

## Treatment Results of Neo-Adjuvant Chemotherapy in Advanced Head and Neck Cancer in Oman

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### ABSTRACT

**Background and Objectives:** A prospective, single-arm study was carried out to evaluate the safety and efficacy of neo-adjuvant chemotherapy in advanced head and neck cancer (HNC) in Oman.

**Materials and Methods:** The study was carried out in the Oncology and Ear, Nose and Throat (ENT) Departments, Muscat, Oman between October 1998 and December 2001. Eligible, previously untreated patients with confirmed diagnosis of locally advanced non-metastatic carcinoma of the head and neck were examined. A maximum of three cycles of neo-adjuvant chemotherapy (Cisplatin 100mg/m<sup>2</sup> Day 1 plus 5-Fluorouracil 1gm/m<sup>2</sup> continuous infusion for four days) were administered, followed by radical radiotherapy according to primary site. The main end-points were toxicity, response rate, disease-free survival and overall survival.

**Results:** Seventy-three patients (45 males and 28 females) were eligible; all were evaluable for response and toxicity. The median age of studied patients was 52 years (range: 17-83 years). Forty-four patients (60%) had stage III disease and 29 (40%) had stage IV disease. After neo-adjuvant chemotherapy, Overall Response (OR) [Complete Response (CR) + Partial Response (PR)] was observed in 50 patients (68%), 33 patients (45%) had clinical CR and 17 patients (23%) had PR. Sixteen patients (22%) showed Stable Disease (SD) and 7 patients (10%) progressed while on chemotherapy. After completion of radiotherapy, the OR rate was 80%. Forty patients (55%) had clinically confirmed CR, 18 (25%) had PR, 9 patients (12%) had SD and 6 patients (8%) had progressive disease (PD). The median follow-up period was 16 months (range 3-48 months). The initial response to chemotherapy had a significant effect on survival ( $p=0.011$ ). The nasopharyngeal primary was significantly associated with high CR and longer survival ( $p=0.01$  and  $0.02$ , respectively).

**Conclusions:** Head and neck carcinoma is not a common malignancy in Oman. The treatment results with cisplatin and 5-FU compare favorably to similar international studies and treatment-related toxicities are tolerable.

**Key Words:** Head and neck cancer (HNC) - Neoadjuvant chemotherapy - Cisplatin/5-FU.

### INTRODUCTION

Carcinoma of the head and neck is the sixth most common cancer worldwide. While the incidence of HNC in Oman is 4% of newly diagnosed cancer cases, it is not among the 10 most common cancers in the country. This could be explained by the low incidence of smoking, the government's efforts in health education to maintain a clean environment and the nature of the population pyramid of Oman, where 43% of the population is under 15 years of age and only 5% of the total Omani population is above the age of 60 [1].

Despite the use of aggressive multimodality management, patients with locally advanced HNC still suffer poor local control, poor quality of life and poor survival [2-4]. The rationale underlying the use of neo-adjuvant chemotherapy in locally advanced HNC patients is the possibility of better drug delivery in well-vascularised tumors. Tumor shrinkage would allow better results when surgery and/or radiotherapy are added, and it will also help to eradicate micro-metastases [5]. The achieved response rates in untreated patients were double that of patients with recurrent disease after surgery and/or radiotherapy [6].

The majority of randomised trials have shown that the combination of 5-Fluorouracil and Cisplatin, compared to other induction regimens, significantly improves survival in patients with locally-advanced HNC [7-9]. The most recent meta-analysis examined 10,850 patients from 65 studies comparing different local treatment (surgery and/or radiotherapy) with or without chemotherapy, and revealed a significant absolute survival advantage of 5%

in the five-year survival ( $p=0.01$ ) in the neo-adjuvant chemotherapy groups when compared to controls [10].

The aim of this study was to evaluate safety and efficacy of neo-adjuvant chemotherapy with the standard 5-Fluorouracil and Cisplatin regimen in patients with locally-advanced non-metastatic HNC in Oman.

### MATERIAL AND METHODS

The study was carried out in the Oncology Department of the Royal Hospital and the ENT Department at Al-Nahda Hospital in Muscat, Oman. Between October 1998 and December 2001, all previously untreated patients with confirmed diagnosis of locally-advanced non-metastatic HNC were examined.

Eligible patients are required to have good general condition with an Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$  [11], creatinine (Cr) level  $\leq 115\mu\text{mol/l}$  or 24-hour creatinine clearance (CrCl)  $\geq 60\text{mL/min}$ , a white cell count  $\geq 4,000/\text{mm}^3$  and a platelets count  $\geq$  of  $100,000/\text{mm}^3$ . All patients underwent thorough clinical examination and pre-treatment endoscopy for tumor staging and measurements. All patients had CT scans of the head and neck and chest X-rays. Clinical staging is determined according to the International Union Against Cancer (UICC) classification [12].

Patients with uncontrolled angina, active infection, or who suffer from another malignancy were ineligible. Informed consent is obtained from all studied patients. This treatment protocol is the department's standard management for such malignancies.

#### *Chemotherapy:*

Chemotherapy regimen consisted of Cisplatin (P) 100mg/mg, day 1 intravenous (IV) infusion over three hours followed by IV continuous infusion of 5-fluorouracil (F) with a dose of  $1\text{gm/m}^2/\text{day}$  on Days 1-4. This treatment was repeated every three weeks for maximum of three cycles. Antiemetics (5-HT antagonist + dexamethasone) were given 15 minutes before every chemotherapy injection. All patients were hospitalised for hydration and chemotherapy infusion. Proper hydration before and after cisplatin infusion was completed for all patients; this consisted of prehydration with an IV infusion of one litre 0.9% Normal Saline (NS) plus

40 mmol Potassium Chloride (KCl) over two hours before Cisplatin infusion, 40mg IV bolus of frusemide just before Cisplatin infusion to induce diuresis and 0.5 litre of IV NS plus KCl 20 mmol with 100 ml 20% manitol over one hour after Cisplatin infusion.

Complete blood counts, creatinine level and electrolytes were checked before each cycle. Dosage modifications for toxicity were based on nadir laboratory data and clinical evaluations after the first cycle. Cisplatin was stopped if serum creatinine level increased over  $400\mu\text{mol/l}$  or creatinine clearance was  $\leq 40\text{ml/min}$ . The dosage of 5-FU is reduced by 25% for a nadir WBC count less than  $2,000/\mu\text{L}$  and/or a platelet count less than  $75,000\mu\text{L}$  and or grade 3-4 mucositis or diarrhoea.

Response was assessed by clinical and radiological examination and reported according to the definitions of the World Health Organization (WHO) [13]. Toxicity was assessed according to the WHO criteria after each cycle of chemotherapy [14].

Clinical assessment of response was completed after each cycle and radiological assessment after the second cycle. Patients who have Complete Response (CR) or Partial Response (PR) aim to complete three cycles of chemotherapy followed by local radiotherapy, while patients who have Stable Disease (SD) after the second cycle or Progressive Disease (PD) either after the first or second cycle start radiation treatment immediately.

All patients have dental checks before starting radiotherapy and correction of dental complaints.

#### *Radiotherapy:*

All patients were treated with megavoltage radiation using linear accelerators 6 MV. Treatment is delivered in fractions of 2 Gy/day, five fractions per week to a total dose of 64-70 Gy. The treatment volume and total radiotherapy dosage was determined according to the site of the primary tumor. The primary tumor and draining lymphatic system are treated isocentrically with 6-MV photons and parallel opposed lateral portals with a source-to-isocenter distance of 100cm. Supraclavicular nodes and nodes in the lower part of the neck are treated with the use of a single anterior field, with midline spinal

cords shielding blocks. The inferior border of the lateral fields and the superior border of the supraclavicular fields coincide on the skin. For nasopharyngeal and oropharyngeal tumors, lateral-field doses are prescribed at midplane, whereas a depth of 3cm is used for the supraclavicular field.

No interstitial radiotherapy was used in this group of patients. Each patient's head was fixed using beam directed shells; mouth-bites were used when necessary. Cord protection and re-planning was done after 40 Gray (Gy). Treatment position was verified with portal films before start of treatment.

Toxicity to radiotherapy was assessed every week during the radiotherapy course for acute reactions and patients were reviewed every month for three months after end of radiotherapy then every two months thereafter. Late toxicity was defined as that persisting more than three months from the beginning of radiotherapy or appearing three months from the beginning of radiotherapy.

#### *Statistical Methods:*

All patients' data were statistically analyzed using the Statistical Package for Social Sciences (SPSS Version 10.0) software program. Overall Survival (OS) was estimated from the start of treatment until last follow-up or death. Disease-Free Period (DFP) was estimated from the date of documented complete remission to the date of relapse. Survival curves and DFP were determined according to the Kaplan-Meier method [15]. The significance of differences between survival curves were tested by the one-sided Log-rank test for equivalence [16]. All reported *p* values <0.05 were considered to be significant. A univariate analysis were carried out to explore the associations of patient characteristics (age, sex, diagnosis, stage, number of lymph nodes, histological subtype, response to chemotherapy, performance status) with the patient's outcome (Disease-Free Survival and Overall Survival). Factors that were significant in the univariate analysis are entered in a multivariate analysis using a Cox regression model [17] to determine which clinical or therapeutic variables are most strongly correlated with the dependant variable (i.e. OS and DFP), the event (either recurrence, or death are categorized as 0/1 for non-occurrence/occurrence, respectively). Multivariate models were constructed using a stepwise

variable selection technique. The regression coefficient ( $\beta$ ) and its standard error were presented for each factor. The results of the multivariate analysis were expressed in terms of relative risks derived from the estimated regression co-efficient along with their 95% Confidence Intervals.

## RESULTS

During the study period (October 1998 to December 2001), 3477 new cancer patients were registered in the sultanate of Oman, and 142 of them had primary HNC, constituting about 4% of all newly diagnosed cancer cases. More than half of the diagnosed HNC patients 85/142 (60%) had locally-advanced non-metastatic stages (Stage III & IV).

Seventy-three eligible patients with histologically confirmed locally-advanced HNC were studied. All were evaluable for toxicity and response. There were 28 females (38.4%) and 45 males (61.6%), ranging from 17-72 years of age with a median age of 52 years. Forty-four patients (60%) had Stage III disease and 29 (40%) had Stage IV non-metastatic disease. Fifty-five patients (75%) had a performance status of 0-1. The clinical characteristics of the studied patients are shown in Table (1). Nasopharyngeal carcinoma was the most common primary site constituting 30% of studied patients. Carcinoma of oral cavity was the least common cancer in this group, representing only 12% of all cases.

All evaluable patients received a maximum of three cycles of neo-adjuvant chemotherapy (range: 1-3 courses) before starting radiotherapy. A total of 202 chemotherapy cycles were analyzed for efficacy and toxicity.

Toxicity of chemotherapy was tolerable. Nausea and vomiting (Grade III, IV) was reported in only 7% and diarrhoea Grade III reported in 4% of cycles. Neutropenia (Grade III) occurred in 4% of cycles while mucositis (Grade III, IV) was reported in 7%. Ten patients (14%) had cycle delays of less than a week and four patients (5%) had delays of more than a week due to reversible toxicities. Reported toxicities during chemotherapy are summarized in Table (2).

Sixty-eight percent of patients completed the intended three neo-adjuvant courses; patients

who had SD or progressed while on chemotherapy started radiotherapy immediately. No cisplatin-related nephrotoxicity occurred and no treatment-related deaths were reported in this study.

After neo-adjuvant chemotherapy, OR was observed in 50 patients (68%), while 33 patients (45%) had CR on repeat endoscopy and/or CT scans, and 17 patients (23%) had PR. Sixteen patients (22%) showed SD, and 7 patients (10%) had PD.

All patients completed their radiotherapy as planned, and total treatment time ranged from 6.5 to 7 weeks. There were no reported radiotherapy interruptions due to toxicity; however, two patients underwent elective tracheostomy along the radiotherapy course to manage progressive airway obstruction. Four patients (two hypopharyngeal and two laryngeal primary tumors) required Per-cutaneous Endoscopic Gastrostomy (PEG) for proper feeding during radiotherapy because of progressive dysphagia/severe mucositis, and feeding tubes were removed after recovery of reactions. Acute and late radiotherapy toxicities were summarized in Table (3).

After completion of radiotherapy, patients were again evaluated for response. The OR was reported in 58 patients (80%), 40 patients (55%) had clinically and/or radiologically confirmed CR, 18 (25%) had PR, 9 patients (12%) had SD and 6 patients (8%) had PD. Table (4) showed the response rates after chemotherapy and after completion of radiotherapy.

The median follow-up period was 16 months (mean 19 months, range 3 to 48 months and SD=14.7). The median DFP was 11 months (95% confidence interval 7.32-14.68) and was found to be affected by the stage at diagnosis and primary tumor site (nasopharynx versus other primaries). The DFP and OS as a function of stage at diagnosis and primary response to neo-adjuvant chemotherapy were shown in Figs. (1,2), respectively.

Univariate analysis showed that the primary site of the tumor, age (< 60 or > 60 years), stage of the disease at presentation and performance status affected both the DFP and OS. In the multivariate analysis shown in Table (5), both initial response to chemotherapy (CR/PR versus PD/NR) and primary nasopharyngeal carcinoma

remained significantly related to overall survival. The median survival for the whole group was 16 months (95% confidence interval 12.68-19.32). The OS and DFS curves for all studied patients were represented in Figs. (3,4), respectively. Nasopharyngeal primary tumors had a CR rate of 86% (19 of 22 patients) versus 41% in other head and neck primaries (21 of 51 patients,  $p=0.02$ ), and was associated with longer survival ( $p=0.01$ ). Nineteen of the 22 patients with nasopharyngeal tumour, Fig. 5 showed the correlation between primary tumor site and OS.

At the end of study 15/73 patients (20%) were still alive, and most of them (60%) had nasopharyngeal carcinoma (nine patients), two patients had hypo-pharyngeal carcinoma and four patients had primary laryngeal carcinoma.

Table (1): Characteristics of studied patients.

Characteristics	Number	%
<i>Age (years):</i>		
Median	52	
Range	17-72	
<i>Sex:</i>		
Male	45	62
Female	28	38
M:F ratio	1.6:1	
<i>Site:</i>		
Nasopharynx	22	30
Larynx	15	21
Oropharynx	15	21
Oral cavity	9	12
Hypopharynx	12	16
<i>Performance status:</i>		
0	30	41
1	25	34
2	18	25
<i>Stage:</i>		
III	44	60
IV	29	40

Table (2): Toxicity of neo-adjuvant chemotherapy in a total of 202 administered chemotherapy cycles.

Toxicity	Number	Grade 3/4	%
Nausea and Vomiting	14	10/4	7
Diarrhoea	8	8/0	4
Neutropenia	8	8/0	4
Mucositis/Dysphagia	14	12/2	7
Renal	0	0	0
Toxic Death	0	0	0

Table (3): Acute and late radiation therapy toxicity in studied patients.

Toxicity	Number	Moderate/ Severe	%
<i>Acute:</i>			
Stomatitis	24	16/8	32
Dysphagia	14	9/5	19
Dry Desquamation	28	20/8	38
Moist Desquamation	10	7/3	13.5
Nausea and Vomiting	3	2/1	4
Neutropenia	2	2/0	3
Need for Feeding Tube	4	—	6
Need for Tracheostomy	2	—	3
<i>Late:</i>			
Xerostomia	9	6/3	13
Taste Changes	5	4/1	6
Cervical Fibrosis	3	2/1	4
Radiation Myelitis	0	0	0

Table (4): Response to neo-adjuvant chemotherapy and radiotherapy.

Response	After Chemotherapy		After Radiotherapy	
	Number	%	Number	%
Complete Response (CR)	33	45	40	55
Partial Response (PR)	17	23	18	25
Stable Disease (SD)	16	22	9	12
Progressive Disease (PD)	7	10	6	8
<b>Total</b>	<b>73</b>	<b>100</b>	<b>73</b>	<b>100</b>

Table (5): Multivariate Cox regression analysis for prognostic factors affecting Overall Survival (OS).

Factor	Overall Survival*				
	Regression Coefficient ( $\beta$ )	Standard Error of ( $\beta$ )	Relative Risk	95% CI	p-value
<i>Primary Tumour:</i>					
*Nasopharyngeal vs Other HNCs	0.756	0.352	0.470	0.236-0.936	0.032
<i>Response to Chemotherapy:</i>					
*CR / PR vs SD / PD	1.500	0.346	4.482	2.273-8.837	0.001

\*Dependant factor: Survival time.

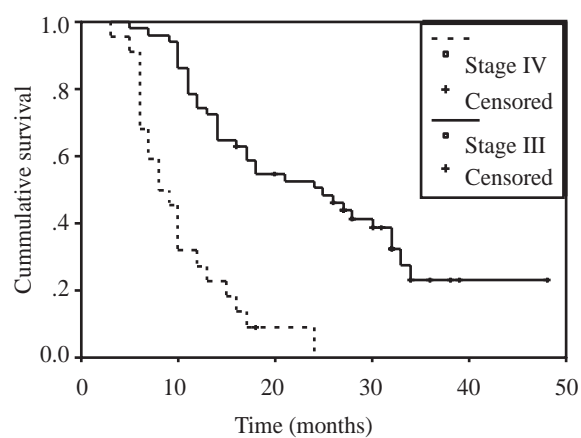


Fig. (1): Disease Free Survival (DFS) as a function of the stage of the disease. Stage III disease (solid line) was associated with a significantly longer DFS than Stage IV (dotted line)  $p=0.01$ .

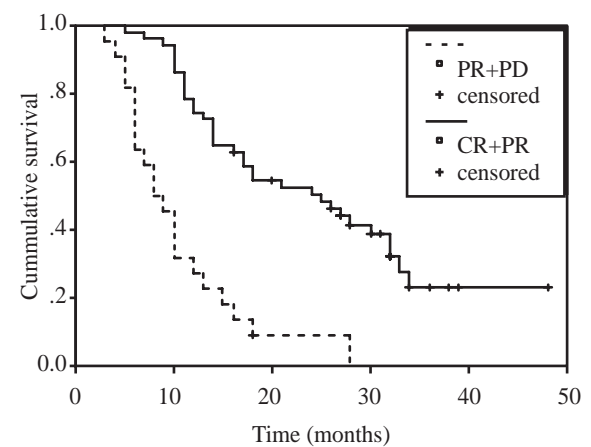


Fig. (2): Overall Survival as a function of initial response to chemotherapy. Complete and partial responders (solid line) had a significantly longer survival time than patients with stable or progressive disease (dotted line)  $p=0.02$ .

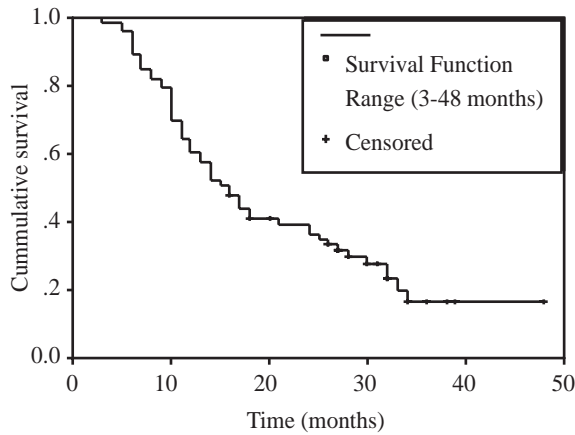


Fig. (3): Overall survival (months) of all studied patients.

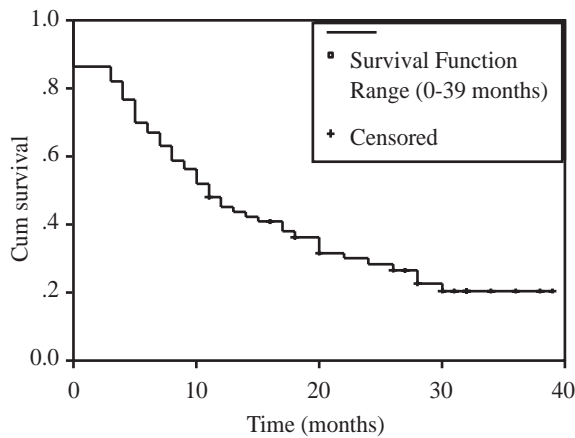


Fig. (4): Disease free survival for the whole group.

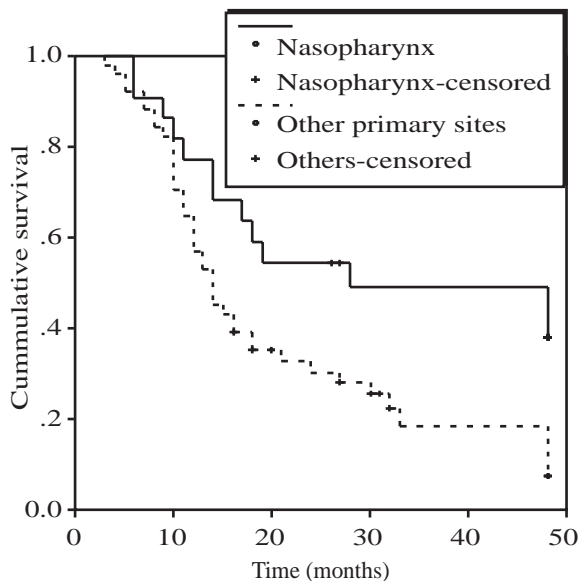


Fig. (5): Overall Survival as a function of the primary site of the tumor. Patients with nasopharyngeal primary are presented by solid line  $p=0.01$ .

## DISCUSSION

In Oman, HNCs are not among the 10 most common cancers in the Sultanate. However, most of the diagnosed patients suffer from locally-advanced or metastatic disease. This is the first report from Oman examining the results of treating this group of patients.

Locally-advanced non-metastatic carcinoma of the head and neck still present a significant therapeutic challenge. Since the Veterans Affairs study in 1991, much has been learned regarding the role of induction chemotherapy, radiation therapy and the combined modality treatment in the management of locally-advanced HNC [18].

Induction chemotherapy is an attractive modality for the treatment of locally-advanced HNC because it allows organ preservation without compromising survival and improves survival in unresectable tumors; the “standard induction regimen” consists of Cisplatin (P) and continuous-infusion fluorouracil (F), and has been associated with a complete response rate of about 30% in randomized trials [19].

A number of different strategies were investigated in an attempt to improve the activity of Cisplatin / 5-FU combination, and this included the use of more than three courses [20], the administration of high-dosage Cisplatin [21,22], and the addition of other cytotoxic agents to the regimen, such as methotrexate and bleomycin [20,23]. However, all of these approaches have so far failed to produce improvements in the CR rates or were associated with prohibitive toxicities. The combination of 5-Fluorouracil and Cisplatin remains the best-studied and most active drug combination [6,24].

The Cisplatin 5-Fluorouracil regimen originally reported a clinical CR rate of 54% in 61 patients with advanced HNCs [24]. However, continued evaluation of the same regimen in inoperable, non-metastatic patients indicated that the actual CR rate was in fact lower, between 20 and 35% [25]. Other reports of two to three cycles of Cisplatin-based neo-adjuvant chemotherapy followed by radiotherapy in patients with locally-advanced nasopharyngeal carcinoma reported overall response rates of 82% to 98% and complete responses in up to 66% of patients [26-28]. In our study, the overall

response rate after neo-adjuvant chemotherapy reached 68%; this relatively higher response could be due to the large number of patients with nasopharyngeal carcinoma, as they comprised 30% of our studied cases.

The results of the treatment used in our center compared favourably to studies investigating similar groups of patients and using similar or more intense treatment schedules. Our results showed an 80% overall response rate (CR+PR) after completing radiotherapy, which is similar to the results reported by Clark, et al. [29], who reported an overall response rate of 81% in 102 Stage III/IV patients who received Cisplatin/5-FU, plus high dosage leucovorin induction chemotherapy, followed by local therapy (radiotherapy or radical surgery). However, toxicity in the Clark study was high, resulting in hospitalization for 19% of the cases.

We conclude that although HNC is not among the common malignancies in Oman, more than half of the newly-diagnosed patients still demonstrate advanced stages, and our treatment results with Cisplatin and 5-FU compare favourably with similar international studies using the same drug combination. Moreover, treatment-related toxicities were tolerable.

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