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A Retrospective Study of the Use of Cisplatinum–5-Fluorouracil Neoadjuvant Chemotherapy in Cervical-node-positive Nasopharyngeal Carcinoma (NPC)

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A retrospective study on 422 nasopharyngeal carcinoma (NPC) patients with cervical nodal metastases treated between 1984 and 1987 was performed. 169 received neoadjuvant chemotherapy (CHEMO) with cisplatinum and 5-fluorouracil for two or three courses prior to definitive radiotherapy and 253 were treated by radical radiotherapy alone (NCHEMO). While the primary tumour (T-stage) prognosticators had been comparable between the two groups, CHEMO had significantly more advanced cervical nodal metastases with bulkier nodes and more low-cervical and supraclavicular nodes ($P < 0.05$) which could account for its overall worse survival, poorer regional tumour control and a trend towards worse systemic tumour control. The worse regional control in CHEMO for Ho's N1 could be the result of more bulky nodes and more tumours infiltrating the skull base and/or causing cranial nerve(s) palsy. There was no statistical or apparent difference between CHEMO and NCHEMO for the same Ho's overall stages of NPC with comparable nodal and primary tumour characteristics for the clinical endpoints of actuarial survival rate (ASR), disease-free survival rate (DFS), free of local failure survival rate (FLF), and free from distant metastases survival rate (FDM), despite the presence of significantly more fixed nodes and bulky nodes. This suggests a possible beneficial effect of the neoadjuvant chemotherapy. However, multivariate analysis has not shown the administration of the neoadjuvant chemotherapy to be of prognostic significance. Even though the chemotherapy was well tolerated with little toxicity, we recommend against the routine use of neoadjuvant chemotherapy in cervical-node-positive NPC outside the context of a prospective randomised clinical trial.

Keywords: neoadjuvant chemotherapy, radical radiotherapy, nasopharyngeal carcinoma

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INTRODUCTION

RADIATION THERAPY (RT) is the mainstay of treatment for nasopharyngeal carcinoma (NPC). However, for those cases with advanced cervical nodal metastases, the prognosis after RT alone is poor [1–14] with distant metastases being the most frequent site of failure [8, 11, 13, 15]. Although there has been much debate as to which is the most significant cervical nodal characteristic affecting prognosis [2, 6, 8, 11, 13, 16], there is a concensus that the presence of supraclavicular nodal metastases (Ho's N3 [4, 16]) which are strongly associated with bulky cervical nodal metastases (>3 cm, UICC/AJCC N2–N3, [17, 18]) predict a high rate of distant metastases and poor survival [8, 11, 13]. In addition, the bulkier nodes often involving multiple Ho's N-levels in the neck [4, 16] are more likely to fail regionally as the first and only failure after radical RT. This may occur despite the practice of boosting up the radiation dose to the neck for those with clinically palpable residual nodes after a routine dose of radiotherapy [5, 7, 8, 11, 13].

On the other hand, in the 1980s, there was much enthusiasm and excitement concerning the use of neoadjuvant chemotherapy in head and neck cancers, mainly based on encouraging tumour response rates and low chemotherapy toxicity reported in various phase II studies [19–21]. Thus, in an endeavour to enhance regional and systemic tumour control for the NPC, a treatment protocol was formulated with the routine use of a cisplatinum–5-fluorouracil neoadjuvant chemotherapy [20] prior to RT when the cervical nodal metastases were considered advanced because of their bulk

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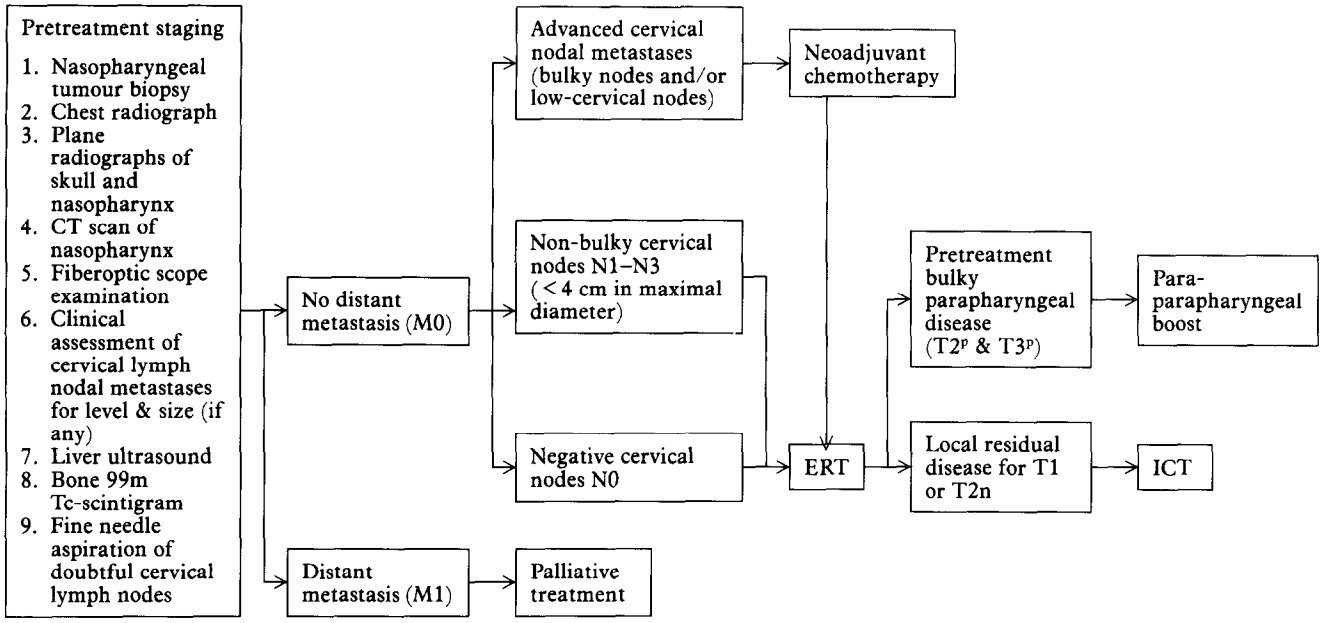
Table 1. *Investigation and treatment protocols in the Prince of Wales Hospital, Hong Kong* (1984–1987)



and/or because of their low-lying position in the neck (Table 1). This protocol was followed from 1984 to 1987 at the Prince of Wales Hospital (PWH) in Hong Kong before the inception of a randomised study of neoadjuvant chemotherapy. The purpose of the present retrospective study is to evaluate the effect of the neoadjuvant chemotherapy on the loco-regional control, systemic control, and survival of NPC.

MATERIALS AND METHODS

From April 1984 to December 1987, 664 newly diagnosed patients with NPC were managed in the Clinical Oncology Department of the Prince of Wales Hospital in Hong Kong. 633 had disease confined to the head and neck region and 31 presented with distant metastases. Only 5/633 were not evaluable because they defaulted treatment. 15 patients defaulted follow-up at 3–45 months after treatment and were evaluated up to the last follow-up. 613/628 had a minimum follow-up of 7 years or up to the time of death. At the time of the retrospective analysis, the median follow-up time was 36 months. The 31 disseminated cases were followed up to death, and were fully evaluated. For the 628 non-disseminated NPCs, in addition to the external radiation therapy (ERT) described by Ho [3, 5, 16], the nasopharynx and the adjacent muscles and bones were treated with 60 Gy/24 fractions/6 weeks by a three-field technique [5, 22] (one anterior and two lateral facial 6 MeV photon fields) or with 62.5 Gy/29 fractions/6 weeks by a shrinking-field technique [5, 22] (two lateral faciocervical 6 MeV photon fields of 40 Gy/20 fractions/4 weeks and then followed by a three-field treatment of 22.5 Gy/9 fractions/2 weeks). The shrinking-field technique was used in the presence of oropharyngeal involvement (T2o) and/or upper cervical lymph nodal metastases near the angle of the mandible. In cases of nasal involvement (T2n), an anterior facial electron field [5, 22] was added to the three-field technique with modification of the weightings of the photon fields [5, 22]. Neoadjuvant chemotherapy was given for bulky and/or advanced Ho's N-stage [4] nodal metastases, parapharyngeal boost radiation was given for bulky (>4 cm from midline) parapharyngeal involvement, and intracavitary ^{192}Ir treatment (ICT) was given for local persistences after ERT [22]. The neoadjuvant chemotherapy [19, 20] consisted of cisdiamminedichloroplatinum II (75–100 mg/m^2 D1) and 5-fluorouracil (1 g/m^2 D1–D3), given for two to three courses, 3 weeks apart. The parapharyngeal boost radiation was delivered by an ipsilateral posterior oblique photon beam (6 MV) (Clinac 6/100, Varian Associates Inc., Palo Alto, California, U.S.A.), below the level of the eyes and the temporal lobes, extending down to the C3 vertebra. A dose of 20 Gy/10 fractions/2 weeks was delivered to the 90% isodose level. The spinal cord and the temporomandibular joints were excluded from the treatment volume. The ICT delivered a dose of 18–24 Gy/3 fractions/2 weeks to 1 cm above the midpoint of the plane of the ^{192}Ir sources, afterloaded into pre-placed nylon tubes with terminal spacers within the nasopharynx.

Of the 628 patients with non-metastatic NPC treated with a curative intent, 174 received neoadjuvant chemotherapy. There were 5 patients without cervical nodal metastases treated with the neoadjuvant chemotherapy—all had very advanced primaries that imposed a technical problem to encompassing all tumorous tissue within the irradiation volume, mainly because of superior tumour extension intracranially and/or anterior tumour extension to involve both orbits and/or extensive infratemporal fossa involvement. Excluding these 5 patients, the remainder (169/174) had neoadjuvant chemotherapy for their nodal metastases. The characteristics of these 169 patients are shown in Table 2, together with 253 contemporary patients with nodal metastases on presentation treated by RT alone.

All patients were prospectively staged according to Ho's classification [4]. However, since all patients had fibreoptic scope and CT evaluation of the primary and the cervical nodal characteristics were recorded in detail at presentation, retrospective staging according to the UICC classification [18] and the AJC classification [17] was considered possible without loss of accuracy. Over 95% (635/664) had anaplastic or

Table 2. Patient and tumour characteristics: comparison between CHEMO and NCHEMO

		CHEMO	NCHEMO	*P*-value
Age	Mean	43.7	48.8	0.016
	Median	43	46	
	Range	13–71	16–76	
Sex	Male	124	182	0.75
	Female	45	71	
Primary tumour				
Ho's	T1	34	69	0.076
	T2	64	103	
	T3	71	81	
Modified Ho's	Early T	59	102	0.26
	Advanced T	110	151	
UICC/AJC	T1	7	15	0.21
	T2	28	54	
	T3	64	103	
	T4	70	81	
Cervical nodal metastasis				
Ho's	N1	35	114	0.0001
	N2	79	93	
	N3	55	46	
Modified Ho's	N1 (=Ho's N1+N2)	114	207	0.07
	N2 (=Ho's N3)	55	46	
UICC/AJC	N1	10	70	0.0001
	N2	57	71	
	N3	102	112	
Maximal nodal size	≤3 cm	35	180	0.0001
	3–6 cm	114	69	
	>6 cm	20	4	
Nodal laterality	Ipsilateral	73	144	0.015
	Contralateral	35	46	
	Bilateral	61	63	
Nodal mobility	Mobile	143	240	0.0001
	Fixed	26	13	
Overall disease stage				
Ho's	II	13	85	0.0001
	III	99	121	0.099 / 0.0001
	IV	57	47	0.099 / 0.0001
Modified Ho's	IIa	35	84	0.002
	IIb	0	0	
	IIIa	79	123	
	IIIb	24	18	
	IVa	31	28	
UICC/AJC	III	3	53	0.0001
	IV	166	200	

undifferentiated carcinoma (WHO type III); the others had moderate- to well-differentiated keratinising squamous cell carcinoma (WHO types I and II). The investigative and treatment protocols are summarised in Table 1. CT of the nasopharyngeal region was performed routinely for all cases confined to the head and neck. Parapharyngeal involvement was defined as the presence of soft tissue swelling deforming the parapharyngeal fibrofatty tissue plane between the pharyngeal constrictors and the pterygoids in two or more axial sections at the level of the C1 vertabra [23]. Parapharyngeal involvement with and without base of skull and/or cranial nerve(s) involvement were classified as T_{3p} and T_{2p}, respectively.

Clinical endpoints including actuarial survival rate (ASR), disease-free survival rate (DFS), free from local failure survival rate (FLF), free from regional failure survival rate (FRF), and free from distant metastases survival rate (FDM) were calculated by the Kaplan–Meir method and comparisons made between the 169 chemotherapy-treated patients (CHEMO) and the 253 NPCs without chemotherapy patients (NCHEMO) by the logrank method. Multivariate analyses by the Cox regression method were also performed to identify significant prognosticators governing the different clinical endpoints and the administration of neoadjuvant chemotherapy was also tested for its significance. Statistical significance was conventionally taken as 0.05 or less.

RESULTS

As according to protocol (Table 1), CHEMO had significantly larger cervical nodal size, and more multiple, contralateral, bilateral, and fixed nodal metastases (Table 2). However, there were 35 NPCs with Ho's N1 and 35 NPCs with maximal nodal size ≤3 cm, respectively, who were given

neoadjuvant chemotherapy not according to the protocol (Table 1); and there were also a significant number of NPCs with advanced cervical nodal metastasis (Ho's N2 and N3 [4, 16]; UICC/AJC N2 and N3 [17, 18]) not given chemotherapy, indicating that the protocol (Table 1) served only as a guideline for treatment and individual oncologists still exercised a high degree of personal preference and autonomy. Overall, CHEMO and NCHEMO were comparable in the ratio of early T-stage to advanced T-stage by the modified Ho's classification [41], and the T-stage distribution by the Ho's [4, 16], the UICC [18], and the AJC [17] stage-classifications were also comparable between CHEMO and NCHEMO (Table 2). CHEMO also had significantly more advanced overall stages than NCHEMO by all classifications (Table 2).

The neoadjuvant chemotherapy was well tolerated by the 169 patients. All of them received at least two courses of chemotherapy prior to radiotherapy. An additional third course of chemotherapy was also given to 41/169 patients after a complete or near complete, cervical nodal response to the first two courses of chemotherapy. There had been no chemotherapy mortality or severe chemotherapy-related toxicity that required dose-reduction or postponement or cancellation of a planned course of chemotherapy. Mucositis of either WHO Grade 1 or 2 occurred in all patients after each course of chemotherapy but none had required parenteral hyperalimentation or gastrostomy or nasogastric tube feeding as a result of dysphagia and poor oral intake. Grade 3 or 4 nausea and vomiting occurred in 20 patients (12%) but was adequately palliated with antimetics. The radical radiotherapy started within 2 weeks of the last day of the last course of chemotherapy in all patients without any delay. The frequency and duration of radiotherapy interruption was comparable between the chemotherapy-treated patients and the patients without chemotherapy, indicating the absence of toxicity carried-over from chemotherapy to radiotherapy and chemotherapy potentiation of radiotherapy toxicity. None of the 169 NPCs receiving chemotherapy had a white blood cell nadir below 1.00×10^9/l or a creatinine clearance below 40 ml/min or a persistently elevated creatinine level due to cisplatin nephrotoxicity.

Since CHEMO had more advanced overall stages and N-stages than NCHEMO (Table 2), it had significantly worse ASR, DFS, and FRF than NCHEMO, as expected, $P < 0.05$, and, there was a trend towards more distant metastasis in CHEMO, though not statistically significant. Comparing CHEMO with NCHEMO for Ho's stage III, Ho's stage IV, and Ho's stage III and IV combined as a group, there was no significant difference in DFS, FDM, FLF and FRF (Figs 1, 2, 3 and 4, respectively). Within Ho's stage II, 13 received neoadjuvant chemotherapy not according to the treatment protocol (Table 1); they had similar ASR, DFS, FDM, FLF and FRF (Fig. 5) to NCHEMO. However, the 35 patients with Ho's N1 disease given neoadjuvant chemotherapy (including the 13 Ho's stage II patients) had significantly worse FRF than the 114 Ho's N1 without chemotherapy (Fig. 6).

By the Cox regression, the significant survival prognosticators for the 422 cervical-node-positive NPCs were identified (Table 3) and the use of neoadjuvant chemotherapy did not affect FLF, FDM, FRF, ASR, or DFS.

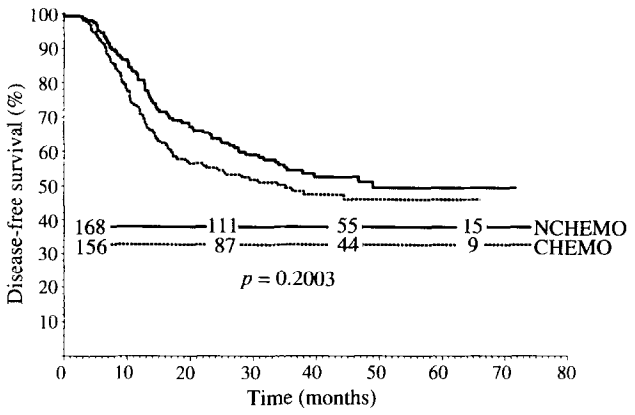


Fig. 1. DFS comparison between CHEMO and NCHEMO for Ho's stages (III + IV).

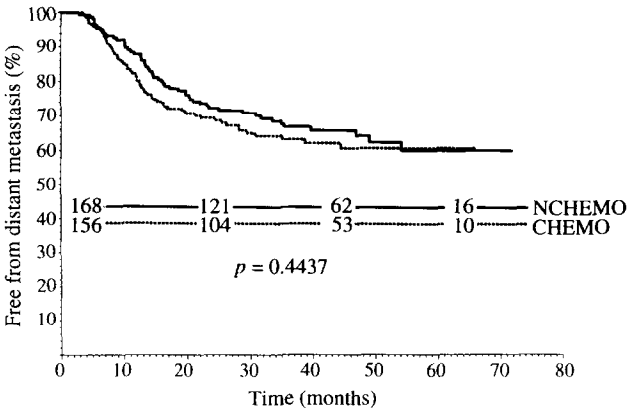


Fig. 2. FDM comparison between CHEMO and NCHEMO for Ho's stages (III + IV).

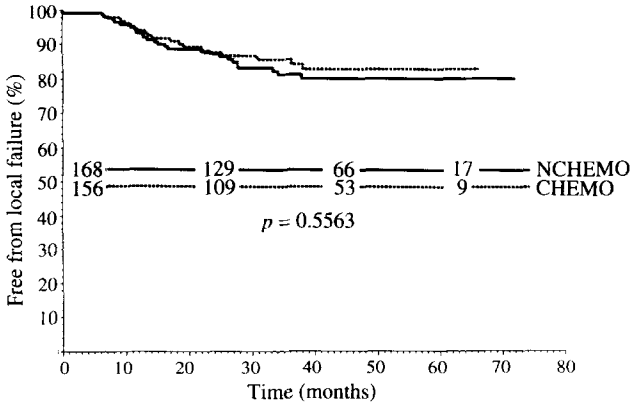


Fig. 3. FLF comparison between CHEMO and NCHEMO for Ho's stages (III + IV).

DISCUSSION

The 422 NPCs in the present study were treated in the same institute within a short period from 1984 to 1987 with little change in the treatment and investigation protocol during the period (Table 1). NCHEMO had significantly older patients than CHEMO (Table 2), and, advanced patients' age should adversely influence NPC prognosis [8, 11, 13]. CHEMO and NCHEMO were comparable in their T-stage. They differed only in the cervical nodal metastases—CHEMO had signific-

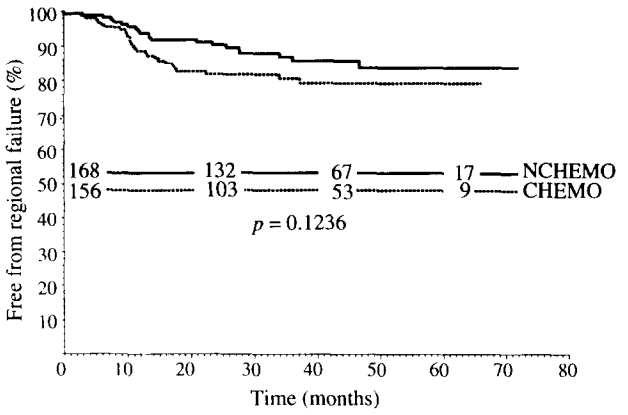


Fig. 4. FRF comparison between CHEMO and NCHEMO for Ho's stages (III + IV).

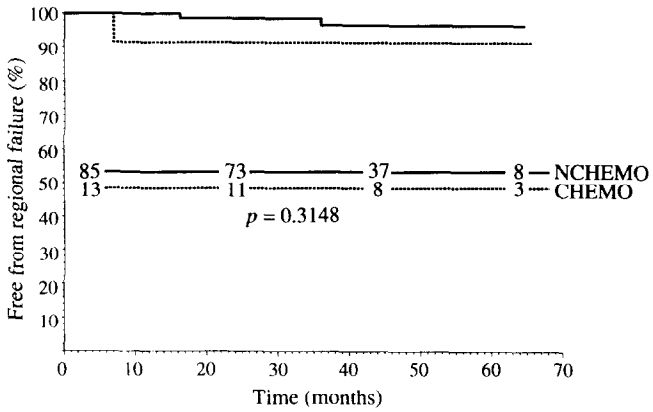


Fig. 5. FRF comparison between CHEMO and NCHEMO for Ho's stage II.

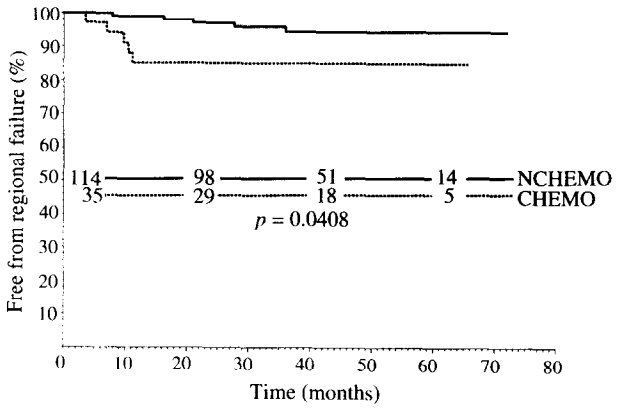


Fig. 6. FRF comparison between CHEMO and NCHEMO for Ho's N1.

antly more advanced nodes with more low-cervical and supraclavicular nodes, more bulky nodes, more bilateral and contralateral nodes, and, more fixed nodes than NCHEMO (Table 2). Ho's N-level in the neck has been unequivocally accepted to be of paramount importance in determining survival and distant metastases after radical RT [4, 8, 11–14, 16], and it accounted for the poorer survival of CHEMO and its trend towards more distant metastases, whereas the bulkier cervical nodal metastases could account for the overall poorer regional tumour control in CHEMO [12, 13].

While one of the main reasons for administering the chemotherapy was the poor regional control of advanced nodal disease by RT alone, the active cisplatinum and 5-fluorouracil combination which had resulted in over 90% NPC response rate [22] fell short of initial expectation to rectify the situation in the present study. In spite of a significantly higher rate of booster radiotherapy to clinically persistent cervical nodes at the completion of conventional RT and a higher rate of salvage radical neck dissection of residual nodes after all RT in CHEMO, as expected because of its more advanced nodes, CHEMO still suffered from significantly worse FRF than NCHEMO for the whole group overall. The significantly worse FRF in Ho's N1 for patients given neoadjuvant chemotherapy (Fig. 6) was also a worrisome observation at first sight. However, further analysis has shown that for Ho's N1, CHEMO had significantly more bulky nodes and more tumours infiltrating the skull base and/or causing cranial nerve(s) palsy (Ho's T3) which in the multivariate analysis was found to be a significant independent predictor for regional failure (Table 3). So, the apparently worse FRF of CHEMO could entirely be accountable for by the presence of worse prognosticators and one could not imply a negative therapeutic effect of the chemotherapy.

More importantly, after neoadjuvant chemotherapy for Ho's stages III and IV, there had been no improvement (or deterioration) in DFS, FDM, FLF and FRF (Figs 1, 2, 3 and 4 respectively) and the same also applied to Ho's stage II. One could argue that this might represent a beneficial effect of the neoadjuvant chemotherapy, because within each Ho's overall stage there were significantly more fixed and more bulky nodal metastases in CHEMO than in NCHEMO while the other prognosticators were evenly distributed between the two. While there has been controversy over the prognostic significance of the size of the nodal metastases [8, 11, 13], the present study's multivariate analysis (Table 3) agreed with Lee *et al.* [8] and Sham and Choy [11] in that fixed cervical nodes predicted a poor disease-free survival and a high distant metastasis rate. Even though comparing CHEMO and NCHEMO for the various clinical endpoints in each of the patient subgroups with identical patient and primary tumour and cervical nodal characteristics did not demonstrate any difference between the two, such an analysis was handicapped by the relatively small patient numbers in some of the subgroups, raising the possibility of Type II errors [24]. So, to supplement, a multivariate analysis by the Cox regression method was performed for each of the five clinical endpoints (ASR, DFS, FDM, FLF and FRF) (Table 3); the use of the neoadjuvant chemotherapy was not demonstrated to be of prognostic significance. Therefore, it can be confidently concluded that the treatment efficacy of the neoadjuvant chemotherapy, if any, must be small when compared to the much more important clinical parameters such as the patient's age and the primary tumour extent and the extent of the nodal metastases.

On the other hand, the study had confirmed the relative lack of morbidity of the neoadjuvant chemotherapy with cisplatinum and 5-fluorouracil in NPC, as reported previously [22]. This was evidenced by the fact that the rates of interruption and the duration of interruption of definitive RT

Table 3. Significant prognostic variables by multivariate analysis of the 422 patients

Clinical endpoint	Prognostic variable	*P*-value	Hazard ratio
ASR	Male	0.0431	1.571
	Cranial nerve palsy	0.0001	2.984
	Fixed cervical node	0.0010	2.522
	Ho's N-level	0.0001	1.704
DFS	Male	0.0071	1.675
	Skull base infiltration	0.0274	1.413
	Cranial nerve palsy	0.0010	2.037
	Fixed cervical node	0.0001	2.593
	Ho's N-level	0.0001	1.565
FDM	Male	0.0345	1.650
	Cranial nerve palsy	0.0189	1.886
	Hypopharynx infiltration	0.0120	2.728
	Fixed cervical node	0.0001	2.683
	Ho's N-level	0.0001	1.725
FLF	Male	0.0111	2.498
	Tumour confined to nasopharynx	0.0366	0.424
	Cranial nerve palsy	0.0073	2.385
	Orbit infiltration	0.0115	2.915
FRF	Skull base infiltration	0.0002	2.832
	Multiple cervical nodes	0.0117	3.687
	Ho's N-level	0.0203	1.657

and the rate of the patient defaulting RT or not completing RT were comparable between CHEMO and NCHEMO. There had been no incidence of chemotherapy-related mortality or cisplatinum-induced renal failure and the mucositis and myelosuppression had invariably been mild. The relatively young age of NPC patients in general, when compared to patients with other head and neck cancers [4, 6, 8, 11, 13], and the present use of 72 h infusions of 5-fluorouracil instead of the 96 or 120 h infusions [19, 20] might account for the paucity of toxicities of the chemotherapy.

NPC is unique among the head and neck cancers in that it is the one with the highest rate of distant metastases [6, 8, 11, 15] and the highest proportion of undifferentiated/anaplastic histology [4, 6, 8, 11, 13], and also because of its high radiosensitivity [1, 4, 8, 10] and chemoresponsiveness [19, 25–28]. Thus, the lack of survival benefit of neoadjuvant chemotherapy on head and neck cancers in general [29, 30] may not be applicable to NPC. However, Tannock *et al.* [31] also found no long-term survival benefit of the neoadjuvant chemotherapy in NPC. Recently there is a retrieval of interest in neoadjuvant chemotherapy after Paccagnella *et al.* [32] reported a significant reduction in distant metastases after the use of neoadjuvant chemotherapy in UICC [18] stage III and IV head and neck cancers. Also, Cvitkovic *et al.* [27] reported a significant difference in disease-free survival favouring the use of three courses of neoadjuvant chemotherapy with an epirubicin–bleomycin–cisplatin combination prior to definitive radiotherapy (RT) in NPC, despite an excess of treatment-related deaths (9% versus 1%) and of RT refusal (7% versus 1%) in the randomised arm given chemotherapy. It therefore remains an attractive possibility that neoadjuvant chemotherapy with active regimens such as cisplatinum–5-fluorouracil can reduce systemic failures and so enhance disease-free survival in NPC. In the present study, the comparability between CHEMO and NCHEMO for DFS and FDM in all Ho's overall stages, despite the presence of significantly more fixed and bulky nodal metastases in CHEMO, could be regarded as indirect evidence to suggest a beneficial effect of the chemotherapy. Reduction in distant metastasis should be of particular relevance to those with advanced cervical nodal metastases, such as Ho's N3 [4] who are the most prone to developing distant metastases.

While it is unethical to use inactive combinations because of their detrimental effect [33], one should still be very careful in experimenting with active regimens in the neoadjuvant setting in NPC because hitherto there has been no proof of its therapeutic efficacy. With the inherent limitations of a retrospective study and the imbalance in prognostic factors between CHEMO and NCHEMO, we could not prove the therapeutic efficacy of the neoadjuvant chemotherapy. We could only infer that the magnitude of benefit conferred by chemotherapy, if any, should be small in comparison with the impact of the patient and tumour prognosticators, and, we could barely suggest that there is a possibility of enhancement of systemic control and survival by chemotherapy based on the absence of any difference between CHEMO and NCHEMO in DFS and FDM in each of Ho's overall stages, despite the presence of significant adverse factors biased against CHEMO. On the other hand, there has been no data to suggest any enhancement of local and/or regional tumour control by chemotherapy in the present study. This very important therapeutic issue with neoadjuvant chemotherapy in NPC can only be settled by high power prospective randomised studies with long-term follow-up. The importance of proper stratification according to the relevant primary tumour and cervical nodal and patient prognosticators in such prospective studies cannot be overemphasized. While waiting for solid proof of its therapeutic advantage, we do not recommend the routine use of neoadjuvant chemotherapy outside the context of a prospective randomised trial.

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