

Concurrent Chemoradiotherapy in Patients with Locally Advanced Nasopharyngeal Carcinoma of the Undifferentiated Type

Y K Ong,*^{MBBS, MRCP, M Med}, E H Tan,**^{FAMS, MRCP, M Med}, J Wee,***^{FAMS, MBBS, FRCR}, C B Goh,****^{MBBS},
K W Fong,***^{FAMS, MBBS, FRCR}, K S Lee,***^{MBBS, FRCR}, E J Chua,[†]^{FAMS, MD, DMRT}

Abstract

The result with radiotherapy alone in patients with locally advanced nasopharyngeal carcinoma (NPC) was disappointing. Encouraging results have been reported with the use of concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck. Hence, we decided to explore the use of this treatment schedule in patients who presented with locally advanced disease (UICC/AJCC classification system).

Between July 1995 and March 1996, 14 patients with locally advanced NPC were treated with the following schedule: radiation therapy was given conventionally to a total of 66 to 70 Gy to both the nasopharynx and neck with or without parapharyngeal/intracavitary boost; chemotherapy consisted of intravenous cisplatin at 20 mg/m²/day and intravenous 5-fluorouracil 1000 mg/m²/day, infused over 8 hours on days 1 to 4 during the first and fifth week of radiation therapy. Depending on the patient's tolerability and clinical assessment of toxicity, a third cycle of chemotherapy was planned 4 to 5 weeks after the second cycle, upon the completion of the radiotherapy.

Twelve patients completed all intended treatment. Two patients failed to do so due to treatment-related mortality. The median follow-up duration was 30 months. Limiting toxicities were myelosuppression and oropharyngeal mucositis. The overall response rate was a 100% at both the primary and nodal sites of disease. The median disease-free survival was 21 months. Forty per cent of the patients were alive at 3 years. This treatment schedule was associated with an unacceptable treatment-related death rate. As a result, this protocol was terminated.

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Introduction

Nasopharyngeal carcinoma (NPC) of the undifferentiated type has a unique geographic distribution and is rather different, biologically and aetiologically, from squamous cell cancer of the head and neck. This disease is of epidemiological concern in Singapore, with an age-standardized rate of 18.4 per 100,000 in Chinese males and 7.3 per 100,000 in Chinese females.¹

Fong et al² reviewed 270 patients with newly diagnosed NPC, treated with conventional radiotherapy between July 1987 and December 1988 at our institution. About 60% of the patients presented with locally advanced disease at diagnosis. This group of patients had either T3, N2 or N3 disease i.e. stage III or IV disease by Ho's classification. The survival outcome for stage IV disease remained dismal despite radical radiotherapy. The median disease-free survival in patients with stage IV disease was only 12 months with a median overall

survival of about 18 months. In addition, about 60% of these patients developed distant metastases within 2 years of treatment and they also faced a higher risk of locoregional relapse.

The past decade has seen much work on the use of chemotherapy concurrently with radiation in patients with locally advanced squamous cell head and neck cancer. The rationale for this approach is simple. Chemotherapy and radiation are independent active treatment modalities. When used together, their synergism may allow for improved locoregional control and the use of chemotherapy may also have an effect on micro-metastases. The concurrent use of both treatments also does not lengthen the total treatment duration.³

Adelstein et al⁴ reported a randomised trial comparing concurrent chemoradiotherapy with radiotherapy alone in patients with resectable stage III and IV squamous cell head and neck cancer. The chemoradiotherapy treat-

* Registrar

** Consultant

Department of Medical Oncology, National Cancer Centre

*** Consultant

**** Resident

† Senior Consultant and Head

Department of Therapeutic Radiology, National Cancer Centre

Address for Reprints: Dr E H Tan, Department of Medical Oncology, National Cancer Centre, 1 Hospital Drive, Singapore 169610.

ment schedule consisted of 5-fluorouracil 1000 mg/m²/day, and cisplatin 20 mg/m²/day, both given as continuous infusion over 96 hours on day 1 and day 22 of the radiotherapy. At a median follow-up of 3 years, an improvement in relapse-free survival, a decrease in distant metastases, and an improvement in overall survival with successful primary site preservation were demonstrated.

Given the positive data on the use of concurrent chemoradiotherapy in squamous cell head and neck cancer, we decided to explore this treatment method in patients with locally advanced NPC of the undifferentiated type.

Materials and Methods

Eligibility Criteria

Eligibility criteria included the following: histological confirmation from the nasopharynx, locally advanced disease, good performance status of ECOG 0-1, adequate renal (serum creatinine <1.7 mg%), hepatic (normal serum bilirubin and serum transaminases <2X upper limit), bone marrow (white cell count $\geq 3000/\text{mm}^3$, platelet $\geq 100,000/\text{mm}^3$) and cardiac function, and informed consent. Distant metastasis was ruled out by normal chest radiograph, bone scan and ultrasound or computerised tomographic (CT) scan of the liver.

Chemotherapy Schedule (Fig. 1)

Each cycle of chemotherapy consisted of i.v. cisplatin 20 mg/m²/day given over an 8-hour infusion each day for 4 days and i.v. 5-fluorouracil 1000 mg/m²/day, given in similar fashion, for 4 days. The 8-hour infusion was chosen so that the patients can receive this treatment schedule on an outpatient basis. Two cycles of chemotherapy were given concurrently on day 1 and day 28 of the radiotherapy. Depending on tolerability and assessment of toxicity, a third cycle of chemotherapy was planned, after completion of radiotherapy, on day 57 of the treatment schedule.

Radiotherapy

The radiotherapy technique consisted of a three-field facial technique to encompass the primary site and the

immediate areas at risk, and a single anterior neck field, which was matched at its superior margin with the primary volume and was bordered inferiorly by the base of the suprasternal notch ("split-field" technique). The brainstem and oral cavity were shielded on the lateral facial fields. A midline cord shield was applied throughout the treatment on the anterior cervical field. In patients who had bulky surgical level II or V nodal disease that would render the placement of high neck field junction unacceptable, the three-field technique was replaced by larger parallel opposed lateral fields which encompassed the primary site and the bulky node/s in one volume ("long field" technique). At 40 Gy, the three-field technique was used in order to limit the dose received by the upper spinal cord to within tolerance level. Bulky neck nodes were boosted with electron beams. The target dose to the postnasal space and adjacent areas at risk was 66 to 70 Gy. The whole neck received an elective dose of 60 Gy to the 90% isodose line at the field center. Palpable nodes were boosted to an additional 10 Gy. Parapharyngeal involvement also received a boost of 10 Gy through lateral oblique portals.

Follow-up

The patients are followed up weekly for assessment of toxicity and clinical response to treatment during the treatment phase. Weekly haematology was done as well. Endoscopic examination of the nasopharynx was done after treatment was completed. A repeat CT scan of the postnasal space was done 3 months after the last fraction of radiation to assess radiological response. Repeat biopsy of the postnasal space was not routinely done unless obvious persistent lesion was seen at least 3 months after completion of treatment.

Toxicity and Response Criteria

Responses and grading of toxicities were defined according to World Health Organization criteria.

Statistics

Survival was calculated from the date of diagnosis and disease-free interval was dated from the day of implementation of the treatment schedule. The survival estimates were estimated using the Kaplan-Meier method.

Results

Patient's Characteristics (Table II)

Between July 1995 and May 1996, a total of 14 patients were accrued on this protocol. The median duration of follow-up was 30 months. The median age of the patients, similar to other reported series, was 48.5 years. The majority were Chinese. Most of the patients had stage IV (non-metastatic) disease when retrospectively based on the latest AJCC/UICC classification (Table I), with a T4 or / and N3 disease.

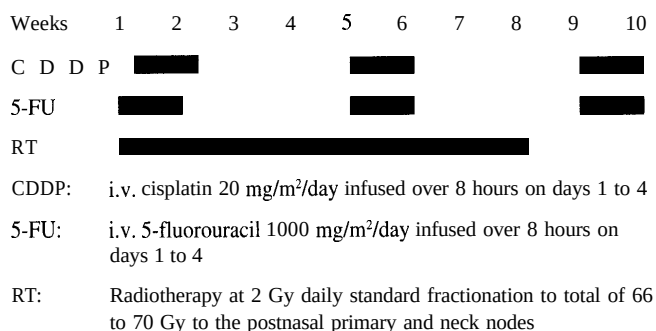


Fig. 1. Treatment schema.

TABLE I: UICC/AJCC TNM CLASSIFICATION AND STAGE GROUPING (1997)

T1	tumour confined to the nasopharynx
T2	tumour extends to soft tissue of oropharynx and/or nasal fossa
	T2a - without parapharyngeal extension
	T2b - with parapharyngeal extension
T3	tumour invades bony structures and/or paranasal sinuses
T4	tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit
N0	no regional lymph nodes metastasis
N1	unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa
N2	bilateral metastases in lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa
N3	metastasis in lymph node(s)
	a) greater than 6 cm in dimension
	b) in the supraclavicular fossa
M0	no distant metastasis
M1	distant metastasis
Stage grouping	
I	T1N0
IIA	T2aN0 IIB T1-2aN1 or T2bN0-1
III	T1-2bN2 or T3N0-2
IVA	T4N0-2
IVB	any TN3
IVC	M1

Delivery of the Treatment (Table II)

Twelve patients completed the minimum intended treatment. Two patients died due to treatment-related toxicities during the treatment and hence did not complete the radiation. All patients completed at least 2 cycles of chemotherapy. Three patients managed to receive the third cycle of chemotherapy. One patient had interruption of the radiation for a week because of oropharyngeal mucositis.

Toxicity (Table III)

A total of 31 cycles of chemotherapy were given and 30 cycles were evaluable for hematological toxicity. Oropharyngeal mucositis and myelosuppression leading to sepsis were the limiting toxicities with this treatment schedule. Two out of 4 patients who received "split field" RT technique developed grade 3 oropharyngeal mucositis and 6 out of 10 patients who received "long field" technique developed grade 3-4 mucositis. The sample size is too small to correlate radiotherapy technique and the degree of oropharyngeal mucositis. Skin toxicities were usually manageable and generally did not pose any hindrance to the treatment. Two patients died from neutropenic sepsis. One was treated with the "split field" technique and the other received the "long field" technique. This unacceptably high rate of treatment-related death resulted in the premature termination of this protocol. These 2 patients were more than 60 years of age, and one of them had poor home and social support. Weight loss was significant with this treatment schedule, with a median percent body weight loss of 9.5% (range 3% to 25%).

TABLE II: PATIENT CHARACTERISTICS (n = 14)

Characteristic	Number	%
Sex		
Male	11	78
Female	3	22
Age (years)		
Median	48.5	
Range	25 to 69	
Primary tumour		
T1	2	14
T3	3	22
T4	9	64
Nodal stage		
N0	1	7
N1	3	22
N2	4	28
N3	6	43
Cycles of chemotherapy		
2 cycles	11	78
3 cycles	3	22
Radiotherapy completed		
Yes	12	86
No	2	14
Interrupted	1	7
Radiotherapy technique		
Long field	10	71
Split field	4	29

TABLE III: TOXICITY (GRADE 3-4)

Toxicity	%
Hematological	
Neutropenia	23
Thrombocytopenia	6.4
Anaemia	3.2
Oropharyngeal mucositis	62
Cutaneous	9.6
Nausea/vomiting	6.4
Percentage weight loss	
Median	9.5
Range	3 to 25
Neutropenic sepsis	28.6
Treatment-related death	14

Response to Treatment (Table IV) and Survival Outcome

Twelve patients were evaluable for response to treatment. All achieved a complete response at the primary site. Ten of the 11 patients with nodal disease achieved complete responses. Two patients were not evaluable for primary site response due to treatment-related deaths.

Seven patients (50%) had relapsed to date; 2 had locoregional, 3 had systemic and 2 had both locoregional and systemic relapses. The median survival was 31 months and the median disease-free survival was 21 months. At 3 years, 40% of the patients were still alive (Fig. 2).

Discussion

Given the high responsiveness of nasopharyngeal car-

TABLE IV: RESPONSE TO TREATMENT

Response	Number	%
Primary disease (n = 14)		
Complete	12	86
Not evaluable	2	14
Nodal disease (n = 13)		
Complete	10	77
Partial	1	7
Not evaluable	2	15

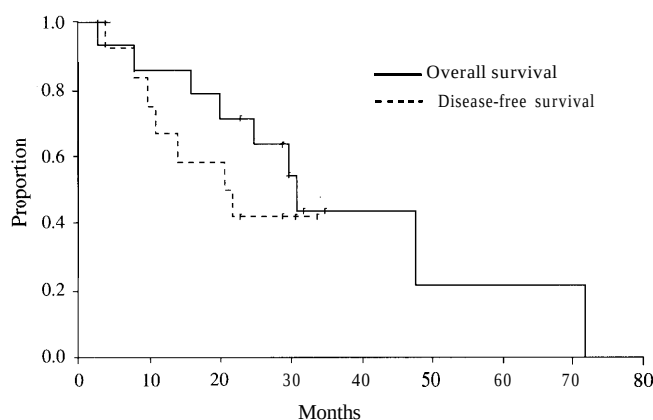


Fig. 2. Overall and disease-free survival.

cinoma to platinum-based chemotherapy and the high risk of locoregional and/or systemic relapse in patients with locally advanced disease, it makes sense to incorporate chemotherapy to radiotherapy in the initial management schema. There are different ways of sequencing chemotherapy with radiation:

- 1) adjuvant, i.e. upon completion of radiotherapy,
- 2) neoadjuvant, i.e. before the commencement of radiotherapy,
- 3) concurrent, i.e. simultaneously with radiation, and
- 4) combinations of the above three methods.

The only randomised trial, which looked at the question of adjuvant chemotherapy, unfortunately, used non-platinum-based chemotherapy regimen using vincristine, cyclophosphamide, and doxorubicin.⁵ Hence, this question is still unanswered though the study failed to show any benefit with adjuvant treatment. The second randomised trial, which incorporated adjuvant chemotherapy using combination of cisplatin, and 5-fluorouracil was a North American Intergroup Study.⁶ However, as patients randomised to receive chemotherapy also received 3 cycles of cisplatin concurrently with radiation, this was not a pure adjuvant study.

The preliminary results of a large randomised trial by the International Nasopharynx Cancer Study Group, comparing neoadjuvant chemotherapy (cisplatin, epirubicin, and bleomycin) followed by radiotherapy

against radiotherapy alone, showed significantly improved disease-free survival in favour of the chemotherapy group.⁷ However, there was an excess of treatment-related deaths in the chemotherapy arm of 8% versus 1%.

The North American Intergroup Study randomised NPC patients with locally advanced disease to receive either radiation alone or radiation with concurrent cisplatin for 3 cycles followed by 3 further cycles of adjuvant cisplatin and 5-fluorouracil.⁶ This study showed significantly improved survival rate in those who received chemotherapy. However, it is difficult to ascribe the beneficial effect to the concurrent chemotherapy, or adjuvant chemotherapy, or both, in this study. Moreover, this treatment programme suffers from the prolonged schedule required.

The use of combination chemotherapy concurrently with radiation as used in our treatment schedule is associated with high toxicity. Although the treatment duration is not more prolonged compared to those who are on radiation alone, greater care is required in the follow-up due to toxicities of combined treatment. Careful selection of patients for this form of aggressive concurrent treatment is required. Although the response rates were very high in our study, the unacceptably high treatment-related death rate mandated premature termination of this protocol. Work to revise the treatment protocol to make it safer and more effective continues.

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