Treatment Results and Prognostic Factors of Pharyngeal Carcinoma Treated with Either Radiotherapy Alone or in Combination with Systemic Chemotherapy

Hala F. Elshazly; Ashraf F. Barakat ; *Hanan S. Gamal El-Deen and Heba H. El Setiha.

Clinical Oncology Department, Tanta University Hospital, Faculty of Medicine, Tanta, Egypt
*hannshawky@yahoo.com

Abstract: Pharyngeal carcinoma has been identified as a significant public health threat. Systematic evaluation of the significant impact of several prognostic factors in pharyngeal carcinoma treated either with radiotherapy alone or in combination with chemotherapy is of great importance to health care providers and policy makers. This study used to evaluate the correlations between disease characteristics, treatment, and survival for patients with pharyngeal carcinoma. Main outcome measures were disease-free survival, overall survival, and treatment response. Methods: This study included 97 patients with pharyngeal carcinoma treated at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital between January 2000 and December 2005. Results: The mean age of all patients was 50.18 years (range; 23 - 75 years). Men made up 61.9% of patients. Pathologic diagnosis was squamous cell carcinoma (SCC) in 77.3% of cases. Younger patients (<50 years) had a much higher frequency of presentation with stage I and II tumors (58.5%). Most tumors were located at the hypopharynx (57.7%) with clinical stage III or IV (63.9%). Treatment response was associated with age, tumor status, nodal status, tumor site, Karnofsky performance status, and clinical stage before treatment. The 2-year overall survival (OS) rate for all patients (n = 97) was 21.6% and the 2-year disease-free survival (DFS) rate for patients who achieved complete response (n = 31) was 51%. The significant prognostic variables were Karnofsky performance status, nodal status and primary tumor volume. Conclusion: A combination of clinical factors, such as primary tumor volume measurement, nodal status, tumor site, Karnofsky performance status, age, and clinical stage are reliable ways to stratify outcome as predictors of overall survival, disease-free survival, and treatment response in pharyngeal carcinoma.
[Hala F. Elshazly; Ashraf F. Barakat ; Hanan S. Gamal El-Deen and Heba H. El Setiha. **Treatment Results and Prognostic Factors of Pharyngeal Carcinoma Treated with Either Radiotherapy Alone or in Combination with Systemic Chemotherap**. Journal of American Science 2011;7(10):207-217]. (ISSN: 1545-1003). http://www.americanscience.org.

Keywords: Pharyngeal carcinoma, Prognosis, Radiotherapy, chemotherapy, chemoradiotherapy.

1. Introduction:

Pharyngeal cancer can develop in any of the three regions of the pharynx; the nasopharynx, the area behind the nose; the oropharynx, consisting of: the base of the tongue, the tonsillar region, the soft palate and the back of the mouth; and the hypo pharynx, or bottom part of the throat, which extends from the oropharynx above to the esophageal inlet below, consisting of three regions or sub sites: the paired pyriform sinuses, the posterior pharyngeal wall, and the postcricoid area [(1)].

Malignant neoplasms of the pharynx are among the major public health problems worldwide, with more than 400 000 new cases diagnosed every year[(2)]. According to American Cancer Society statistics, 34 360 new cases and 7550 deaths were expected in the United States in 2007[(3)]. According to the triennial report 2000-2002 of Gharbiah population-based cancer registry, the incidence of cancer pharynx in Gharbiah, Egypt in males was 1.7/100,000 and in females it was 1.2/100,000 with male: female ratio of 1.4:1. The nasopharynx accounts for 32.8%, the oropharynx 13.1% and the hypopharynx 45.8% of pharyngeal carcinoma[(4)].

Historically, surgery and radiotherapy have been the main treatments of choice for early-stage pharyngeal cancers and can result in 5-year survival rates ranging from 70 to 90%. More advanced tumors have had poorer survival rates owing to their propensity for both local recurrence and distant metastatic spread. Chemotherapy has thus been added with the aim of increasing the curability of these advanced lesions[(5-7)]. Theoretically, the main advantage of neoadjuvant chemotherapy (NAC) for locally advanced head and neck cancer is that it induces tumor reduction before definitive local therapy is performed, improving survival, organ preservation and local–regional control, as well as, decrease of the distant metastatic rate[(8-10)].

Most studies on prognostic factors in pharyngeal cancer include other head and neck tumors[(11,12)]. Tumor extension has traditionally been assessed through TNM staging, and it has been used as the main variable for dividing patients into prognostic groups[(13)]. Besides tumor extension, other clinical and pathological variables, not included in the TNM system, have been identified as prognostic predictor variables. Clinical factors such as the patient's performance status, symptoms, and co-morbidities have been described as significant

prognostic factors in functional staging[14-16]. Identifying predictors of treatment response and prognostic factors is important for the evaluation of cancer recurrence risk and treatment planning[12,13].

The objective of this study was to evaluate treatment results, in patients with pharyngeal carcinoma subjected to radiotherapy alone or in combination with chemotherapy, and analysis of factors associated with treatment response and prognosis.

Patients and Methods

Patients

We conducted analysis of 97 patients with pharyngeal carcinoma treated either with radiotherapy alone (n = 41) or in combination with chemotherapy (n = 56), at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital between January 2000 and December 2005. The inclusion criteria were pharyngeal carcinoma not previously treated and not presenting with distant metastases at diagnosis. Clinical and treatment variables were studied. Patients were required to have a Karnofsky performance status ≥ 70, adequate bone marrow reserve, hepatic and renal functions. The patients who had not finished the planned treatment, those who had a double primary cancer or who had non-epithelial cell types of cancer were excluded from this study. We also excluded patients with nonmalignant systemic disease that precluded them from receiving study therapy (eg, active infection, renal impairment, any clinically significant cardiac arrhythmia, or congestive heart failure) or patients who were pregnant were not eligible. Patient and tumor characteristics are listed in table 1.

This study included 97 patients with pharyngeal carcinoma (60 men and 37 women), mean age was 50.18 years, range: 23 to 75 years. The primary sites of the pharyngeal carcinoma were the nasopharynx (n=26), the hypopharynx (n=56), and the oropharynx (n=15). The clinical staging system adopted was the American Joint Committee on Cancer (AJCC)[17]. The AJCC stage was Stage I in 16 patients, Stage II in 19, Stage III in 27 and Stage IV in 35 patients.

Treatment Protocol

A total of 41 patients were treated by RT alone using ^{60}Co gamma rays and daily fractions of 1.8 to 2.0 Gy on 5 consecutive days a week. Two parallel opposing lateral fields (right and left) technique with individually shaped portals were used to irradiate the primary tumor, and the upper regional neck nodes for a total dose of 40 Gy. Two parallel opposing lateral fields (right and left) cord-sparing technique with individually shaped portals were used for delivering additional 20 Gy to the primary tumor, and the upper regional neck nodes. Posterior tangential portals sparing the spinal cord can be used to boost the dose to the posterior cervical lymph nodes to doses of 65 – 70 Gy if they were positive. Right and left two parallel opposing lateral fields with individually shaped portals were used for delivering additional 15 Gy to the primary tumor.

The lower neck nodes and supraclavicular areas were treated with the use of single anterior field, with mid line blocking to prevent spinal cord injury. The use of single anterior field was discontinued after 50 Gy had been administered if there were no palpable lymph nodes in the lower part of the neck, the dose reached 60 Gy if lymph nodes in the lower part of the neck were palpable.

Chemotherapy has been administered simultaneously with RT to 56 patients. Chemotherapy was applied in the 56 patients in the form of DCF regimen which consisted of docetaxel (75 mg/m^2 intravenous infusion on day 1), cisplatin (75 mg/m^2 intravenous infusion on day 1), and 5-fluorouracil (750 mg/m^2 intravenous infusion on days 1-5). Cisplatin was administered with adequate pre- and post-hydration to avoid cisplatin-induced nephrotoxicity as a 6-hour infusion. Before docetaxel, standard premedication was administered with dexamethasone 20 mg orally, diphenhydramine 50 mg intravenously (IV) and cimetidine 300 mg IV (or ranitidine 50 mg IV) 24 hours before chemotherapy and again 6 hours and 30 minutes before chemotherapy and for 2 days after administration. Antiemetics were administered at the oncologist's discretion.

Cycles were repeated after 21 days for a total of 4 cycles followed by radiation therapy. On each arm, cycles were not started unless WBC was ≥3.0×10^3 per mm^3 and platelets were ≥100×10^3 per mm^3. On both arms, dose was adjusted for non-hematologic toxicity, including mucositis. The patient was excluded from study analysis if a cycle was delayed for more than 4 weeks.

Supportive care included blood transfusions, growth factors and the administration of antiemetics and analgesics, as appropriate. Prophylactic use of growth factors was not recommended in this study.

Criteria for Response, Follow-Up, and Late Toxicity

The primary objective of this retrospective study was the evaluation of the overall survival of all studied patients. Secondary objectives were comparisons of objective tumor responses, time to local recurrence, time to distant metastases, and toxicity in the two treatment arms.

During treatment, blood counts and serum chemistries were performed weekly, and creatinine

clearance was calculated before chemotherapy. Patients were assessed weekly for weight and before each cycle for performance status. Three to four weeks after completion of RT/RCT, response quality was evaluated according to WHO criteria. Treatment response was divided into the following categories: complete response, partial response, stationary disease, and progressive disease. Partial response was assigned when tumors or lymph nodes diminished by at least 50% on clinical or imaging examinations. Finally, the response was considered complete when patients presented no documented evidence of the disease once the treatment was concluded and remained free of disease for at least 3 months.

In case of CR, patients were observed at 3-month intervals for the first 2 years and every 6 months thereafter. Evaluations consisted of pertinent medical history, physical examination, complete blood counts and blood chemistry, and imaging examinations with biopsies of any suspected areas. In case of persistent or recurrent tumor, additional treatment, was recommended and initiated at the earliest opportunity. Evaluation of late treatment-related toxicity was performed according to the grading system of late effects of normal tissue (LENT)[18], while acute toxicity was graded according to the standard WHO toxicity criteria[19].

Statistical analysis

The prognostic indicators in this study were age, gender, the site of the primary tumor, the primary tumor volume (<10 cm^3 or ≥10 cm^3), the nodal status, Karnofsky performance status, clinical stage and the tumor status. All of the variables were first analyzed independently to estimate their effect on the overall survival (OS) (the interval between the date of diagnosis and the date of death from any cause or the most recent follow-up), and the disease-free survival (DFS) (from the end of treatment to the date of tumor local recurrence or distant metastases). The survival rates were calculated by the Kaplan-Meier method[20], and the differences between the survival curves were statistically analyzed with the log-rank test. SPSS [Statistical package] (version 12.0) was used for data analysis. Mean and standard deviation were estimates of quantitative data. Chi-square/ Fischer exact were tests of proportion independence. A *P*-value of 0.05 or less was considered to be statistically significant.

3. Results

A total of 97 cases of pharyngeal carcinoma were evaluated. Of these, 60 patients were male (61.9%) and 37 (38.1%) female (Table 1).The patients' ages ranged from 23 to 75 years (mean, 50.18 years). Weight loss was observed in 28 patients (28.9%). Most of the patients (58.8%) were tobacco smokers. Co-morbidities were not observed in 41 patients (42.3%). Pulmonary diseases were the most frequent comorbidities (40 cases [41.2%]), followed by cardiac diseases in 16 (16.5%). Dysphagia was the most common symptom (71 cases [73.19%]) followed by enlarged neck nodes (23 cases [23.7%]).

Radiotherapy alone was used in 41 patients (42.3%) and radiotherapy combined with chemotherapy in 56 patients (57.7%), in the form of cisplatin, docetaxel and fluorouracil drug combinations. The dose of radiotherapy ranged from 60 to 70 Gy (median, 64.19 Gy).

A total of 42 patients (43.3%) achieved a partial response, 31 patients (32%) developed a complete response, and 24 patients (24.7%) either experienced disease progression or stationary disease during the treatment. The response rates were significantly influenced by age, tumor stage before treatment, nodal status, tumor status, Karnofsky performance status**,** and site of the primary tumor (Table 2).

We observed a higher rate of complete response in patients who treated with radiotherapy combined with chemotherapy, 37.5% (21/56): than those treated with radiotherapy alone, 24.4% (10/41) (Table 2).

Two-year overall- survival rates for all patients (n = 97) in this study was 21.6% (Fig. 1) and the 2-year disease-free survival (DFS) rate for patients achieved complete response (n = 31) was 51% (Fig. 2).

Patients aged 50 years or older had the lowest OS rates (p = 0.025), (Fig. 3) but this variable was not significantly associated with DFS (p = 0.119), (Table 3). Statistically significant differences in OS (Fig. 4) and DFS rates (Table 3) were associated with tumor site, in favor of nasopharyngeal carcinoma. None of the patients with oropharyngeal or hypopharyngeal carcinoma survived for 2 years. Patients with low Karnofsky performance status, tumors > 10 cm, and advanced nodal status had statistically significant increase in the incidence of treatment failure (Table 4), but not significantly associated with OS rates.

Chemotherapy did not have a statistically significant effect on DFS {p=0.636} (Fig.5) and OS rates (no chemotherapy used, 14.6% 2-year OS; and combined chemo-radiotherapy, 26.8% 2-year OS, {p=0.213}) (Fig. 6).

Acute Toxicity and Chronic Sequelae

Typical acute radiation-induced side effects, such as transient mucositis and dysphgia, were easily managed by symptomatic treatment. The percentages of patients experiencing grade 3 or greater hematologic or nonhematologic acute toxicity and the

impact of the radiation therapy alone, as well as, the addition of chemotherapy are listed in table 5.

The percentages of patients sustaining grade 3 or greater chronic sequelae reported during the follow-up period of this study are listed in table 5. Mild skin reaction, xerostomia, and subcutaneous fibrosis with joint stiffness occurred in 10% to 20% of assessable patients. Five patients experienced late mucosal reaction grade 3 toxicity.

Table 1. Pretreatment Patient and Tumor Characteristics (n = 97)

Patients and tumors' characteristics	No.	%
Age in years		
≤ 50	41	42.3
>50	56	57.7
Gender		
Male	60	61.9
Female	37	38.1
Smoking		
Smokers	57	58.8
Non smokers	40	41.2
Karnofsky performance status		
<80	36	37.1
80-90	61	62.9
Tumor site		
Nasopharynx	26	26.8
Hypopharynx	56	57.7
Oropharynx	15	15.5
Tumor size		
≥10cm^3	50	51.5
<10 cm^3	47	48.5
Pathological tumor type		
Squamous cell carcinoma	75	77.3
Anaplastic carcinoma	22	22.7
Tumor grading		
Grade I/II	46	47.4
Grade III/VI	51	52.6
Tumor stage		
T1	29	29.9
T2	20	20.6
T3	36	37.1
T4	12	12.4
Nodal status		
N0	49	50.5
N1	26	26.8
N2	19	19.6
N3	3	3.1
Stage before treatment		
I	16	16.5
II	19	19.6
III	27	27.8
IV	35	36.1
Line of treatment		
Radiotherapy alone	41	42.3
Radio-chemotherapy	56	57.7

Table 2. Predictive Factors of Treatment Response of Patients with Pharyngeal Carcinoma Treated With Radiotherapy Alone or in Combination with Chemotherapy

Predictive factors	No. of patients	Objective response								P- value
		Complete response		Partial response		Stationary disease		Progressive disease		
		No.	%	No.	%	No.	%	No.	%	
Age in years										
≤ 50	41	17	41.5	23	56.1	1	2.4	0	0	0.002*
>50	56	14	25	19	33.9	19	33.9	4	7.1	
Gender										
Male	60	19	31.7	23	38.3	15	25	3	5	0.477
Female	37	12	32.4	19	51.4	5	13.5	1	2.7	
Karnofsky performance status										
<80	36	6	16.7	17	47.2	10	27.8	3	8.3	0.04*
80-90	61	25	41	25	41	10	16.4	1	1.6	
Tumor site										
nasopharynx	26	20	76.9	6	23.1	0	0	0	0	
hypopharynx	56	9	16.1	30	53.6	15	26.8	2	3.5	0.001*
oropharynx	15	2	13.3	6	40	5	33.3	2	13.3	
Tumor size										
<10cm^3	47	20	42.	18	38.3	8	17.02	1	2.1	0.098
≥10 cm^3	50	11	22	24	48	12	24	3	6	
Tumor stage										
T1	29	19	65.5	8	27.6	2	6.9	0	0	
T2	20	10	50	8	40	2	10	0	0	
T3	36	2	5.6	24	66.7	9	25	1	2.8	0.001*
T4	12	0	0	2	16.7	7	58.3	3	25	
Nodal status										
N0	49	15	30.6	31	63.3	3	6.1	0	0	
N1	26	10	38.5	9	34.6	6	23.1	1	3.8	0.001*
N2	19	6	31.6	1	5.3	10	52.6	2	10.5	
N3	3	0	0	1	33.3	1	33.3	1	33.3	
Stage before treatment										
I	16	12	75	4	25	0	0	0	0	
II	19	10	52.6	6	31.6	3	15.8	0	0	
III	27	5	18.5	12	44.4	9	33.3	1	3.7	0.001*
IV	35	4	11.4	20	57.1	8	22.9	3	8.6	
Line of treatment										
Radiotherapy alone	41	10	24.4	15	36.6	14	34.1	2	4.9	
Radio-chemotherapy	56	21	37.5	27	48.2	6	10.7	2	3.6	0.06

Table 3. Correlation between Two-Year DFS Rates and Different Prognostic Factors

Studied Variables	2-year DFS (%)	P
Age in years		
≤ 50	7.8	0.119
>50	0.0	
Gender		
Male	5.2	0.635
Female	3.3	
Karnofsky performance status		
<80	0.0	0.293
80-90	6.6	
Tumor site		
nasopharynx	15.4	
hypopharynx	0.0	0.004*
oropharynx	0.0	
Tumor stage		
T1 & T2	4.6	1.00
T3 & T4	3.1	
Nodal status		
N0 & N1	6.2	0.299
N2 & N3	0.0	
Stage before treatment		
I & II	7.0	0.319
III & IV	1.9	
Line of treatment		
Radiotherapy alone	24	0.636
Radio-chemotherapy	74	

Table 4. Correlation between Treatment Failure and Different Prognostic Factors

Prognostic factor	No. of patients	Incidence of treatment failure		P value
		No.	%	
Age in years				
≤ 50	41	16	42.1	0.986
>50	56	22	57.9	
Gender				
Male	60	18	47.5	0.142
Female	37	20	52.5	
Karnofsky performance status				
<80	36	25	65.8	0.002*
80-90	61	13	34.2	
Tumor site				
nasopharynx	26	6	15.8	
hypopharynx	56	26	68.4	0.384
oropharynx	15	6	15.8	
Tumor size				
≥10cm^3	50	28	73.7	0.019*
<10 cm^3	47	10	26.3	
Tumor stage				
T1	29	4	10.5	
T2	20	8	21.05	0.097
T3	36	18	47.4	
T4	12	8	21.05	

Nodal status				
N0	49	10	26.3	
N1	26	10	26.3	0.006*
N2	19	17	44.8	
N3	3	1	2.6	
Stage before treatment				
I	16	3	7.9	
II	19	7	18.4	0.501
III	27	10	26.3	
IV	35	18	47.4	
Line of treatment				
Radiotherapy alone	41	23	56	0.237
Radio-chemotherapy	56	20	33.7	

Table 5. Grade 3/4 Acute and Late Toxicity in All (n=) 97 Patients with Pharyngeal Carcinoma

Grade 3/4 Acute Toxicity				
Treatment related toxicity	**RT alone (n = 41)**		**RCT With DCF (n = 56)**	
	No	%	No	%
Leucopenia	0	0	27	48.2
Thrombocytopenia	0	0	2	3.6
Anemia	0	0	4	7.1
Nephrotoxicity	0	0	2	3.6
Diarrhea	0	0	2	3.6
Dysphagia	8	19.5	12	21.4
Nausea/vomiting	0	0	9	16.1
Mucositis	23	56.09	43	76.8
Xerostomia	28	68.3	41	73.2
Neutropenic sepsis	0	0	5	8.9
Skin reaction	20	48.8	27	48.2
Hoarseness of voice	0	0	2	3.6
Grade 3/4 Late Toxicity				
Treatment related toxicity	**RT alone (n = 41)**		**RCT With DCF (n = 56)**	
	No	**%**	**No**	**%**
Mucositis	1	2.4	4	7.1
Skin reaction	1	2.4	2	3.6
Arytenoids edema	2	4.8	0	0
Xerostomia	3	7.3	4	7.1

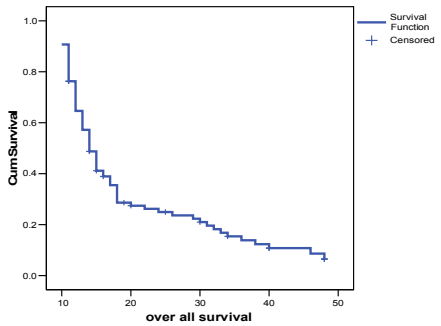

Figure 1. Overall- survival for all patients (n = 97) in both treatment groups.

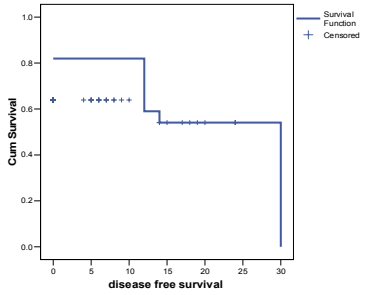

Figure 2. Disease-free survival for patients who achieved complete response (n = 31) in both treatment groups.

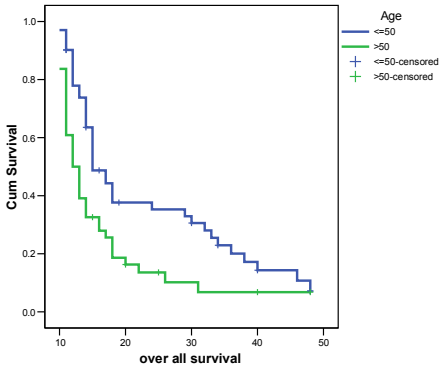

Figure 3. Overall- survival according to age.

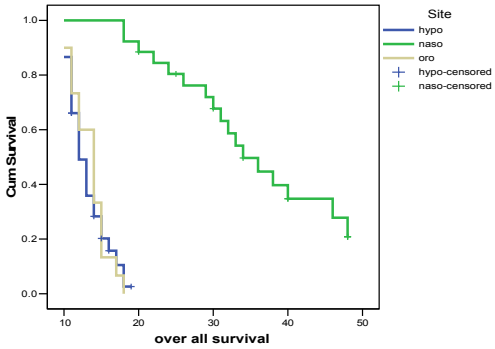

Figure 4. Overall- survival according to tumor site.

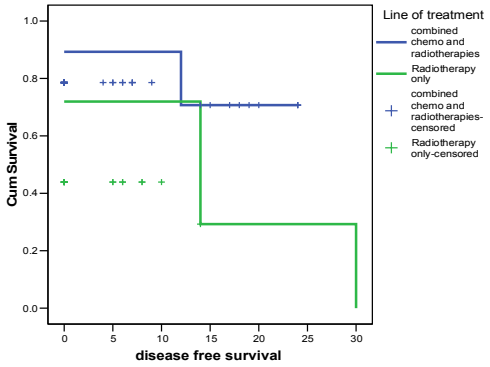

Figure 5. Disease-free survival according to line of treatment.

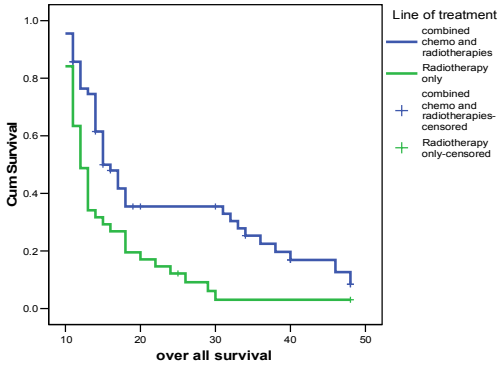

Figure 6. Overall- survival according to line of treatment.

4. Discussion

Pharyngeal cancer is usually diagnosed at advanced clinical stages (approximately 70% of the reported cases)[2,21,22]. Indeed, in the present study, most of the cases (63.9%) were diagnosed at advanced stages (stages III and IV disease).

The 2-year OS was 16.7% for patients with stages III and IV disease in both treatment groups. This survival rate is rather low compared with the 2-year survival rates for patients with stages III and IV disease reported in other studies (30%-50%)[2,23], this difference may be attributed in our series to that, our patients with advanced disease living in socioeconomically disadvantaged populations usually have significant co-morbidities and weight loss. Another major factor is that in our study we included patients with different pharyngeal tumor sites, who were remained in the survival analysis to obtain the actual results of this group of patients.

The TNM stage is a major prognostic factor in most studies on head and neck cancer[11,24-26]. In the present study, the T and N clinical stages significantly correlated with treatment response (all $p = 0.001$) and N clinical stages significantly correlated with treatment failure ($p = 0.006$), similar to the findings reported in other studies[14,23,25,26].

The current study showed that lymph node status at physical examination was an important but not significant prognostic factor for 2-year OS (23.1% for N0-1 and 18.8% for N2-3) similar to the findings reported in other studies[14,23,25,26].

The male patients had higher (but not significant) OS and DFS rates than did the female patients (2-year OS was 25% and 16.2% respectively {$p = 0.447$}, while, the 2-year DFS was 5.2% and 3.3% respectively {$p = 0.635$}). These findings were similar to the findings reported by **Ilstad *et al.***[27] in

multivariate analysis of determinants of survival for patients with squamous-cell carcinoma of the head and neck[27]. However, **Carvalho *et al.*** [22] and **Johansen *et al.*** [25] in their studies have shown that women have a better prognosis[22,25].

The functional effects of the tumor on the patient may be assessed by means of symptoms, the patient's performance status, and co-morbidities[16,28,29]. At diagnosis, patients with several types of cancer can present with functional alterations that impair their physical capabilities or general medical conditions[16,28]. A number of studies have shown the importance of the performance status of the patient in the assessment of survival rates and treatment response[16,30]. Karnofsky performance status is a significant predictor of mortality in several neoplasias, including pharyngeal cancers. The low performance status before treatment is a significant prognostic factor[30,31]. In the present study, Karnofsky performance status was a significant predictor of treatment response ($p = 0.04$), and treatment failure ($p = 0.002$).

There was no statistically significant difference in the 2-year DFS ($p = 0.119$) between patients aged 50 years or less and patients aged more than 50 years, while patients older than 50 years had a significant lowest OS rates ($p = 0.025$). Similar data were reported by **Caroline *et al.*** [32], and **Grabenbauer *et al.*** [33]. In addition, in our study, patients aged 50 years or less had a statistically significant ($p = 0.002$) better complete response rates (41.5% {17/41}) than patients older than 50 years (25% {14/56}). On the other hand, **Lund and Howard**[34]**,** reported a worse prognosis in younger patients (40 years or less). This can be explained in our study that the majority of patients who aged ≤50 years presented with stage I and II tumors (58.5%), while the majority of the patients aged >50 years presented with stage III and IV tumors (80.4%). Also the ratio of grade (I/II) tumor to grade (III/IV) in the group of patients ≤50 years was 1.7:1 compared to 0.56: 1 in the group of patients >50 years.

The selection of patients for radiotherapy[35] has been a challenge because there are no reliable criteria for the prediction of treatment response. Tumor site, macroscopic appearance, and tumor extension have been described as possible predictors of tumor response to treatment[26]. In the present study, we showed a significant better complete response for nasopharynx (76.9% {20/26}) than for tumors of the oropharynx (13.3% {2/15}) and hypopharynx (16.1% {9/56}); ($p = 0.001$). Similarly, the OS and DFS survival rates were higher for nasopharyngeal cancers (2-year OS 80.8% and 2-year DFS 15.4%), while, none of the patients with oropharyngeal or hypopharyngeal carcinoma survived for 2 years and the differences were statistically significant ($p = 0.001$ and $p = 0.004$, respectively). This was in agreement with **Bentzen *et al.*** [36], **Kramer *et al.*** [37], **Tombolini *et al.*** [38], **Mu-Tai *et al.*** [39], **Bijan *et al.*** [40] and **Wang**[41], who reported that the best locoregional control is obtained in case of nasopharyngeal carcinomas. On the other extreme, **Wang**[41] and **Pigott *et al.*** [42]**,** reported that the postcricoid region as the worst site for local control by radical radiotherapy and that hypopharyngeal cancers generally have a poorer prognosis than other head and neck subsites.

The results of this study are disappointing when compared with the more recent literature on chemoradiotherapy[43,44]. These differences deserve future investigation. Possibly we are dealing with different carcinogenesis of pharyngeal carcinomas. In several parts of the world, human papilloma virus is a major risk factor[45-48]. However, in our population the prevalence of human papilloma virus infection is very low. The main risk factor in our population is heavy smoking. These patients usually have significant co-morbidities and weight loss that can explain the poor results.

In this study, we examined the safety and efficacy of radiation therapy either alone or in combination with chemotherapy in patients with newly diagnosed pharyngeal carcinoma. In our study grade 3 mucositis (76.8%) and xerostomia (73.2%) were the commonest acute radiotherapy related complications. Similar findings were reported by **Wendt *et al.*** [49].

In this study Myelo suppression, a well-documented side effect of the combined radiation therapy and chemotherapy in particular neutropenia, was the predominant hematologic toxicity, G3 occurred in 48.2% of patients, followed by anemia in 7.1%. Similar data were reported by **Marshall *et al.*** [50].

There are some controversies about the use of combined radiotherapy and chemotherapy or postoperative radiotherapy in treating pharyngeal cancer[2,10,21]. A number of studies have shown that the association of radiotherapy and chemotherapy can improve the survival results when compared with radiotherapy alone[9,23]. Most of them include only patients who have high performance status, which is not the common situation for patients with advanced disease diagnosed in socioeconomically disadvantaged populations. In the present study, we did not observe any statistically significant difference in survival rates according to the treatment modality (radiotherapy alone or radiotherapy in combination with chemotherapy).

Patients with pharyngeal cancer like those included in this study should probably be considered

in future clinical trials aiming to introduce advances in the treatment of socially disadvantage patients living in geographic areas outside developed world.

Corresponding author
Hanan S. Gamal El-Deen E-mail:
Mailing address: Radiation Oncology Department, Tanta University Hospital, Elbahr street, Tanta, Egypt. hannshawky@yahoo.com

References

1. Mendenhall WM, Riggs CE Jr, Cassisi NJ(2005). Treatment of head and neck cancers. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds.: Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005: pp 662-732.
2. Carvalho AL, Nishimoto IN, Califano JA, *et al*.(2005). Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int J Cancer; 114 (5): 806-816.
3. Jemal A, Siegel R, Ward E, *et al.* (2007). Cancer statistics, 2007. CA Cancer J Clin.; 57 (1): 43-66.
4. Ibrahim AS, Abdel-Bar I, Hussein H, *et al.* (2007). Cancer in Egypt, Gharbiah: triennial report of 2000 – 2002. Gharbiah population-based cancer registry, 1st ed., Egypt; 96-7.
5. Wirth LJ, Allen AM, Posner MR, *et al.* (2010). Phase I dose-finding study of paclitaxel with panitumumab, carboplatin and intensity-modulated radiotherapy in patients with locally advanced squamous cell cancer of the head and neck. Ann Oncol.; 21:342-247.
6. Rosenthal DI, Harris J, Forastiere AA, *et al.* (2009). Early postoperative paclitaxel followed by concurrent paclitaxel and cisplatin with radiation therapy for patients with resected high-risk head and neck squamous cell carcinoma: report of the phase II trial RTOG 0024. J Clin Oncol.; 27: 4727-4732.
7. Haddad R, Sonis S, Posner M, *et al.* (2009). Randomized phase 2 study of concomitant chemoradiotherapy using weekly carboplatin/paclitaxel with or without daily subcutaneous amifostine in patients with locally advanced head and neck cancer. Cancer; 115: 4514-4523.
8. Kies MS, Holsinger FC, Lee JJ, *et al.* (2010). Induction chemotherapy and cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. J Clin Oncol.; 28: 8-14.
9. Posner MR. (2010). Integrating systemic agents into multimodality treatment of locally advanced head and neck cancer. Ann Oncol.; 21 (7): *Pp. vii246-vii251. doi: 10.1093/annonc/mdq291.*
10. Pignon JP, le Maitre A, Maillard E, *et al.* (2009). Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17 346 patients. Radiother Oncol.; 92: 4-14.
11. Chung EJ, Lee NJ, Baek SK, *et al.* (2009). Clinical Efficacy of Primary Tumor Volume Measurements: Comparison of Different Primary Sites. Clin Exp Otorhinolaryngol.; 2 (2): 78-84.
12. Chen PH, Shieh TY, Ho PS, *et al.* (2007). Prognostic factors associated with the survival of oral and pharyngeal carcinoma in Taiwan. BMC Cancer; 7: 101.
13. Burke HB, Henson DE (1993). The American Joint Committee on Cancer: criteria for prognostic factors and for an enhanced prognostic system. Cancer; 72 (10): 3131-3135.
14. Pugliano FA, Piccirillo JF, Zequeira MR, *et al.* (1999). Symptoms as an index of biologic behavior in head and neck cancer. Otolaryngol Head Neck Surg.; 120 (3): 380-386.
15. Piccirillo JF (2000). Importance of comorbidity in head and neck cancer. Laryngoscope; 110 (4): 593-602.
16. Ribeiro KCB, Kowalski LP, Latorre MRDO (2000). Impact of comorbidity, symptoms, and patients' characteristics on the prognosis of oral carcinomas. Arch Otolaryngol Head Neck Surg.; 126 (9):1079-1085.
17. Greene FL, Page DL, Fleming ID, *et al.* (2002). AJCC Cancer Staging Manual. 6. New York: Springer – Verlag.
18. Rubin P, Constine LS, Fajardo LF, *et al.* (1995). RTOG Late Effects Working Group. Overview: Late effects of normal tissue (LENT) scoring system. Int J Radiat Oncol Biol Phys.; 31 (5): 1041-2.
19. Mangino P, Taft B, Djulbegovic B. (1997). Criteria for grading toxicity. In Decision Making in Oncology Evidence Based Management 1st ed., New York, Churchill Livingstone; 454-68.
20. Kaplan EL, Meier P. (1958). Nonparametric estimation from incomplete observations. J Am Stat Assoc.; 53: 457-81.
21. Carvalho AL, Magrin J, Kowalski LP (2003). Sites of recurrence in oral and oropharyngeal cancers according to the treatment approach. Oral Dis.; 9 (3):112-118.
22. Carvalho AL, Ikeda MK, Magrin J, *et al.* (2004). Trends of oral and oropharyngeal cancer survival over five decades in 3267 patients treated in a single institution. Oral Oncol.; 40 (1): 71-76.
23. Kovács AF, Mose S, Bottcher HD, *et al.* (2005). Multimodality treatment including postoperative radiation and concurrent chemotherapy with weekly docetaxel is feasible and effective in patients with oral and oropharyngeal cancer. Strahlenther Onkol.; 181 (1): 26-34.
24. American Joint Committee on Cancer (1997). Purposes and principles of staging. In: AJCC Cancer Staging Manual. 6th ed. Philadelphia, PA: Lippincott-Raven; 1997:3-9.
25. Johansen LV, Grau C, Overgaard J. (2000). Squamous cell carcinoma of the oropharynx an

analysis of treatment results in 289 consecutive patients. Acta Oncol.; 39 (8): 985-994.
26. Sundaram K, Schwartz J, Har-El G, *et al.* (2005). Carcinoma of the oropharynx: factors affecting outcome. Laryngoscope; 115 (9): 1536-1542.
27. Ilstad ST, Tollerud DJ, Bigelow ME, *et al. (*1988). A multivariate analysis of determinants of survival for patients with squamous-cell carcinoma of the head and neck. Ann Surg.; 209 (2): 237 – 241.
28. Piccirillo JF, Feinstein AR (1996). Clinical symptoms and comorbidity: significance for the prognostic classification of cancer. Cancer; 77 (5): 834-842.
29. Piccirillo JF, Wells CK, Sasaki CT, *et al.* (1994). New clinical severity staging system for cancer of the larynx: five-year survival rates. Ann Otol Rhinol Laryngol.; 103 (2): 83-92.
30. Mick R, Vokes EE, Weichselbaum RR, *et al.* (1991). Prognostic factors in advanced head and neck cancer patients undergoing multimodality therapy. Otolaryngol Head Neck Surg.; 105 (1): 62-73.
31. Awwad HK, Khafagy Y, Barsoum M, *et al.* (1992). Accelerated versus conventional fractionation in the postoperative irradiation of locally advanced head and neck cancer. Radioth Oncol.; 25: 261 – 6.
32. Caroline HS, Brian LS, Richard CK (2005). Tongue and tonsil carcinoma, increasing trends in the U.S. population ages 20 – 44 years. Cancer; 103: 1843 – 9.
33. Grabenbauer GG, Stieninger H, Meyer M, *et al.* (1998). Nodal density and total tumor volume as prognostic factors after radiation therapy of stage III and IV head and neck cancer. Radioth Oncol.; 47: 175 – 183.
34. Lund VJ, Howard DJ (1990). Head and neck cancer in the young: a prognostic conundrum? J Laryngol Otol.; 105: 544-8.
35. Ko C, Citrin D (2009). Radiotherapy for the management of locally advanced squamous cell carcinoma of the head and neck. Oral Dis.; 15 (2): 121–132.
36. Bentzen SM, Johansen LV, Overgaard J, *et al.* (1991). Clinical radiobiology of squamous cell carcinoma of the oropharynx., Int J Radiat Oncol Biol Phys.; 20: 1197-1206.
37. Kramer S, Victor MA, Pajak FT, *et al.* (1986). Prognostic factors for locoregional control and metastasis and the impact on survival. Int J Radiat Oncol Biol Phys.; 12: 573-8.
38. Tombolini V, De Sanctis V, Donato V (2001). Prognostic features and treatment outcome in patients with nasopharyngeal carcinoma: an experience of 20 years. Anticancer Res.; 21: 1413-8 **.**
39. Mu-Tai L, Chang-Yao H, Tung-Hao C (2003). Prognostic Factors Affecting the Outcome of Nasopharyngeal Carcinoma. *Japanese Journal of Clinical Oncology*; 33: 501-508.
40. Bijan K, Jalal M, Shapour O (2006). Treatment Results of Nasopharyngeal Carcinoma: A 15-Year Single Institutional Experience. Journal of the Egyptian Nat. Cancer Inst.; 18 (2): 147-155.
41. Wang CC (1990). Radiation Therapy for Head and Neck Neoplasm: Indications, Techniques, and Results. 2nd ed., Chicago, Year Book Medical Publisher Inc.: pp 110-281.
42. Pigott KH, Hische S, Saunders MI (1993). The long term outcome after radical radiotherapy for advanced head and neck cancer, Clin Oncol.; 5: 343-349.
43. Milisavljevic D, Stankovic M, Zivic M, *et al.* (2009). Factors affecting results of treatment of Hypopharyngeal Carcinoma. Hippokratia; 13 (3): 154–160.
44. Cognetti DM, Weber RS, Lai SL (2008). Head and Neck Cancer: An Evolving Treatment Paradigm. Cancer; 113 (7): 1911–1932.
45. Chaturvedi AK, Engels EA, Anderson WF, *et al.* (2008). Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol.; 26: 612-619.
46. Gillison ML, Harris J, Westra W, *et al.* (2009). Survival outcomes by tumor human papillomavirus (HPV) status in stage III-IV oropharyngeal cancer (OPC) in RTOG 0129. J Clin Oncol.; 27 Suppl. (Abstr 6003).
47. Rischin D, Young R, Fisher R, *et al.* (2009). Prognostic significance of HPV and p16 status in patients with oropharyngeal cancer treated on a large international phase III trial. J Clin Oncol.; 27 Suppl. (Abstr 6004).
48. Fakhry C, Westra WH, Li S, *et al.* (2008). Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst.; 100:, 261-269.
49. Wendt GT, Gerhard GG, Claus MR (1998). Simultaneous Radiochemotherapy Versus Radiotherapy Alone in Advanced Head and Neck Cancer: A Randomized Multicenter Study. J Clin Oncol.; 16 (4): 1318-24.
50. Marshall RP, Diane MH, Cesar RB (2007). Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer **.** N Engl J Med.; 357 (17): 1705-15.

9/26/2011