Management of nasopharyngeal carcinoma

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Nasopharyngeal carcinoma (NPC) is different from other head and neck cancers for its unique epidemiology, natural behavior and therapeutic considerations. Radiation therapy (RT) is the main modality of treatment, but therapeutic margin is notoriously narrow due to anatomical proximity of critical structures. To achieve the highest chance of locoregional control with minimal toxicity, accurate delineation of tumour target by modern imaging, meticulous immobilization, optimal dose fractionation, best conformal technique and precision in treatment delivery are all demanded. Experience in Hong Kong showed gratifying improvement in overall treatment results: the 5-year disease-specific survival increased from 50% in the period 1976–1985 [1] to 80% in 1996–2000 [2].

Development of intensity-modulated RT is a valuable tool for maximizing conformity of dose distribution; excellent locoregional control has been reported [3]. The best affordable technique should be used. The most commonly used dose schedule is 1.8–2 Gy per fraction to a total dose of 70 Gy. Retrospective studies suggest that dose escalation beyond 60 Gy could further improve outcome. Excellent local control has been reported by adding stereotactic boost [4], but the recent update showing 7% of temporal lobe necrosis is worrisome. Dose escalation remains difficult for tumours with intracranial extension.

Prolongation of overall treatment time is detrimental, but data on whether accelerated fractionation (AF) could lead to significant improvement for undifferentiated NPC remains scant. Excessive neurological damages have been observed in series using multiple fractions per day with dose $\geqslant$1.6 Gy per fractions [5], extra caution is demanded in designing fractionation schedules for NPC. A pilot study using 2 Gy per fraction, 6 daily fractions per week to 66 Gy showed encouraging improvement in local control for T3–4 tumours without excessive late toxicity [6], but further confirmation is needed.

Presenting stage is the most important prognostic factor for outcome; the importance of early detection cannot be over-emphasized. Unfortunately, majority of patients still present with advanced locoregional disease even in current times. Review of literature on series staged with the UICC staging system, 5th edition [7] showed that the 5-year overall survival (OS) achieved by RT alone ranged from 71%–90% for Stage I to 30%–52% for Stage IVA-B [2]. The notorious propensity for distant metastases remains a sinister problem for patients with advanced disease. The general consensus is that patients with Stages I–II disease should be treated with RT alone, while those with Stages III–IVB with combined RT and chemotherapy.

The systematic review by Langendijl and colleagues [8] showed a significant interaction for the sequencing of RT and chemotherapy: concurrent chemoradiotherapy (CRT) was the only effective way to improve OS, adjuvant chemotherapy was ineffective in all aspects, induction chemotherapy could improve both locoregional and distant control, though this was not translated into significant benefit in OS. Of the four published trials on CRT, two achieved significant improvement in both OS and progression/failure-free survival (FFS) [9,10], while two showed borderline improvement in OS ($P > 0.06$) and no significant improvement in FFS ($P > 0.14$) [11–13].

The Intergroup-0099 Study is the most important milestone [9]; with the impressive 30% gain in OS (78% vs. 47% at 3-year) for patients with Stages II–IVB by the current UICC staging system, concurrent cisplatin plus adjuvant cisplatin + 5-fluorouracil has become the regimen most widely used for advanced NPC. However, this is also the most controversial trial, due particularly to the exceptionally poor results of its RT arm. Preliminary results from a confirmatory trial on patients with N2-3 disease [14], supports that the IGS regimen could significantly improve FFS (72% vs. 62% at 3-year, $P = 0.027$), particularly at locoregional sites. However, the 3-year OS rates were almost identical (78%), and there was significant increase in late toxicities (28% υ 13%, $P = 0.024$). Hence, while the data supports the use of CRT for advanced NPC, patients should be duly informed that with improving RT technologies, the differential gain in survival might

be small and there is risk of significant increase in toxicities.

Exploration for more effective strategy is needed. New strategies include combining CRT with AF, changing the CRT sequence to induction-concurrent, or combination of both. Theoretically, induction chemotherapy could eradicate micro-metastases more effectively and shrink down the primary tumour to give wider margin for RT, excellent results have been reported by Rischin and colleagues [16]. A pilot study using induction-concurrent CRT with AF (6 daily fractions per week to 70 Gy) showed encouraging results for the worst prognostic group with tumours infiltrating/ abutting neurological structures [17]. Confirmation of therapeutic benefit by these new strategies is warranted. Furthermore, more accurate prognostication to tailor treatment strategy for different risk groups, and ways for minimisation of toxicities should be explored.

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