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Paclitaxel, 5-fluorouracil and hydroxyurea concurrent with radiation in locally advanced nasopharyngeal carcinoma

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Background: Concurrent chemoradiotherapy (CRT) is the standard treatment for locally advanced nasopharyngeal carcinoma (NPC). We conducted a phase II trial using paclitaxel, 5-fluorouracil and hydroxyurea concurrent with radiation (TFHX).

Patients and methods: Fifty-nine patients with locally advanced NPC were treated with CRT consisting of 4-day continuous infusions of paclitaxel (20 mg/m^2/d) and 5-fluorouracil (600 mg/m^2/d), and oral hydroxyurea 500 mg bid for nine doses, every 3 weeks concurrent with radiotherapy (RT). RT consisted of once daily 200cGy fractions 5 times per week to a total of 7000cGy.

Results: Complete response was seen in 86% and 71% of patients at 4 and 12 months after CRT. The median follow-up was 34 months. Twenty-three patients experienced relapse. Sixteen deaths occurred: 13 from progressive disease. Three-year overall survival and progression-free survival were 72% and 54% respectively, with locoregional and distant control rates of 83% and 64% at 3 years respectively. Grade 3 to 4 acute toxicities included oropharyngeal mucositis in 81% of patients treated, dermatitis in 63%, weight loss in 32%, and neutropenia in 22%. Neutropenic fever was seen in 14%. There were no treatment-related deaths from acute toxicity.

Conclusions: TFHX is shown to be feasible in NPC. Non-cross resistant induction chemotherapy should be further studied with this regimen.

Key words: 5-fluorouracil, hydroxyurea, nasopharyngeal carcinoma, paclitaxel, radiotherapy

introduction

Nasopharyngeal carcinoma (NPC) is the sixth most common cancer in Singaporean males, with an age-standardized incidence rate of 10.8/100 000/year [1]. Most cases are undifferentiated carcinoma on histology and Epstein-Barr virus (EBV) positive. The cancer has a peak incidence between ages 40 and 65 years [1]. Majority of cases present with locally advanced disease: American Joint Committee on Cancer (AJCC) stage III–IVB [2], for which concurrent chemoradiotherapy (CRT) is the standard treatment [3–6].

With standard concurrent CRT regimes for NPC using cisplatin, with or without 5-fluorouracil (5-FU) [3–6], significant proportions of patients still relapse. For example, Chan et al. [7] reported 28% of patients experiencing recurrence after a median follow up of 2.7 years. We hypothesized that increasing the radiosensitization effects of concurrent chemotherapy might improve results. Paclitaxel, 5-FU and hydroxyurea given concurrently with radiotherapy (TFHX) has shown impressive tumor control rates in patients with locally advanced squamous cell carcinoma of the head and neck (HNSCC) [8, 9]. Paclitaxel and 5-FU are both potent radiation (RT) sensitizers with single-agent activity in NPC [10, 11]. Hydroxyurea has synergistic activity with 5-FU as it depletes intracellular deoxyribonucleotide pools, and is a known RT sensitizer [12]. We conducted a study of this intensified non-platinum regimen, TFHX, to determine its tolerability in the light of a more extensive RT field in NPC, as well as its efficacy in this disease.

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patients and methods

eligibility

Eligible patients were above 18 years of age with biopsy proven WHO type III (undifferentiated) NPC, of stage III or IV disease [2]. Patients had to have a Karnofsky performance status of ≥70%, adequate hepatic function (total bilirubin <1.25 times the upper limit of normal, ALT,

AST ≤2 times the upper limit of normal), renal function (creatinine ≤2 mg/dl) and blood counts (total WBC ≥3500/μl, absolute neutrophil count ≥1800/μl, and platelet count ≥100 000/μl). No prior chemotherapy or radiotherapy to the head and neck region was allowed. Those with metastatic (M1) disease, prior malignancies within 10 years (except skin cancer) or severe intercurrent illness were excluded. The Institutional Review Board of the National University Hospital gave approval for the study and informed consent from each patient was obtained.

pretreatment evaluation

All patients had the diagnosis confirmed by nasoendoscopic biopsy. Locoregional staging was done by physical examination, fibre-optic endoscopy and computed tomography (CT) scan or magnetic resonance imaging (MRI) of the post-nasal space (PNS) and neck. Distant metastases were excluded by chest radiograph (CXR), bone scan and ultrasound or CT scan of the liver. Dental clearance and audiology assessment were done pre-treatment. Baseline blood counts with differential count, biochemistry for renal and liver function, and EBV serologies were taken.

radiotherapy

All patients received CT planning of the head and neck region for the initial and the boost treatment volume delineation and isodose line determination. The external beam irradiation was delivered with 6 MV Linear Accelerators. Initial radiation portals included nasopharynx with a 1.5–2.0 cm margins, anterior and posterior neck, and supraclavicular area. The lower neck and supraclavicular fossa were treated with AP/PA fields with photon. The planned total dose to the primary tumor and neck lymphadenopathy was 70 Gy in 35 daily fractions; and the dose of radiation to the subclinical neck nodal area, including bilateral posterior neck and bilateral supraclavicular fossa, was 50 Gy.

concurrent chemotherapy

Chemotherapy was administered concurrently with radiotherapy during the 1st, 4th and 7th week of treatment, according to the treatment schema: oral hydroxyurea 500 mg bid for a total of nine doses, with concomitant continuous intravenous (IV) infusion of 5-FU 600 mg/m^2/day and paclitaxel 20 mg/m^2/day for 4 days using an infusion pump. Central venous access was obtained via a peripherally inserted central catheter (PICC). Routine premedications for paclitaxel and anti-emetics were administered.

treatment modification

There was no treatment delay for radiotherapy except for neutropenic fever. For chemotherapy, pretreatment absolute neutrophil counts had to be above 1800/μl, and platelets above 100 000/μl. Chemotherapy was delayed 1 week for count recovery, and was not delayed for mucositis.

Patients who developed neutropenic fever had subsequent dose reduction of chemotherapy: IV paclitaxel 20 mg/m^2/day for 3 days, IV 5-FU 600 mg/m^2/day for 3 days, oral hydroxyurea 500 mg bid for seven doses. There was no dose reduction for mucositis, diarrhea or dermatitis. Patients with impaired renal function (serum creatinine 1.6 to 2 mg/dl) received hydroxyurea at 500 mg per day for total of five doses.

patient assessment

Patients were seen weekly during treatment, and at 1 week, 1, 2 and 4 months after completion of RT. During chemotherapy, blood counts and biochemistries were monitored. Acute toxicities were defined as toxicities occurring during treatment and within 4 months from the end of RT. Subsequent clinical follow up was 4 monthly in year 1, 6 monthly in year 2, and 8 monthly afterwards, with routine CXR and liver function tests done at 12 months post RT.

Response evaluation was conducted 4 and 12 months after the completion of RT with CT scan of the PNS and neck, clinical and endoscopic examination. Routine PNS biopsy was done at the 4 months assessment. Complete response (CR) was defined as absence of tumor on endoscopic examination of the local site with no radiologic evidence of progression of the primary tumor, and absence of residual cervical lymphadenopathy on clinical examination and imaging. A negative PNS biopsy was required for CR at the 4 months assessment. Partial response (PR) was defined as residual tumor on endoscopic examination with no radiologic evidence of progression of the primary tumor, or residual cervical lymph-adenopathy of at least 1.5 cm in maximum length on clinical examination or imaging. A positive PNS biopsy without residual tumor on endoscopic examination at 4 months was also considered PR. Progressive disease (PD) was defined as an increase by 25% or greater of the product of perpendicular diameters of tumor lesions or appearance of new lesions either on clinical examination or imaging.

treatment for relapse or residual disease

Neck dissections were considered for residual neck nodes at 4 months after completion of primary treatment. Patients with disease progression were offered chemotherapy or re-irradiation according to the discretion of the treating physician.

statistical considerations

Duration of follow-up was defined as the time from first day of treatment to the last follow-up date. Time to progression was the time from first day of treatment to the time of documented progression. 'Locoregional' was defined as disease in the primary tumor region, the neck, or both. Overall survival (OS) was measured from first day of treatment to day of death from any cause or to last follow-up visit. In the progression-free survival (PFS) analysis, an event was defined as the occurrence of locoregional progression, distant progression, or death without progression. OS, PFS, time to locoregional progression and time to distant progression were analyzed by the Kaplan–Meier method.

results

patient characteristics

From May 1999 to May 2003, 59 eligible patients were enrolled. Median age was 47 (range 26 to 71), and 75% of patients were Chinese males. Ninety-eight percent of patients had WHO type III tumors. We included one patient with WHO type II NPC and positive EBV serology. Fifty-one percent were stage IV cancers, including 22% with T4 primary tumors and 34% with N3 nodal disease. Supraclavicular lymph node involvement was documented in 17% of patients (Table 1). Staging included MRI of the PNS and neck in 12 (20%) patients.

locoregional response to chemoradiation

At 4 months post CRT, locoregional tumor response was as follows: CR 86%, PR 10%, PD 0%, not assessable 3%. Of the two patients not assessable for response, one refused PNS biopsy and one had neither imaging nor biopsy done. At 12 months post CRT, 71% maintained locoregional CR, 2% maintained PR, 8% developed PD locoregionally, and 19% were not assessable. Of the 11 patients who were not assessable for response: three patients already died from distant metastases, four did not have routine imaging, and four defaulted follow up.

survival and pattern of failure

The median follow-up time was 34 months (range 9 to 69 months). A total of 23 patients (39%) experienced relapse (Table 2). The total number of distant failures was 21 (36%) while the total number of locoregional failures was nine (15%). Seven patients (12%) had concomitant distant and loco-regional failure. Median time to relapse was 17 months.

A total of 16 deaths had occurred: 13 died from progressive NPC (at a median time of 19 months from start of treatment, range 9 to 38 months), one patient died from meningococcal meningitis during an outbreak (21 months), one from aspiration pneumonia (22 months), and one from acute epiglotitis (33 months). We attribute the non-NPC deaths to treatment-related causes, including the case of meningitis, to which lowered loco-regional immunity after CRT could have contributed. Three-year OS and PFS was 72% and 54% respectively with the median OS and PFS not reached (Figure 1). Three-year locoregional and distant control rates were 83% and 64% respectively (Figure 2).

Table 1. Patient characteristics

Characteristic	No. of patients	%
Total patients	59	100
Median age, years	47	
Range, years	26–71	
Sex		
Male	48	81
Female	11	19
Race		
Chinese	53	90
Malay	5	8
Indian	1	2
Karnofsky Performance Status		
>80%	59	100
Pathology (WHO classification)		
Type III	58	98
Type II	1	2
Stage[a]		
III	29	49
IV	30	51
T classification[a]		
T1	19	32
T2	15	25
T3	12	20
T4	13	22
N classification[a]		
N0	4	7
N1	4	7
N2	31	53
N3	20	34
Supraclavicular fossa involvement		
No	49	83
Yes	10	17

WHO, World Health Organization.
[a]American Joint Committee on Cancer 1997.

Table 2. Patterns of failure

Failure site(s)	No.	%
Total progression/relapse	23	39
Locoregional only	2	3
Distant only	14	24
Both locoregional and distant	7	12
Total locoregional	9	15
Total distant	21	36

toxicity and compliance

Acute toxicities are listed in Table 3. Oropharyngeal mucositis, radiation dermatitis and weight loss were experienced by all patients. Severe (National Cancer Institute Common Toxicity Criteria grade 3 to 4) oropharyngeal mucositis rate was 81% and severe radiation dermatitis was encountered in 63% of patients. Nasogastric tube or feeding gastrostomy was required in 53% of patients, with 32% of patients encountering weight loss of over 20%. Severe neutropenia occurred in 22% of patients. Eight patients (14%) developed neutropenic fever, with one patient having two episodes of neutropenic fever. A total of 44 episodes of non-neutropenic fever were encountered in 33 patients (56%). Duration of severe neutropenia or anemia was brief, most resolving within 1 week. Only one patient had prolonged grade 3 anemia, lasting 8 weeks. Forty patients (68%) received inpatient treatment of acute complications with a median duration of stay of 11 days (range 1–35 days). Severe oropharyngeal mucositis and dermatitis had resolved within 1 month after completion of RT in most patients. There were no deaths from treatment-related acute toxicity.

Median time from diagnosis to start of radiotherapy was 27 days (range 10–50 days). The median time taken to complete the course of radiotherapy was 7.5 weeks (range 7 to 10 weeks). Fifty-nine percent of patients completed all three cycles of chemotherapy, and 98% of patients received at least two cycles of chemotherapy. Chemotherapy omissions were largely related to toxicity. Planned dose reductions occurred in five patients (8%) each during the second and third chemotherapy cycles. Prior neutropenic fever was the cause of planned dose reductions in more than half of the cases.

discussion

In an attempt to improve on conventional cisplatin-based regimens in concurrent CRT for locally advanced NPC [3–6], we adopted the triple-agent radiosensitization combination in TFHX previously developed at the University of Chicago [13–17], of which the recommended phase II doses were paclitaxel 20 mg/m^2/day for 5 days, with 5-FU 600 mg/m^2/day for 5 days and hydroxyurea at 500 mg every 12 h for 11 doses [16]. When this regimen was administered concomitantly with hyperfractionated RT to a group of mainly stage IV HNSCC patients, 3-year PFS of 63% (locoregional control 86%, systemic control 79%) and 3-year OS of 60% was obtained [8]. In view of the larger RT field in NPC compared to HNSCC and its expected increased toxicity, we reduced the chemotherapy doses in the original TFHX regimen by 20%.

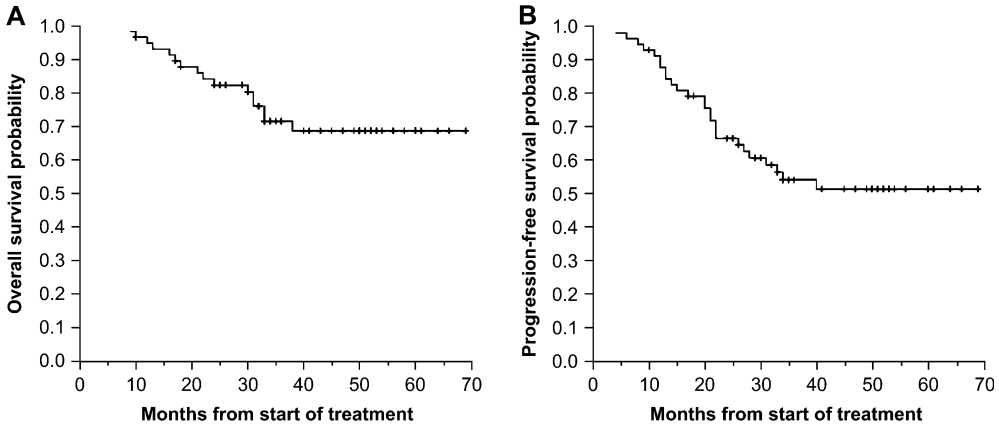

Figure 1. (**A**) Overall survival of 59 patients. (**B**) Progression-free survival of 59 patients.

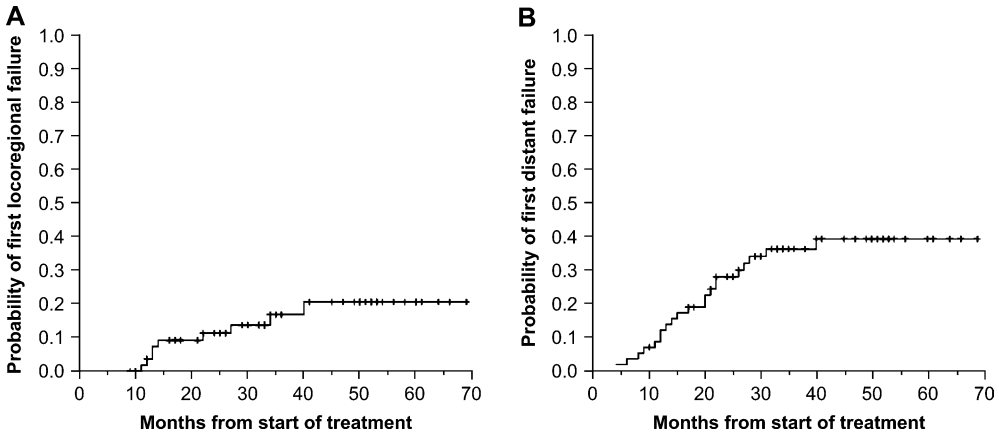

Figure 2. (**A**) Time to locoregional failure of 59 patients. (**B**) Time to distant failure of 59 patients.

Using the 1997 AJCC criteria, 49% of our patients had stage III and 51% had stage IV NPC. This is a more advanced group of patients compared to those in two earlier phase III trials of concurrent CRT versus RT for undifferentiated NPC. The Hong Kong study [4] included 26% of patients with stage II disease (AJCC 1997) on the CRT arm. The Taiwanese trial [5] used 1992 AJCC definitions for their study (24% stage III, 76% stage IV patients on the CRT arm), which hence meant comparatively less advanced cases [18].

We encountered a high incidence of in-field acute toxicities, similar to and already published with TFHX [8, 9]. Severe weight loss was seen in a third of patients hence prophylactic feeding gastrostomies or nasogastric tubes should be considered. Mucositis and the presence of indwelling PICC lines undoubtedly contributed to the number of febrile episodes. Despite the short-term morbidities, there were no deaths related to acute toxicity. Also, 59% of patients completed all three planned cycles of chemotherapy, a figure similar to that in the Intergroup study using cisplatin [3].

We achieved high response rates with TFHX. Although CT scans were routinely performed, the presence of residual radiological abnormalities is common and not necessarily an indicator of viable tumor, especially at the primary site [19]. In fact, it was found that abnormal CT scans of the PNS done routinely in the early post-radiation period had very low positive predictive value when assessed against PNS biopsy results [19]. Our definition for response took this into account. Because of potential variability in assessing tumor response across different studies, PFS and OS are more important indicators of treatment effectiveness.

In our study, with a median follow up time of 34 months, we achieved encouraging 3-year outcomes: OS 72%, PFS 54%. We compared our results with those of the concurrent CRT arms from the three published Asian phase III trials [4–6]. The Hong Kong study recorded a 5-year OS and PFS of 70% and 60% respectively [4], while the Taiwanese obtained a 5-year OS and PFS of 72% and 71% respectively [5]. However, both studies included earlier stage patients who are expected to have a much better prognosis [20]. In the Singapore study, 3-year OS and disease-free survival on the CRT arm was 80% and 72% respectively [6]. However, the percentage of patients staged with MRI scans was not mentioned in that study, whereas the majority (80%) of our patients only had CT-staging. MRI has been known to be more sensitive than CT scan in the staging of

Table 3. Acute toxicity

Toxicity	NCI CTC Grade[a]					
	0		1–2		3–4	
	No.	%	No.	%	No.	%
Anemia[b]	4	7	51	88	3	5
Neutropenia[b]	22	38	23	40	13	22
Thrombocytopenia[b]	49	84	9	16	0	0
Mucositis	0	0	11	19	48	81
Dermatitis	0	0	22	37	37	63
Nausea/Vomiting	17	29	38	64	4	7
Diarrhea	41	69	16	27	2	3
Weight loss	0	0	40	68	19	32
5 to <10%			5	8		
10 to <20%			35	59		

NCI CTC: National Cancer Institute Common Toxicity Criteria.

[a]Worst toxicity recorded for each patient.

[b]One patient not assessable.

NPC [21–23]. The effect of differential staging systems and imaging methods on the results of trials in NPC has been commented on by other authors [24].

Using this treatment, we achieved good locoregional control, but the risk of distant failure was still high. Neoadjuvant chemotherapy added to concurrent CRT could improve on these results. In fact, there was a trend to improvement in relapse-free and overall survival noted in previous randomized trials of neoadjuvant chemotherapy followed by RT versus RT alone [25, 26]. A recent meta-analysis found that neoadjuvant chemotherapy significantly reduced the risk of locoregional recurrence and distant metastases [27]. Moreover, recent phase II studies of neoadjuvant chemotherapy before concurrent CRT have shown feasibility and encouraging long-term results [28, 29]. Using the intensive TFHX regime in the concurrent phase may have therapeutic advantage since a non-cross resistant platinum-based regime with a high response rate (e.g. cisplatin plus gemcitabine [30, 31]) can be applied in the neoadjuvant phase.

While the doses of 5-FU and hydroxyurea in this study are known to be appropriate for radiation sensitization, it had not been established that this low rate of continuous infusion of paclitaxel achieves concentrations that are relevant for radiation sensitization. We analysed paclitaxel concentrations in 52 patients and found all concentrations of paclitaxel to be above that relevant for radiation sensitization, and the infusion rate of paclitaxel maintained these concentrations at steady state for the duration of infusion (data not shown).

In summary, we showed TFHX to be tolerable and efficacious in a high-risk group of locally advanced NPC patients. Given the good locoregional control achieved with TFHX, we believe that this regimen should be further explored in conjunction with non-cross resistant cisplatin-based neoadjuvant chemotherapy to reduce distant failure.

references

1. Seow A, Koh WP, Chia KS et al. Singapore Cancer Registry Report No 6: Trends in Cancer Incidence in Singapore 1968–2002. Singapore: Singapore Cancer Registry, 2004.
2. Fleming ID, Cooper JS, Henson DE et al. (eds). American Joint Committee on Cancer Staging Manual, 5th edition. Philadelphia: JB Lippincott, 1997.
3. Al-Sarraf M, LeBlanc M, Giri PG et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomised Intergroup Study 0099. J Clin Oncol 1998; 16: 1310–1317.
4. Chan AT, Leung SF, Ngan RK et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. J Natl Cancer Inst 2005; 97: 536–539.
5. Lin JC, Jan JS, Hsu CY et al. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol 2003; 21: 631–637.
6. Wee J, Tan EH, Tai BC et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. J Clin Oncol 2005; 23: 6730–6738.
7. Chan AT, Teo PM, Ngan RK et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. J Clin Oncol 2002; 20: 2038–2044.
8. Kies MS, Haraf DJ, Rosen F et al. Concomitant infusional paclitaxel and fluorouracil, oral hydroxyurea, and hyperfractionated radiation for locally advanced squamous head and neck cancer. J Clin Oncol 2001; 19: 1961–1969.
9. Vokes EE, Stenson K, Rosen FR et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. J Clin Oncol 2003; 21: 320–326.
10. Au E, Tan EH, Ang PT. Activity of paclitaxel by three-hour infusion in Asian patients with metastatic undifferentiated nasopharyngeal cancer. Ann Oncol 1998; 9: 327–329.
11. Fandi A, Taamma A, Azli N et al. Palliative treatment with low-dose continuous infusion 5-fluorouracil in recurrent and/or metastatic undifferentiated nasopharyngeal carcinoma type. Head Neck 1997; 19: 41–47.
12. Schilsky RL, Ratain MJ, Vokes EE et al. Laboratory and clinical studies of biochemical modulation by hydroxyurea. Semin Oncol 1992; 19(3 Suppl 9): 84–89.
13. Vokes EE, Panje WR, Schilsky RL et al. Hydroxyurea, fluorouracil, and concomitant radiotherapy in poor-prognosis head and neck cancer: a phase I-II study. J Clin Oncol 1989; 7: 761–768.
14. Haraf DJ, Vokes EE, Weichselbaum RR et al. Concomitant chemoradiotherapy with cisplatin, 5-fluorouracil and hydroxyurea in poor prognosis head and neck cancer. Laryngoscope 1992; 102: 630–636.
15. Vokes EE, Haraf DJ, Mick R et al. Intensified concomitant chemoradiotherapy with and without filgrastim for poor prognosis head and neck cancer. J Clin Oncol 1994; 12: 2351–2359.

16. Brockstein B, Haraf DF, Stenson K et al. Phase I study of concomitant chemoradiotherapy with paclitaxel, fluorouracil, and hydroxyurea with granulocyte colony-stimulating factor support for patients with poor-prognosis cancer of the head and neck. J Clin Oncol 1998; 16: 735–744.
17. Brockstein B, Haraf DF, Stenson K et al. A phase I-II study of concomitant chemoradiotherapy with paclitaxel (one-hour infusion), 5-fluorouracil and hydroxyurea with granulocyte colony stimulating factor support for patients with poor prognosis head and neck cancer. Ann Oncol 2000; 11: 721–728.
18. Beahrs OH, Henson DE, Hutter RVP, Kennedy BJ (eds). Manual for Staging of Cancer, 4th edition. Philadelphia: JB Lippincott, 1992.
19. Chao SS, Loh KS, Tan LK. Modalities of surveillance in treated nasopharyngeal cancer. Otolaryngol Head Neck Surg 2003; 129: 61–64.
20. Chien CR, Chen SW, Hsieh CY et al. Retrospective comparison of the AJCC 5th edition classification for nasopharyngeal carcinoma with the AJCC 4th edition: an experience in Taiwan. Jpn J Clin Oncol 2001; 31: 363–369.
21. Chong VF, Fan YF. Skull base erosion in nasopharyngeal carcinoma: detection by CT and MRI. Clin Radiol 1996; 51: 625–631.
22. Ng SH, Chang TC, Ko SF et al. Nasopharyngeal carcinoma: MRI and CT assessment. Neuroradiology 1997; 39: 741–746.
23. Chung NN, Ting LL, Hsu WC et al. Impact of magnetic resonance imaging versus CT on nasopharyngeal carcinoma: primary tumor target delineation for radiotherapy. Head Neck 2004; 26: 241–246.
24. Cheng SH, Huang AT. Comments on concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a mist of mysterious results. J Clin Oncol 2005; 23: 2864–2865.
25. International Nasopharynx Cancer Study Group. VUMCA I Trial. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (≥N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. Int J Radiat Oncol Biol Phys 1996; 35: 463–469.
26. Ma J, Mai HQ, Hong MH et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2001; 19: 1350–1357.
27. Langendijk JA, Leemans CR, Buter J et al. The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: a meta-analysis of the published literature. J Clin Oncol 2004; 22: 4604–4612.
28. Oh JL, Vokes EE, Kies MS et al. Induction chemotherapy followed by concomitant chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal cancer. Ann Oncol 2003; 14: 564–569.
29. Chan AT, Ma BB, Lo YM et al. Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: therapeutic monitoring with plasma Epstein-Barr virus DNA. J Clin Oncol 2004; 22: 3053–3060.
30. Ngan RK, Yiu HH, Lau WH et al. Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. Ann Oncol 2002; 13: 1252–1258.
31. Jiang Y, Wei YQ, Luo F et al. Gemcitabine and cisplatin in advanced nasopharyngeal carcinoma: a pilot study. Cancer Invest 2005; 23: 123–128.