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Nasopharyngeal carcinoma

Potential improvement of tumor control probability by induction chemotherapy for advanced nasopharyngeal carcinoma

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Abstract

***Purpose*: To assess the reduction of tumor bulk and improvement of tumor control probability (TCP) by using induction chemotherapy for advanced nasopharyngeal carcinoma (NPC).**

***Materials and methods*: From February to December 2005, 20 patients with Stage III—IVB NPC were treated with induction-concurrent chemotherapy and intensity-modulated radiotherapy with accelerated fractionation. Combination of cisplatin and 5-fluorouracil was used in the induction phase and single agent Cisplatin in the concurrent phase. All patients were irradiated at 2 Gy per fraction, 6 daily fractions per week, to a total dose of 70 Gy.**

***Results*: Nineteen (95%) patients completed all 3 cycles of induction chemotherapy and 90% had $\geqslant$2 cycles of concurrent chemotherapy. Induction chemotherapy achieved significant down-staging of T-category in 35% of patients ($p = 0.016$) and reduction of gross tumor volume (GTV_P) from 55.6 to 22.9 cc (mean 61.4%, $p < 0.001$). Although the mean radiation dose did not show any substantial change, the volume within GTV_P that failed to reach 70 Gy was reduced from 10.2% to 3.8% ($p = 0.017$). The estimated local TCP increased from 0.83 to 0.89 ($p = 0.002$).**

***Conclusions*: Induction chemotherapy using cisplatin—5-fluorouracil could significantly reduce tumor bulk leading to potential improvement in tumor control.**

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Keywords: Nasopharyngeal cancer; Tumor control probability; Induction chemotherapy

Although nasopharyngeal carcinoma (NPC) is a radiosensitive tumor, treatment of advanced locoregional disease remains difficult due to anatomical proximity to critical structures and notorious predilection for distant metastases. Meta-analyses confirmed that addition of chemotherapy in concurrence with radiotherapy (RT) was the most potent sequence for improving tumor control and survival [1]. With supporting evidence from 3 randomized trials [2—4], the most widely recommended treatment scheme was the Intergroup-0099 regimen which composed of a concurrent phase using single agent cisplatin, and an adjuvant phase using cisplatin and 5-fluorouracil.

However, the exact contribution of the adjuvant phase remains uncertain as adjuvant chemotherapy per se failed to achieve significant benefit in any end-points [1,5—7]. Furthermore, the tolerance to chemotherapy during the post-RT phase is generally poor, only 55% of patients in the original Intergroup-0099 Trial did actually receive the scheduled 3 cycles [2].

Although induction chemotherapy per se did not significantly improve overall survival (OS) [1,8—11], meta-analyses showed that this could significantly reduce the risk of locoregional failures by 24% and distant failures by 35% [1], and the Trial by the International Nasopharynx Cancer Study Group achieved significant improvement in event-free survival [10]. Hence changing the timing of chemoradiotherapy (CRT) to induction-concurrent sequence is a logical strategy to be explored.

Thus far, there have been seven Phase II studies [12—18] testing induction-concurrent CRT and all showed very encouraging results. However, there are yet no data on the actual magnitude of benefit attributed to induction chemotherapy. The purpose of the current analyses is to assess this interesting impact on primary tumor bulk, the resultant dose distribution and tumor control probability (TCP).

Materials and methods

Patient characteristics

Twenty consecutive patients with newly diagnosed NPC treated with induction-concurrent CRT from February to

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December 2005 were analyzed; their characteristics are summarized in Table 1.

Staging investigations included complete physical examination, fiberoptic nasopharyngoscopy, magnetic resonance imaging (MRI) of the nasopharyngeal and cervical region. Metastatic work-up by chest X-ray, ultrasound of liver and isotope bone scan were performed for those with Stage IV disease; one patient had additional investigation with positron emission tomography.

Using the International Union Against Cancer staging system (UICC 6th edition) [19], 35% patients were classified as Stage III, 50% Stage IVA and 15% Stage IVB. The primary tumor was classified as T3 in 45% and T4 in 55% patients.

Induction-concurrent chemoradiotherapy

Details of treatment schedule and dose modifications were described in the previous publication [15]. The induction chemotherapy consists of cisplatin 100 mg/m^2 intravenously and 5-fluorouracil 1000 mg/m^2/day by 120-h infusion. This combination was scheduled every 3 weeks for 3 cycles unless patient showed intolerance or progressive disease. Concurrent CRT was scheduled 3 weeks after the last cycle of induction chemotherapy, cisplatin at 100 mg/m^2 was given intravenously every 3 weeks for 2–3 cycles depending on the overall treatment time (OTT).

All patients had reassessment of locoregional disease by fiberoptic nasopharyngoscopy and MRI about 2 weeks after completion of the last dose of induction chemotherapy. Tumor response was defined according to the World Health Organization criteria [20].

The gross tumor volumes of the primary tumor (GTV_P) based on the two sets of MRI were delineated by the same radiologist (K.Y. Lau) and oncologist (A. Lee). These images were fused into the planning computed tomography which was performed after the last cycle of induction chemotherapy. The actual radiation plan was based on the pre-chemotherapy GTV_P. The resultant dose distribution was applied to the post-chemotherapy set for comparison.

Table 1
Patient characteristics

Patient characteristics	
Age	
Median (range)	54 (39–67) years
Gender	
Female	30%
Male	70%
Performance status (ECOG)	
0	85%
1	15%
Histological type	
Keratinizing	5%
Non-keratinizing	95%
Staging	
Stage III – T3N2	35%
Stage IVA – T4N2	50%
IVB – T3N3	10%
T4N3	5%

All patients were irradiated with 6 MV photons using intensity-modulated (IMRT) technique throughout the whole course. The clinical target volumes (CTV) were delineated at three levels: CTV_1 covered the GTV_P and the whole nasopharynx with 5 mm margin (2 mm for tumor infiltrating neurological structures), CTV_2 covered high-risk structures (including the adjacent structures at the base of skull and upper cervical region), while CTV_3 covered the low-risk structures (the remaining potential sites of local infiltration up to the roof of the sphenoid sinus and bilateral cervical lymphatics down to the supraclavicular fossae). An additional 2 mm margin was added to set the corresponding planning target volume (PTV).

The radiation plans aimed to deliver $\geqslant$95% of the intended dose to 100% of the respective target volumes without exceeding the tolerance for critical neurological structures (Table 2 shows the guideline used for setting dose constraints). A total dose of 70 Gy at 2 Gy/fraction, with accelerated fractionation (AF) of 6 daily fractions per week (Monday–Saturday), was prescribed to PTV_1, while PTV_2 and PTV_3 received 61.25 Gy and 52.5 Gy, respectively, at 1.75 Gy/fraction.

Patient assessments and follow-up

Acute toxicities were graded according to the Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE-v3) [21]. Incidence rates of toxicities grade $\geqslant$3 (except nausea or alopecia) were recorded.

Post-treatment reassessment included fiberoptic nasopharyngoscopy at around 8 weeks and progress MRI at 3–4 months after completion of the basic course of RT. Patients were followed up at least every 3 months during the first 3 years, and then every 6 months thereafter.

Statistical methods

To evaluate the performance of induction chemotherapy, Wilcoxon Signed Ranks test was used to compare pre- *vs.* post-chemotherapy status of T-category, and Students' paired-*t* test was used to compare the volume of GTV_P and CTV_1, the radiation doses to GTV_P and CTV_1, and the primary tumor control probability (TCP).

The TCP calculation was based on the model by Brenner [22] taking into account of inter-patient variation of tumor radio-sensitivity as described by Webb and Nahum [23].

$$\mathrm{TCP} = K\int_{\alpha=0}^{\infty}\exp\left(-\frac{(\alpha-\alpha_0)^2}{2\sigma^2}\right)T(\alpha)\,\mathrm{d}\alpha \quad (1)$$

where α_0 is the mean value of the radio-sensitivity parameter α, K is the normalization factor for the Gaussian distribution of α and $T(\alpha)$ is the tumor control probability for a single value of α:

$$T(\alpha) = \exp\left(-\rho\sum_i V_i \exp\left(-\alpha D_i - \beta\frac{D_i^2}{n}\right)\right) \quad (2)$$

where ρ is the clonogenic cell density, V_i is the sub-volume (in cc) of GTV_P receiving a total dose D_i in n fractions. The values of $\alpha_0 = 0.31\ \mathrm{Gy}^{-1}$ and $\sigma = 0.06\ \mathrm{Gy}^{-1}$ were estimated from our previous study on the relationship between tumor control and dose distribution of the GTV_P [24], assuming a