was lost during the follow-up period.

Discussion

NPC is considered unresectable due to its anatomical location and thus far radiation has been the conventional treatment approach (6,7). Changing failure pattern has been noted in several publications and distant metastasis rates may be as high as 30%, even with the integration of aggressive concurrent chemoradiotherapy schedules (8,9).

Concurrent chemoradiation is an attractive approach to overcome the problem of distant metastases. However, it requires further investigation, since available post-experience data are sparse (10-13). China has reported the largest series of concurrent chemotherapy and IMRT data, with 323 locoregionally advanced NPC patients. The overall 3-year OS rate was 87.2%. In the present study, the estimated 5-year PFS and OS rates were 50.4 and 80.4%, respectively (14). Concurrent chemotherapy for locoregionally advanced NPC has been shown to be feasible and effective for local control, with high compliance. Although all our patients had locally advanced disease (stages III and IV), they exhibited excellent local control rates following concurrent chemotherapy or even salvage therapy.

The histopathological type and involvement of lymph nodes in the lower neck have been well-established as prognostic factors of NPC (15). In addition to these factors, tumor invasive range has been recognized as an important prognostic factor in the treatment of malignancy. Recently, tumor invasive range has been actively studied in head and neck malignancies. NPC is a tumor with a highly infiltrative growth pattern and a propensity to spread along the parapharyngeal space, as well as to the skull base and foramina (16). The invaded area may affect prognosis and may vary from extensive invasion, involving multiple sites, to only a small localized area, which, in some patients, may be the only site of extranasopharyngeal spread. The skull base foramina represent an unimpeded channel for tumor spread, although direct invasion of the bones bordering these foramina often occurs as well. The foramen ovale and foramen lacerum are the two most commonly involved foramina, which provide a route for tumor spread into the cranium. The inferior spread of the tumor, involving the hypoglossal nerve canal and jugular foramen, is less common. Orbital invasion usually occurs by direct tumor spread from the pterygopalatine fossa; the tumor may also spread directly to the cavernous sinus, leading to multiple cranial nerve palsies. This phenomenon suggests that NPC has an infiltrative growth pattern, often with a highly irregular tumor contour.

In this study, our results demonstrated that T-classification was a significant prognostic factor for PFS and OS. The subgroup analysis revealed that pterygopalatine fossa, foramen rotundum, foramen ovale, foramen lacerum and cavernous sinus invasion were all associated with the long-term results of concurrent chemotherapy for patients with NPC.

Other factors that contribute to the apparent tumor radioresistance must be considered. Although this study demonstrated an inverse correlation between tumor control and disease volume, several failures in small tumors and cures in cases with massive disease have been observed. These observations suggest that other factors, aside from those observed in this study, contribute to radiation response. Moreover, cellular factors, such as repopulation, intrinsic radioresistance, reoxygenation and redistribution, have been suggested as important variables for tumor control (17).

In conclusion, volumetric analysis of the primary tumor and lymph nodes, anatomical sites involved and intracranial extension should be included in the current TNM staging system for NPC, in order to optimize the staging system.

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