AIM OF THE WORK

The aim of this retrospective study is to review the files of patients with oral cavity, oropharynx and hypopharyngeal cancer presented to clinical oncology and nuclear medicine department, Alexandria University from January 2003 to December 2012 aiming at:

1. Reviewing the demographic data and clinicopathological features of these patients.
2. Reviewing all the treatment lines received by these patients (local and systemic lines of treatment).
3. Assessing the treatment results.
4. Developing an electronic data sheet for these patients as a part of a computerized system for future data entry.

MATERIALS & METHODS

Patients:

299 patients diagnosed with oral, oropharyngeal, or hypopharyngeal cancer were registered in Alexandria clinical oncology and nuclear medicine Department (ACOD) registry between January 2003 and December 2012.

A total of 255 patients who had detailed medical records were included in this study. Those patients presented to ACOD, Alexandria Main University Hospital between January 2003 and December 2012, and were diagnosed with oral, oropharyngeal or hypopharyngeal cancer.

Methods

Medical records were retrospectively reviewed and the following data were retrieved:

1. Patients' age and sex.
2. Associated comorbidities.
3. Primary tumor site.
4. History of predisposing risk factors including smoking, oral hygiene, broken tooth, and precancerious lesions such as leukoplakia.
5. Presenting signs and symptoms.
6. Documented Pathological data.
7. Investigations done to assess patients' general condition and stage of the disease.
8. Staging was done using the recorded clinical examination & radiological data according to American Joint Commission of Cancer (7th edition, 2010) staging guidelines.
9. Treatment administered at our hospital.
10. Survival outcomes: patients who were lost to follow up after finishing their treatment were excluded from survival outcomes analysis, in addition to those patients presented to our hospital in the year 2012. Overall survival (OS) was measured from the date of diagnosis to the date of death or the date of the last follow-up visit. Disease free survival (DFS) was measured from the date of completion of treatment to the date of first relapse (local, regional, or distant) or the date of last follow-up.

All these data were collected and arranged in a master table for statistical analysis.

Statistical Methods

Data were fed to the computer and analyzed using IBM *SPSS software package version 20.0.*

Qualitative data were described using numbers and percents. Quantitative data were described using median, minimum and maximum, as well as mean and standard deviation.

The rates of overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method.

Association between categorical variables was tested using chi square test.

Significance of the obtained results was judged at the 5% level.

RESULTS

Distribution of study cases among head and neck cancers:

Oral, oropharyngeal, and hypopharyneal cancers constitute an average of 29.9 cases annually, nearly about 29.2% of head and neck cancers excluding thyroid cancer, and about 1.22% of all body tumors. Table (1) demonstrates distribution of our study cases annually.

Table (1): Distribution of the studied cases in relation to all head and neck cancer and all body tumors:

	All cancer cases	H&N cancer cases	Oral, oroph and hypoph cancer cases		
			No	% from H&N cancer cases	% from all body tumors
2003	2600	93	23	24.7	0.9
2004	2576	84	23	27.4	0.9
2005	2413	78	24	30.8	1.0
2006	2429	91	26	28.6	1.1
2007	2567	104	35	33.7	1.4
2008	2489	128	34	26.6	1.4
2009	3436	162	46	28.4	1.3
2010	2574	132	34	25.8	1.3
2011	1989	82	21	25.6	1.1
2012	1811	81	33	40.7	1.8
Mean	**2488.4±428**	**103.5±28.09**	**29.9±7.8**	**29.2±4.8**	**1.22±0.3**

Distribution of patients according to primary tumor site:

Patients diagnosed with hypopharyngeal cancer were 104 (40.8%), oral cavity cancer were 98 (38.4%), and oropharyngeal cancers were 53 (20.8%). Table (2) demonstrates distribution of our study cases according to primary diagnosis.

Table (2): Distribution of the studied cases according to primary site (n=255)

	No	%
Diagnosis		
Hypopharyngeal	104	40.8
Oral cavity	98	38.4
Oropharyngeal	53	20.8
Total	**255**	**100.0**

Distribution of hypopharyngeal cancer patients according to primary involved subsite:

Table (3) demonstrates hypopharyngeal cancer patients' distribution according to primary involved subsite. Postcricoid region was the most common involved primary subsite, constituting about 76.0% of all hypopharyngeal cancer patients.

Table (3): Distribution of hypopharynx cancer cases according to primary involved subsite (n=104)

Hypopharynx	No	%
Primary site		
Postcricoid region	79	76.0
Pyriform fossa	16	15.3
Lat. pharengeal wall	9	8.7
Total	**104**	**100.0**

Distribution of oral and oropharyngeal cancer patients according to primary involved subsite:

Table (4) demonstrates oral and oropharyngeal cancer patients' distribution according to primary involved subsite. The tongue was the most commonly involved subsite at diagnosis (about 57.6% of cases) followed by tonsils (about 15.2% of cases) and retromolar trigone (about 8.6% of cases).

Table (4): Distribution of oral and oropharynx cancer cases according to primary site (n=151)

Oral and oropharynx	No	%
Primary site		
Tongue	87	57.6
Tonsils	23	15.2
Retromolar trigone	13	8.6
Soft palate	10	6.6
Floor of mouth	6	4.0
Buccal mucosa	6	4.0
Alveolar ridge	5	3.3
Hard palate	1	0.7
Total	**151**	**100.0**

Patients' characteristics (age & sex):

Mean age at diagnosis was about 52.91 ± 13.23 for hypopharyngeal cancer patients and about 54.40 ± 12.66 for oral and oropharyngeal cancer patients. Males were more commonly involved among oral and oropharyngeal cancer patients, while among hypopharyngeal cancer patients females were slightly more commonly affected (54.8%). Table (5) demonstrates oral and hypopharyngeal cancer patients' characteristics.

Tables (5): Distribution of studied patients according to epidemiologic data

Hypopharynx (n=104)	**No**	**%**
Age		
<50	36	34.6
>50	68	65.4
Total	**104**	**100.0**
Sex		
Male	47	45.2
Female	57	54.8
Total	**104**	**100.0**
Actual age		
Min. – Max.	16.0 – 85.0	
Mean ± SD	52.91 ± 13.23	
Oral and Oropharynx (n=151)	**No**	**%**
Age		
<50	57	37.7
>50	94	62.3
Total	**151**	**100.0**
Sex		
Male	86	57.0
Female	65	43.0
Total	**151**	**100.0**
Actual age		
Min. – Max.	26.0 – 83.0	
Mean ± SD	54.40 ± 12.66	

Associated comorbidities

Table (6) shows distribution of associated diseases among all patients. Diabetes mellitus and hypertension were the most common associated diseases found in 30 patients (11.8% of all patients).

Tables (6): Distribution of studied cases according to associated co morbidities: (n=255)

Medical conditions	No	%
No Associated comorbidities	211	82.7
Diabetes mellitus (DM)	10	3.9
hypertension (HTN)	15	5.9
DM&HTN	5	2.0
TB	1	0.4
Cholecystitis	1	0.4
Bronchial Asthma	1	0.4
HCV (+VE)	8	3.1
Cardiac disease	2	0.8

Predisposing risk factors

As regards predisposing risk factors, 40.8% of all patients were smokers, 28.6% showed poor oral hygiene, 7.8% of patients had broken tooth, and 2.7% of patients had precancerious leukoplakia lesions. Alcohol consumption couldn't be assessed due to unavailable data. Table (7) demonstrates predisposing risk factors among study patients.

Tables (7): Distribution of all patients according to predisposing factors (n = 255)

Predisposing factors	No	%
No evident predisposing factor	108	42.35
Smoking	104	40.8
Bad oral hygene	73	28.6
Broken tooth	20	7.8
Leukoplakia	7	2.7

Clinical presentation

The most common symptom at presentation was clinically apparent regional LNs involvement in 59.2% of all patients followed by dysphagia in 54.1%, ulcer in 40.4%, pain in 35.3%, and weight loss in 23.9% of all patients. Other less common symptoms were hoarseness, sore throat, odynophagia, stridor, hemoptysis and otalgia. Table (8) demonstrates distribution of studied patients according to presenting signs and symptoms.

Table (8): Distribution of our study patients according to presenting signs and symptoms (n=255)

Signs and symptoms	No	%
Cervical LNs enlargement	151	59.2
Dysphagia	138	54.1
Ulcer	103	40.4
Pain	90	35.3
Wt loss	61	23.9
Hoarseness	36	14.1
Sore throat	25	9.8
Odynoghagia	24	9.4
Stridor	10	3.9
Hemoptysis	11	4.3
Otalgia	11	4.3

Histopathological data

Squamous cell carcinoma (Sq.CC) is the most common histopathologic type among all patients constituting about 92.6%. Moderately differentiated tumors were the most common variant representing nearly 54.1% of all patients. Other types included lymphoma, adenocarcinoma and anaplastic carcinoma. Table (9) demonstrates distribution of all patients according to histopathological data.

Tables (9): Distribution of all patients according to histopathological types (n = 255)

Pathology	No	%
Well diff Sq.CC	51	20.0
Moderate diff. Sq.CC	138	54.1
Poorly diff. Sq.CC	30	11.8
Sq.CC (unspecified)	17	6.7
Sq.cc acantholytic adenoid	1	0.4
Adenocarcinoma	6	2.4
Lymphoma (NHL)	11	4.3
Anaplastic carcinoma	1	0.4
Total	**255**	**100.0**

Staging of hypopharyngeal cancer patients: (according to AJCC 2010)

Table (10) shows staging of hypopharyngeal cancer patients. Most of patients presented at advanced disease stage (stage III, IV), about 90.3% of all patients. 6 patients (5.8%) were metastatic at diagnosis.

Tables (10): Distribution of hypopharynx cancer cases according to stage at diagnosis (n=104)

	No	%
Staging T		
T1	0	0.0
T2	7	6.7
T3	49	47.1
T4a	33	31.7
T4b	7	6.7
Unspecified	8	7.7
Total	**104**	**100.0**
Staging N		
N0	32	30.8
N1	15	14.4
N2a	4	3.8
N2b	39	37.5
N2c	6	5.8
N3	0	0.0
Unspecified	8	7.7
Total	**104**	**100.0**
Staging M		
M0	90	86.5
M1	6	5.8
Unspecified	8	7.7
Total	**104**	**100.0**
Stage (AJCC 2010)		
0	0	0.0
I	0	0.0
II	5	4.8
III	31	29.8
IVA	43	41.3
IVB	14	13.5
IVC	6	5.8
Unspecified	5	4.8
Total	**104**	**100.0**

Staging of oral and oropharyngeal cancer patients: (according to AJCC 2010)

Table (11) describes staging of oral and oropharyngeal cancer patients. Nearly 71.3% of patients presented at stage III, IV disease, and 20.7% of patients presented at stage I, II disease. Only one patient was metastatic at diagnosis.

Tables (11): Distribution of oral and oropharynx cancer cases according to stage (n=140)

	No	%
Staging T		
T1	4	2.9
T2	44	31.4
T3	54	38.6
T4a	19	13.6
T4b	5	3.6
Unspecified	14	10.0
Total	**140**	**100.0**
Staging N		
N0	48	34.3
N1	42	30.0
N2a	2	1.4
N2b	31	22.1
N2c	2	1.4
N3	1	0.7
Unspecified	14	10.0
Total	**140**	**100.0**
Staging M		
M0	125	89.3
M1	1	0.7
Unspecified	14	10.0
Total	**140**	**100.0**
Stage (AJCC)		
0	0	0.0
I	3	2.1
II	26	18.6
III	60	42.9
IVA	32	22.9
IVB	7	5.0
IVC	1	0.7
Unspecified	11	7.9
Total	**140**	**100.0**

Clinical and imaging investigations of all patients

Data about investigations done for evaluation of patients are presented in table (12). Ultrasonography of the neck was done in 39.2% of patients, chest x-ray was done in 76.9%of patients and CT of neck and chest was done in 87.5% and 24.3% of patients. Regarding endoscopy, 52.9% of patients underwent either indirect laryngoscopy or panendoscopy. BA swallow was done in 38% of patients.

Tables (12): Distribution of all cases according to investigations (n=255)

	No	%
Lab		
unknown	32	12.5
Normal	202	79.2
Abnormal	21	8.2
Total	**255**	**100.0**
Us neck		
Not done	155	60.8
done	100	39.2
Total	**255**	**100.0**
CT neck		
Not done	32	12.5
done	223	87.5
Total	**255**	**100.0**
CXR		
Not done	59	23.1
done	196	76.9
Total	**255**	**100.0**
BA swallow		
Not done	158	62.0
Yes	97	38.0
Total	**255**	**100.0**
CT chest		
Not done	193	75.7
done	62	24.3
Total	**255**	**100.0**
Endoscopy		
Not done	120	47.1
laryngoscope	64	25.1
Pan endoscopy	71	27.8
Total	**255**	**100.0**

Type of biopsy

22.3% and 63.2%of patients underwent either excision or incision surgical biopsy. Punch biopsy done during endoscopy was done in 10.3% of patients. 4.1% of patients were diagnosed using FNA from pathologically enlarged LN. Details about numbers and percentages of patients underwent various biopsy types are showed in table 13.

Tables (13): Distribution of the all patients according to type of biopsy

	No	%
Type of biopsy		
Incisional	154	63.1
Excisional	54	22.3
Endoscopic	25	10.3
FNA of enlarged LN	11	4.1
Total	**244**	**100.0**

Patients who were managed at our hospital:

Only those patients who were managed at our hospital were included in statistical analysis of survival outcomes. Lymphoma cases (11 patients diagnosed with oral or oropharyngeal lymphoma) were excluded from further analysis. Table (14) demonstrates number and percentage of patients managed at our department.

Tables (14): Distribution of the studied cases according to whether patients received treatment or not

Patients who received treatment	No	%
Hypopharynx		
No	27	26.0
Yes	77	74.0
Total	**104**	**100.0**
Oral and Oropharynx		
No	15	9.9
Yes	136	90.1
Total	**151**	**100.0**

Therapeutic modalities

Various treatment options were used in management of our study patients. 22 patients (28.6%) who had hypopharyngeal cancer and 43 patients (34.4%) who had oral or oropharyngeal cancer were managed by surgery followed by adjuvant treatment. Chemoradiotherapy (CRTx) was used in 25 patients with hypopharyngeal cancer and in 21 patients with oral or oropharyngeal cancer. CRTx includes both induction chemotherapy followed by radiation therapy and concomitant chemoradiotherapy. Table (15) demonstrates various treatment types administered to our study patients.

Table (15): Distribution of all patients according to treatment modality

Type of treatment	No	%
Hypopharynx (n = 77)		
Surgery + RTx	12	15.6
Surgery + CCRTx	6	7.8
Surgery + chemo + CCRTx	4	5.2
Induction chemotherapy + RTx	9	11.7
Definitive CCRTx	6	7.8
Induction chemotherapy + CCRTx	10	13
Radiotherapy only	7	9
Surgery only	9	11.7
Chemotherapy only	11	14.3
Surgery + Chemotherapy	3	3.9
Oral and Oropharynx (n = 125)		
Surgery +RTx	25	20
Surgery + chemo + RTx	3	2.4
Surgery + CCRTx	13	10.4
Surgery + chemo + CCRTx	2	1.6
Induction chemotherapy + RTx	10	8
Definitive CCRTx	7	5.6
Induction chemotherapy + CCRTx	4	3.2
Radiotherapy only	18	14.4
Surgery only	27	21.6
Chemotherapy only	13	10.4
Surgery + Chemotherapy	3	2.4

Surgery

Some patients underwent surgery as a primary treatment. Radical surgery or conservative approaches were both options according to disease stage at diagnosis. 40.3% of hypopharyngeal cancer patients were managed by surgery which was either total laryngopharyngectomy or partial laryngopharyngectomy with LNs dissection. In addition, 58.8% of oral and oropharyngeal cancer patients were managed by surgery. Table (16) demonstrates distribution of all patients according to surgical treatment.

Table (16): Distribution of all patients according to surgical treatment

Surgery	No	%
Hypopharynx (n = 77)		
Surgery not done	43	59.7
Total laryngopharyngectomy	31	36.4
Partial laryngoph. + LN dis.	3	3.9
Oral and Oropharynx (n = 125)		
Surgery not done	52	41.1
Hemiglossectomy	3	2.4
Hemiglossectomy & LN dis.	37	29.8
Tumor excision & LN dis.	33	26.6

Post operative pathological data

Table (17) demonstrates details of available data regarding multiple positive LNs and surgical margin status. Data were very limited regarding post operative pathological risk features. Comments on pathological LNs and surgical margin were available in few medical records but not detailed. Data about extracapsular nodal extension, lymphovascular invasion, and perineural invasion were mostly not available.

Tables (17): Distribution of the studied cases according to multiple positive LNS and positive margin

Hypopharynx (n = 34)	No	%
Multiple positive LNS		
No	26	74.2
Yes	8	25.8
Positive margin		
No	33	96.8
Yes	1	3.2
Oral and Oropharynx (n = 73)	**No**	**%**
Multiple positive LNS		
No	48	65.8
Yes	25	34.2
Positive margin		
No	69	94.5
Yes	4	5.5

Surgery-radiation time interval

Most of patients were delayed to receive postoperative adjuvant therapy as described in table 18. Surgery radiation time interval ranged from 4 to 25 weeks for hypopharyngeal cancer patients (mean value of 12.16 ± 7.09) and from 4 to 24 weeks for oral and oropharyngeal cancer patients (mean value of10.85 ± 5.05).

Tables (18): Distribution of the studied cases according to surgery radiation time interval

Surgery radiation time interval (weeks)	Min. – Max.	Mean ± SD	Median
Hypopharynx	4.0 – 25.0	12.16 ± 7.09	10.0
Oral and Oropharynx	4.0 – 24.0	10.85 ± 5.05	10.0

Chemotherapeutic regimens

Tables (19, 20) show description of chemotherapeutic regimens administered to hypopharyngeal, oral, and oropharyngeal cancer patients. Cisplatin-5FU was the most commonly used chemotherapeutic regimen for both hypopharyngeal and oral cancer patients. Mean value for number of cycles was about (3.16 ± 2.01) for hypopharyngeal cancer patients and about (2.86 ± 1.50) for oral and oropharyngeal cancer patients.

Table (19): Distribution of all hypopharyngeal cancer patients according to chemotherapeutic treatment

Hypopharynx (n = 77)	No	%
Chemotherapy		
No	40	51.9
Yes	37	48.1
Regimen 1 (n = 37)		
Cisplatin-5fu	36	97.3
TPF	1	2.7
No of cycles (n = 37)		
Min. – Max.	1.0 – 11.0	
Mean ± SD	3.16 ± 2.01	
Median	3.0	
Response (n = 37)		
lost follow up	7	18.9
Complete clinical response	6	16.2
Partial response	16	43.2
Progressive disease	8	21.6
Regimen 2 (n = 2) **(on disease progression)**		
Methotexate (weekly)	1	50.0
TPF	1	50.0
No of cycles (n = 2)		
Min. – Max.	1.0 – 2.0	
Mean ± SD	1.50 ± 0.71	
Median	1.50	

Tables (20): Distribution of all oral and oropharyngeal cancer patients according to chemotherapeutic treatment

Oral and Oropharynx (n = 125)	No	%
Chemotherapy		
No	90	72.0
Yes	35	28.0
Regimen1 (n = 35)		
Cisplatin-5fu	35	100.0
No of cycles (n = 35)		
Min. – Max.	1.0 – 6.0	
Mean ± SD	2.86 ± 1.50	
Median	3.0	
Response (n = 35)		
lost follow up	5	14.3
Complete clinical response	4	11.4
Partial response	18	51.4
Progressive disease	8	22.9
Regimen 2 (n = 1) (on disease progression)		
Taxol-carboplatin	1	100.0
No of cycles (n = 1)	4.0	

Concomitant chemo-radiotherapy (CCRTx) in hypopharyngeal cancer patients

33.8% of hypopharyngeal cancer patients received CCRTx either as a definitive treatment or as an adjuvant therapy after surgery. Mean total radiation dose was about 51.38 ± 13.51Gy over 1.8 – 2Gy/fraction concomitantly administered with a median of 3 chemotherapy cycles (mostly weekly cisplatin). It is of note that Rtx was interrupted in 92.3% of patients. Table (21) describe details of CCRTx administered to hypopharyngeal patients

Tables (21): Distribution of hypopharyngeal cancer patients according to concomitant chemo-radiotherapy (CCRTx)

Hypopharynx (n = 77)	No	%
CCRTx		
Yes	26	33.8
No	51	66.2
CC regimen (n = 26)		
Cisplatin wkly	18	69.2
Cisplatin-5fu	7	26.9
Carboplatin-5fu	1	3.8
No of cycles (n = 26)		
Min. – Max.	1.0 – 9.0	
Mean ± SD	3.58 ± 1.72	
Median	3.0	
Total radiation dose (n = 26)		
Min. – Max.	16.0 – 72.0	
Mean ± SD	51.38 ± 13.51	
Median	45.0	
No of fractions (n = 26)		
Min. – Max.	8.0 – 36.0	
Mean ± SD	25.42 ± 7.28	
Median	25.0	
RTx interruption (n = 26)		
Yes	24	92.3
No	2	7.7
Response (n = 26)		
Lost follow up	4	15.4
Complete clinical response	11	42.3
Partial response	8	30.8
Progressive disease	3	11.5

Concomitant chemo-radiotherapy (CCRTx) in oral& oropharyngeal cancer patients

20.8% of oral and oropharyngeal cancer patients were managed by CCRTx either as a definitive treatment or as an adjuvant therapy after surgery. Mean value of total radiation dose was about 53.96 ± 12.54Gy over 1.8 – 2Gy/fraction administered concomitantly with median of 4 chemotherapy cycles (mostly weekly cisplatin). RTx was interrupted in 88.5% of patients. Table (22) describes CCRTx administered to oral and oropharyngeal cancer patients.

Tables (22): Distribution of Oral and Oropharynx cases according to concomitant chemo-radiotherapy

Oral and Oropharynx (n = 125)	No	%
CCRTX		
Yes	26	20.8
No	99	79.2
CC regimen (n = 26)		
Cisplatin weekly	23	88.5
Cisplatin-5fu	3	11.5
No of cycles (n = 26)		
Min. – Max.	2.0 – 6.0	
Mean ± SD	3.81 ± 1.21	
Median	4.0	
Total radiation dose (n = 26)		
Min. – Max.	14.0 – 70.0	
Mean ± SD	53.96 ± 12.54	
Median	57.0	
No of fractions (n = 26)		
Min. – Max.	7.0 – 35.0	
Mean ± SD	27.08 ± 6.29	
Median	28.50	
Rtx interruption (n = 26)		
Yes	23	88.5
No	3	11.5
Response (n = 26)		
Lost follow up	7	26.9
Complete clinical response	12	46.2
Partial response	6	23.1
Progressive disease	1	3.8

Radiation therapy in hypopharyngeal cancer patients

28 hypopharyngeal cancer patients (36.4% of patients) received RTx either as an adjuvant therapy or as a primary treatment. Mean value of radiation dose was 44.57 ± 14.54 divided on a mean of 21.89 ± 8.01 fractions using conventional fractionation. It must be noted that 75% of patients experienced interruption of radiation therapy. Table (23) describes details of radiation therapy administered to hypopharyngeal cancer patients.

Tables (23): Distribution of Hypopharyngeal cancer patients according to radiotherapy

Hypopharynx (n = 77)	No	%
Radiotherapy		
No	49	63.6
Yes	28	36.4
Total radiation dose (n = 28)		
Min. – Max.	14.0 – 64.0	
Mean ± SD	44.57 ± 14.54	
Median	45.0	
No of fractions (n = 28)		
Min. – Max.	7.0 – 32.0	
Mean ± SD	21.89 ± 8.01	
Median	22.0	
R interup (n = 28)		
No	7	25.0
Yes	21	75.0
Response (n = 28)		
Lost follow up	8	28.6
Complete clinical response	12	42.9
Partial response	6	21.4
Progressive disease	2	7.1

Radiation therapy in oral & oropharyngeal cancer patients

56 oral or oropharyngeal cancer patients (44.8%of patients) received RTx either as an adjuvant therapy or as primary treatment. Mean value of radiation dose was 46.54 ± 15.28 divided on a mean of 23.05 ± 8.13 fractions using conventional fractionation. It must be noted that 87.5%of patients experienced interruption of radiation therapy. Table (24) describes details of radiation therapy administered to oral and oropharyngeal cancer patients.

Tables (24): Distribution of Oral and Oropharyngeal cancer patients according to radiotherapy

Oral and Oropharynx (n = 125)	No	%
Radiotherapy		
No	69	55.2
Yes	56	44.8
Total radiation dose (n = 56)		
Min. – Max.	10.0 – 66.0	
Mean ± SD	46.54 ± 15.28	
Median	45.0	
No of fractions (n = 56)		
Min. – Max.	5.0 – 33.0	
Mean ± SD	23.05 ± 8.13	
Median	22.0	
R interup (n = 56)		
No	7	12.5
Yes	49	87.5
Response (n = 56)		
Lost follow up	23	41.1
Complete clinical response	25	44.6
Partial response	3	5.4
Progressive disease	5	8.9

Relapse of disease

11 patients (14.3%) of hyphopharyngeal cancer patients and 25 patients (20%) of oral and oropharyngeal cancer patients who were managed at our department developed recurrence either loco-regional or distant metastatic disease during follow up. Table (25) describes recurrence of disease in patients who were managed at our hospital.

Tables (25): Distribution of all patients according to development of relapse

Hypopharynx (n = 77)	No	%
Recurrence		
No	66	85.7
Yes	11	14.3
Site (n=11)		
Loco-regional	8	72.7
Distant	2	18.2
Both	1	9.1
Site of distant (n=3)		
Lung	1	33.3
Liver	1	33.3
Brain	1	33.3
Oral and Oropharynx (n = 125)	**No**	**%**
Recurrence		
No	100	80.0
Yes	25	20.0
Site (n=25)		
Loco-regional	19	76.0
Distant	0	0.0
Both	6	24.0
Site of distant (n= 6)		
Lung	5	83.3
Brain	1	16.7

Salvage therapy of hypopharyngeal cancer patients

8 patients out of 11 relapsed hypopharyngeal cancer patients received salvage treatment. 4 patients received palliative chemotherapy, 3 patients received palliative chemoradiotherapy and one patient underwent surgery. Table (26) describes salvage therapy used in management of recurrent disease in hypopharyngeal cancer.

Tables (26): Distribution of hypopharynx cancer patients according to salvage therapy

Hypopharynx	No	%
Salvage Therapy (n = 11)		
No	3	27.3
Yes	8	72.7
Type		
Chemotherapy (C)	4	50.0
C + Rtx	3	2.9
Surgery only	1	12.5
Chemotherapy Regimen		
Cisplatin-5fu	4	57.1
TAXOL	1	14.3
TAXOL CARBO 5FU	1	14.3
methotrxate weekly	1	14.3
No of cycles		
Min. – Max.	1.0 – 5.0	
Mean ± SD	2.57 ± 1.40	
Median	2.0	
Surgery		
No	10	90.0
Debulking surgery	1	10.0
Ccrtx		
No	10	90.0
Yes	1	10.0
Dose	30.0Gy	
No of fr	10.0	
RTX		
No	9	81.8
Yes	2	18.2
Dose		
Min. – Max.	30.0 – 36.0	
Mean ± SD	33.0 ± 4.24	
Median	33.0	
No of fractions		
Min. – Max.	10.0 – 12.0	
Mean ± SD	11.0 ± 1.41	
Median	11.0	

Salvage therapy of oral and oropharyngeal cancer patients

17 patients received salvage treatment for management of relapsed disease out of 25 patients who developed disease relapse. 10 patients were managed by palliative chemotherapy, 3 patients were managed using palliative chemoradiotherapy, one patient received radiation therapy and 2 patients were managed by surgery and post operative radiation therapy. Table (27) describes salvage therapy for the management of recurrent disease in oral and oropharyngeal cancer patients

Tables (27): Distribution of oral and oropharyngeal cancer patients according to salvage therapy

Oral and Oropharynx	No	%
Salvage Therapy (n = 25)		
No	8	29.2
Yes	17	70.8
Type		
CHEMO	10	58.8
RTx	1	5.9
C+R	3	17.6
CCRTX	2	5.9
S+R	2	11.8
Chemotherapy Regimen		
Cisplatin-5fu	9	60.0
MTX THEN TAXOL	1	6.7
TAXOL CARBO 5FU	5	33.3
No of cycles		
Min. – Max.	1.0 – 6.0	
Mean ± SD	3.07 ± 1.53	
Median	3.0	
Surgery		
No	23	91.3
Hemiglossectomy & LN dis.	1	4.3
tumor excision	1	4.3
Ccrtx		
No	23	91.3
Yes	2	8.7
Dose	66.0Gy	
No of fr	33.0	
RTX		
No	19	72.7
Yes	6	27.3
Dose		
Min. – Max.	20.0 – 40.0	
Mean ± SD	28.33 ± 7.53	
Median	30.0	
No of fractions		
Min. – Max.	5.0 – 20.0	
Mean ± SD	12.50 ± 5.24	
Median	12.50	

Second primary malignancies

six patients developed second primary malignancy after management of the primary tumor. Table (28) shows distribution of patients who developed second primaries and site of these tumors.

Tables (28): Distribution of the studied cases according to 2nd primary

2nd primary	No.	%
Hypopharynx (n = 77)		
No	76	98.7
Tongue	1	1.3
Oral and Oropharynx (n = 125)		
No	120	96.0
Yes	**5**	**4.0**
Tongue	1	0.8
Alveolar margin	1	0.8
Esophagus	1	0.8
Nasopharynx	2	1.6

Palliative measures

According to medical records 10 patients underwent trachesotomy &/or Gastrostomy as shown in table (29).

Tables (29): Distribution of the studied cases according to palliation

Palliation (n = 202)	No.	%
Tracheotomy	7	3.3
Gastrostomy	1	0.5
Tracheotomy + Gastrostomy	2	0.9

Condition at last visit

Large number of patients who were managed at our hospital didn't show up again for follow up. Those patients were excluded from further survival outcomes analysis. Table (30) shows distribution of all patients according to condition at last visit

Tables (30): Distribution of the studied cases according to Condition at last visit

Condition at last visit	No.	%
Hypopharynx (n = 77)		
No evidence of disease	20	24.7
Alive with disease	38	53.4
Lost follow up	18	20.5
Dead	1	1.3
Oral and Oropharynx (n = 125)		
No evidence of disease	42	37.7
Alive with disease	48	43.4
Lost follow up	35	18.9
Dead	0	0.0

Survival outcomes of oral, oropharyngeal, and hypopharyngeal cancer patients

A total of 57 hypopharyngeal cancer patients and 86 oral or oropharyngeal cancer patients were included in survival outcomes analysis. Those patients were managed and presented for post treatment follow up at Alexandria clinical oncology department (ACOD) between January 2003 and December 2011. Overall and disease free survival estimates for oral, oropharyngeal, and hypopharyngeal cancer patients (using Kaplan-Meier method) are shown in figure (1.B&2). For hypopharyngeal cancer patients, Median OS was about 18 months and median DFS was about 6.5 months, while five years OS and DFS were about 17.5% and 56.3% respectively. For oral and oropharyngeal cancer patients, median OS and DFS were about 37 months and 139 months respectively. Five years OS was about 36%, while five years DFS was about 52.2%. By the end of the study (144 months) 24% patients were still alive but 0% were free of disease.

Overall survival

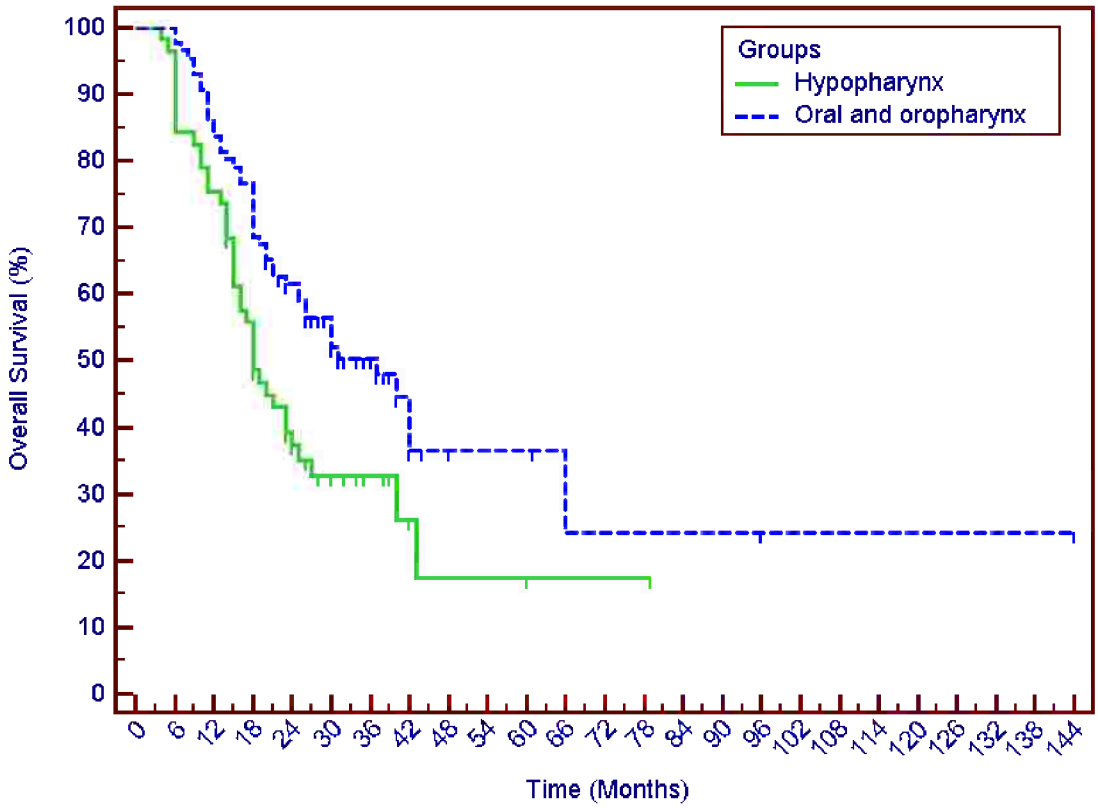

Figure (1.B): Kaplan-Meier overall survival estimates for oral, oropharyngeal, and Hypopharyngeal cancer patients

	Mean (months)	Median (months)	12 month (%)	24 month (%)	36 month (%)	End of study (%)
Hypopharynx	29.83	18.0	75.4	37.3	32.8	17.5
Oral and oropharynx	57.29	37.0	83.7	61.5	50.4	24.3

Disease free survival

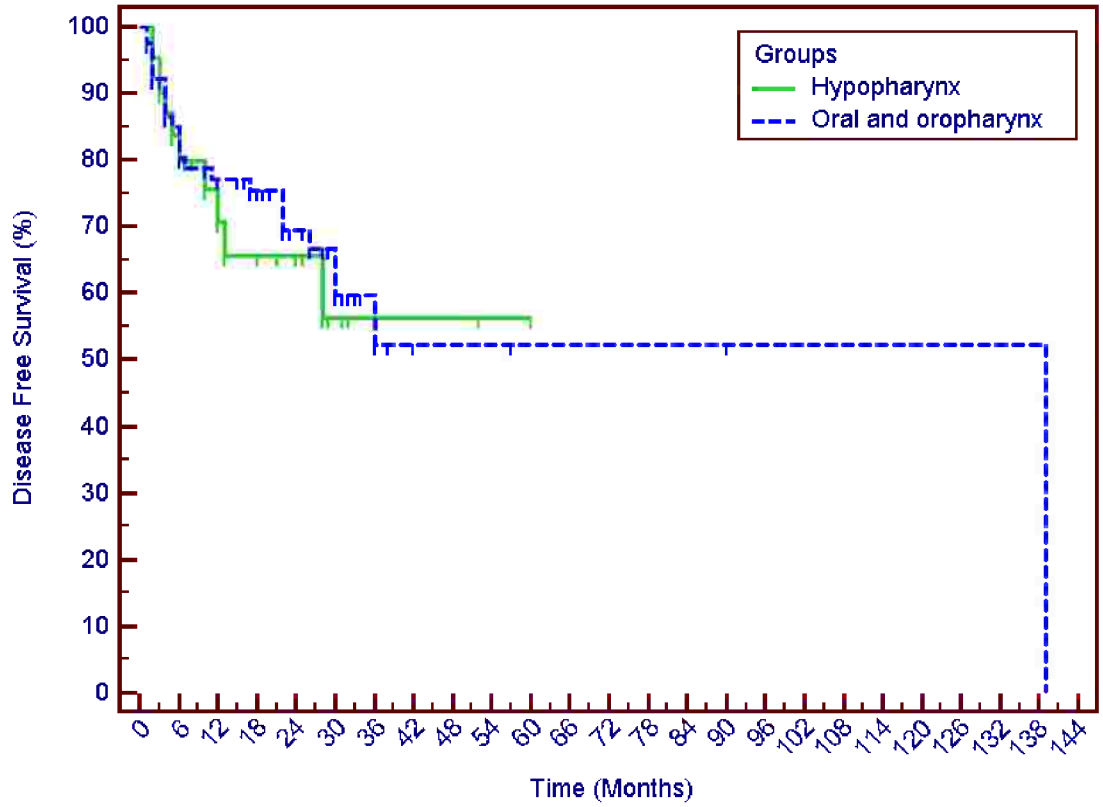

Figure (2): Kaplan-Meier disease free survival estimates for oral, oropharyngeal, and Hypopharyngeal cancer patients

	Mean (months)	Median (months)	12 month (%)	24 month (%)	36 month (%)	End of study (144 months) (%)
Hypopharynx	38.85	6.5	70.8	65.7	56.3	56.3
Oral and oropharynx	80.72	139.0	77.2	69.5	52.2	0.0

In a univariate analysis using Kaplan Meier method, OS and DFS estimates were studied in relation to age of patients, tumor differentiation, overall disease stage, T-stage, N-stage, and treatment modality administered. Effect of other pathological risk features (e.g. multiple positive LNs and positive surgical margin) on survival of patients couldn't be assessed due to limited available data.

Age of patients

Age of patients is significantly associated with better OS for patients less than 50 years of age (log rank p value of <0.001 for hypopharyngeal cancer patients and log rank p value of 0.001 for oral and oropharyngeal cancer patients), but not significantly associated with better DFS (log rank p value of 0.604 & 0.103 respectively).

Regarding hypopharyngeal cancers, median OS was about 18 months for patients less than 50 years of age, 23months for patients between 50 and 70 years of age, and about 6 months for patients more than 70 years of age. Mean value of DFS for hypopharyngeal cancer patients was about 42.30 months for younger age of less 50 years and about 20.69 months for patients between 50 and 70 years of age. Correlation of OS and DFS with age of hypopharyngeal cancer patients is shown in tables 31 & 32.

Table (31): Overall survival estimates of hypopharyngeal cancer patients in relation to patients' age

Age	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
<50	36.37	18.0	89.5	42.1	42.1	28.1	21.672*	<0.001*
50 – 70	24.48	23.0	78.8	40.3	31.7	0.0		
>70	7.0	6.0	-	-	-	0.0		

Table (32): Disease free survival estimates of hypopharyngeal cancer patients in relation to patients' age

Age	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
<50	42.30	-	66.8	66.8	66.8	66.8	0.269	0.604
50 – 70	20.69	28.0	73.8	64.6	-	32.3		
>70	-	-	-	-	-	-		

While in oral and oropharyngeal cancer patients, five years OS deteriorated from 64.7% for patients less than 50 years of age to 23% and 33.3% for patients between 50 and 70 years of age and those patients above 70 years of age respectively. Mean value of DFS for oral and oropharyngeal cancer patients was better for patients less than 50 years about 109.33 months compared to 44.21 months for patients between 50 and 70 years and 13.83 months for patients more than 70 years. As demonstrated in tables 33 & 34

Table (33): Overall survival estimates of oral and oropharyngeal cancer patients in relation to patients' age

Age	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
<50	101.44	-	93.3	83.3	71.9	64.7	13.432*	0.001*
50 – 70	37.05	25.0	85.1	53.1	40.9	12.1		
>70	15.89	11.0	44.4	33.3	-	33.3		

Table (34): Disease free survival estimates of oral and oropharyngeal cancer patients in relation to patients' age

Age	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
<50	109.33	139.0	89.0	76.3	76.3	0.0	4.544	0.103
50 – 70	44.21	30.0	69.7	66.0	36.3	36.3		
>70	13.83	-	66.7	-	-	66.7		

Degree of tumor differentiation

Well and moderately differentiated hypopharyngeal tumors are significantly associated with better DFS (log rank p value of 0.004). Near significant association was found with OS (log rank p value of 0.057). Tables 35 & 36 show correlation of tumor differentiation with OS and DFS.

Table (35): OS estimates in relation to degree of tumor differentiation in hypopharyngeal cancer patients

Pathology	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
Well diff Sq.CC	16.60	15.0	60.0	20.0	-	20.0	5.716	0.057
Moderate diff. Sq.CC	34.09	25.0	74.3	50.4	42.3	22.5		
Poorly diff. Sq.CC	15.56	16.0	77.8	0.0	-	0.0		

Table (36): DFS estimates in relation to degree of tumor differentiation in hypopharyngeal cancer patients

Pathology	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
Well diff Sq.CC	10.67	-	100.0	-	-	100.0	11.057*	0.004*
Moderate diff. Sq.CC	15.76	-	82.5	75.0	62.5	62.5		
Poorly diff. Sq.CC	4.57	-	38.1	-	-	38.1		

Regarding oral and oropharyngeal cancer patients, correlation between degree of tumor differentiation and OS was statistically significant in favor of well differentiated tumors compared to less differentiated tumors (log rank p value of 0.010). Correlation was not significant for better DFS (log rank p value of 0.102). (Table 37 &38)

The analysis showed that five years OS deteriorated from 64.3 % for well differentiated tumors and 52% for moderately differentiated tumors to 0% for poorly differentiated tumors. While, Five years DFS was about 78.1% for well differentiated tumors, 48.6% for moderately differentiated tumors and 33.3 % for poorly differentiated tumors, but it was not statistically significant association.

Table (37): OS estimates in relation to degree of tumor differentiation in oral and oropharyngeal cancer patients

Pathology	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
Well diff Sq.CC	45.18	-	90.0	69.6	64.3	64.3	9.235*	0.010*
Moderate diff. Sq.CC	58.54	37.0	86.0	61.8	52.0	24.9		
Poorly diff. Sq.CC	17.80	13.0	60.0	30.0	-	0.0		

Table (38): DFS estimates in relation to degree of tumor differentiation in oral and oropharyngeal cancer patients

Pathology	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
Well diff Sq.CC	45.32	-	78.1	78.1	78.1	78.1	4.575	0.102
Moderate diff. Sq.CC	78.0	36.0	83.3	69.9	48.6	0.0		
Poorly diff. Sq.CC	10.50	5.0	33.3	-	-	33.3		

Stage stratified OS and DFS estimates

OS and DFS were correlated with stage of the disease at presentation (shown in figure 3&4). Regarding hypopharyngeal cancer, most of patients presented at advanced disease stage (52 patients compared to only 5 patients presented at early stage). Correlation was not statistically significant for either DFS or OS (log rank p value of 0.915 & 0.109 respectively).

While for oral and oropharyngeal cancer patients, early stage disease is associated with statistically significant better OS (log rank p value of 0.003), but is not significantly associated with better DFS (log rank p value of 0.243). Five years OS was 56.8% for early stage disease compared to 31% for advanced stage disease.

OS analysis of patients presented with unresectable and/or metatastatic disease revealed a dismal prognosis manifested in median OS of about 7 months. A separate analysis of OS and DFS estimates in relation to T- stage and N-stage of the disease was done. It revealed that earlier T-stage (T1, T2 relative to T3, T4) was associated with significantly better OS (log rank p value of 0.016 for hypopharyngeal cancer patients, and <0.001 for oral and oropharyngeal cancer patients), but not DFS (log rank p value of 0.931 for hypopharyngeal cancer patients, and 0.354 for oral and oropharyngeal cancer patients). In addition, analysis showed also that N0 N1 stage disease was significantly associated with better OS compared to N2 N3 stage disease (log rank p value of 0.030 for hypopharyngeal cancer patients and <0.001 for oral and oropharyngeal cancer patients), but not significantly associated with better DFS (log rank p value of 0.424 for hypopharyngeal cancer patients, and 0.784 for oral and oropharyngeal cancer patients).

Stage stratified OS

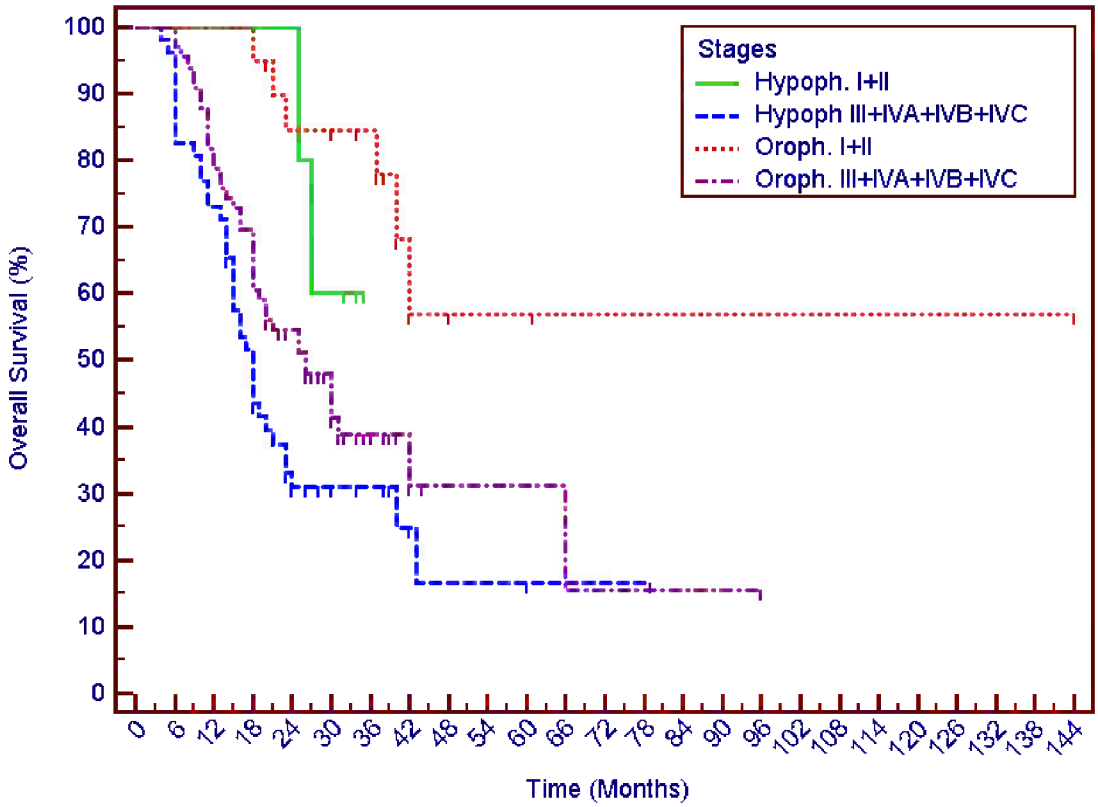

Figure (3): Kaplan-Meier Stage stratified overall survival estimates for oral, oropharyngeal, and Hypopharyngeal cancer patients

Stage (AJCC)	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
Hypoph. I+ II	31.40	-	100.0	100.0	60.0	60.0	2.566	0.109
Hypoph. III+ IVA+ IVB+ IVC	28.43	18.0	73.1	31.0	31.0	16.5		
Oroph. I+ II	96.144	-	100.0	84.4	84.0	56.8	8.611*	0.003*
Oroph. III+ IVA+ IVB+ IVC	39.09	26.0	78.8	54.5	38.9	15.6		

Stage starified DFS

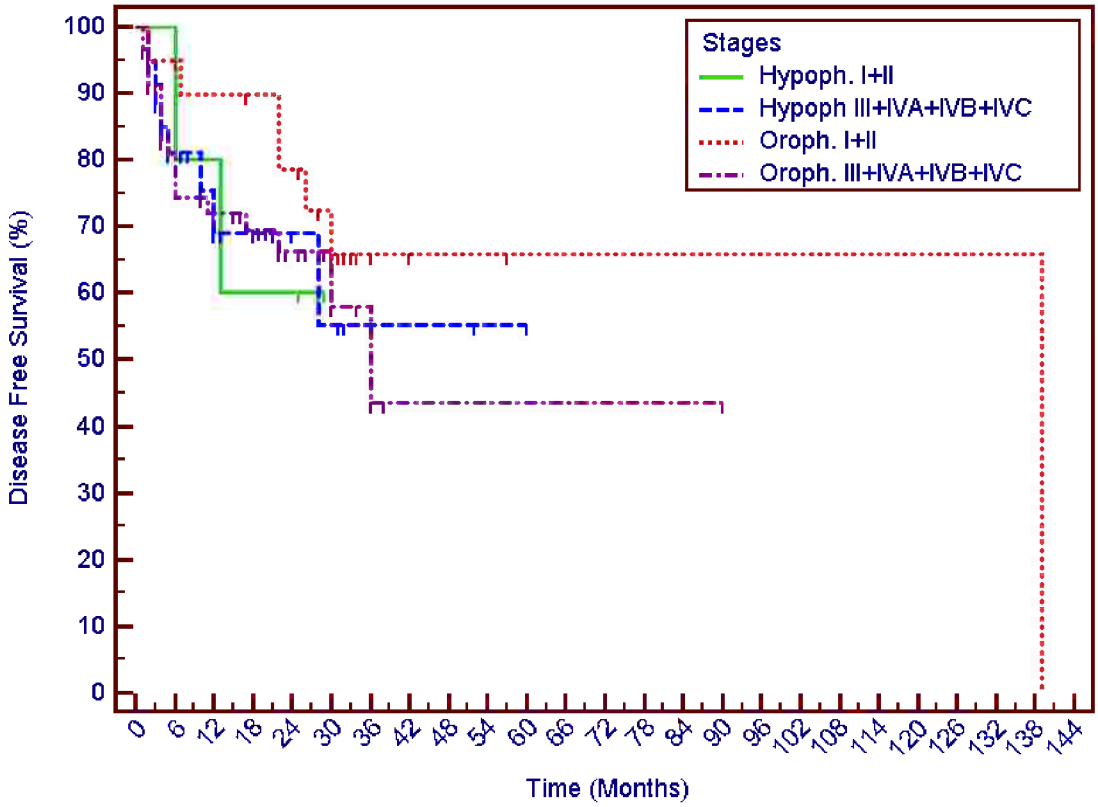

Figure (4): Kaplan-Meier Stage stratified disease free survival estimates for oral, oropharyngeal, and Hypopharyngeal cancer patients

Stage (AJCC)	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
Hypoph. I+ II	21.20	-	80.0	60.0	-	60.0	0.012	0.915
Hypoph. III+ IVA+ IVB+ IVC	38.96	-	69.0	69.0	55.2	55.2		
Oroph. I+ II	98.06	139.0	89.7	78.5	65.9	0.0	1.366	0.243
Oroph. III+ IVA+ IVB+ IVC	49.16	36.0	71.9	66.2	43.4	43.4		

Type of treatment

Type of treatment administered to hypopharyngeal cancer patients was not a statistically significant factor affecting either OS or DFS as shown in figure 5& 6.

Overall survival

Median OS was about 40 months for surgery followed by adjuvant treatment, 16 months for chemoradiotherapy, 21 months for surgery only and 13 months for radiotherapy only (log rank p value 0.149).

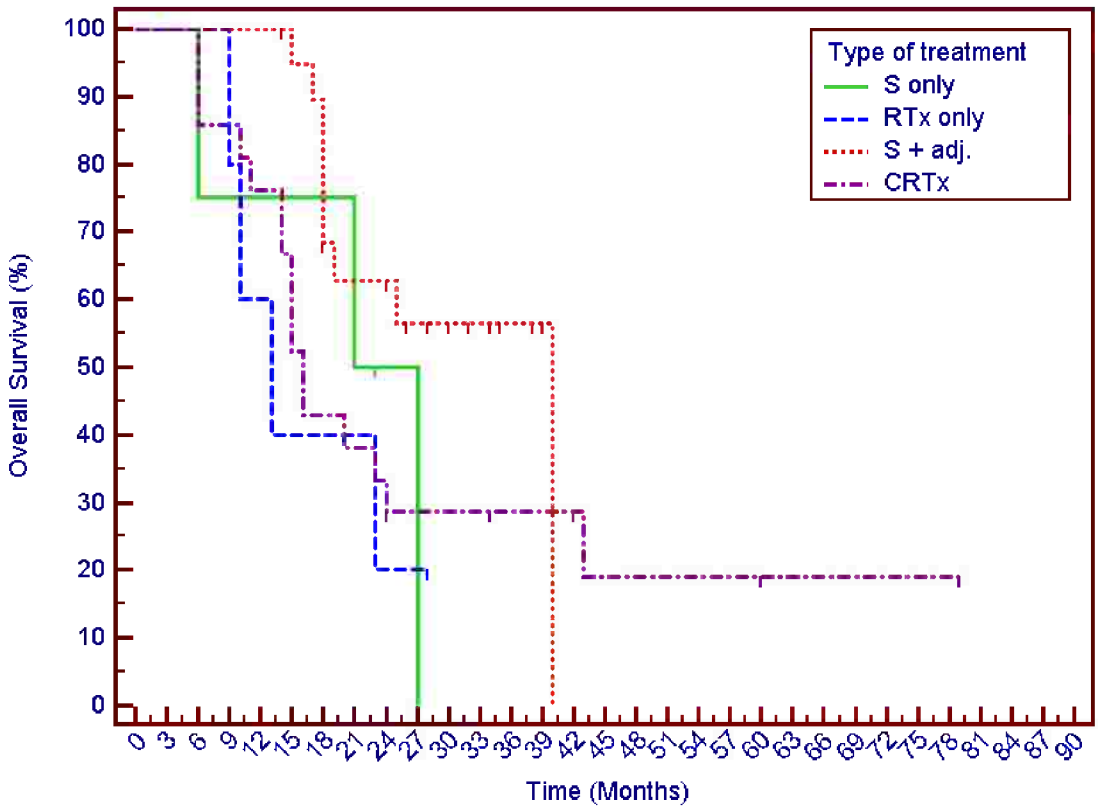

Figure (5): Kaplan Meier OS estimates in relation to type of treatment administered to hypopharyngeal cancer patients

Type of treatment	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
S only (n = 4)	20.25	21.0	75.0	50.0	-	0.0	5.327	0.149
RTx only (n = 5)	16.60	13.0	60.0	20.0	-	20.0		
S + adj. (n = 20)	30.70	40.0	100.0	62.7	56.4	0.0		
CRTx (n = 21)	29.19	16.0	76.2	28.6	28.6	19.0		

Disease free survival

Mean value of DFS was about 27.26 months for surgery followed by adjuvant treatment, 31.13 months for chemoradiotherapy, 13.0 months for surgery only and 10.0 months for radiotherapy only, but correlation was not significant (log rank p value 0.166).

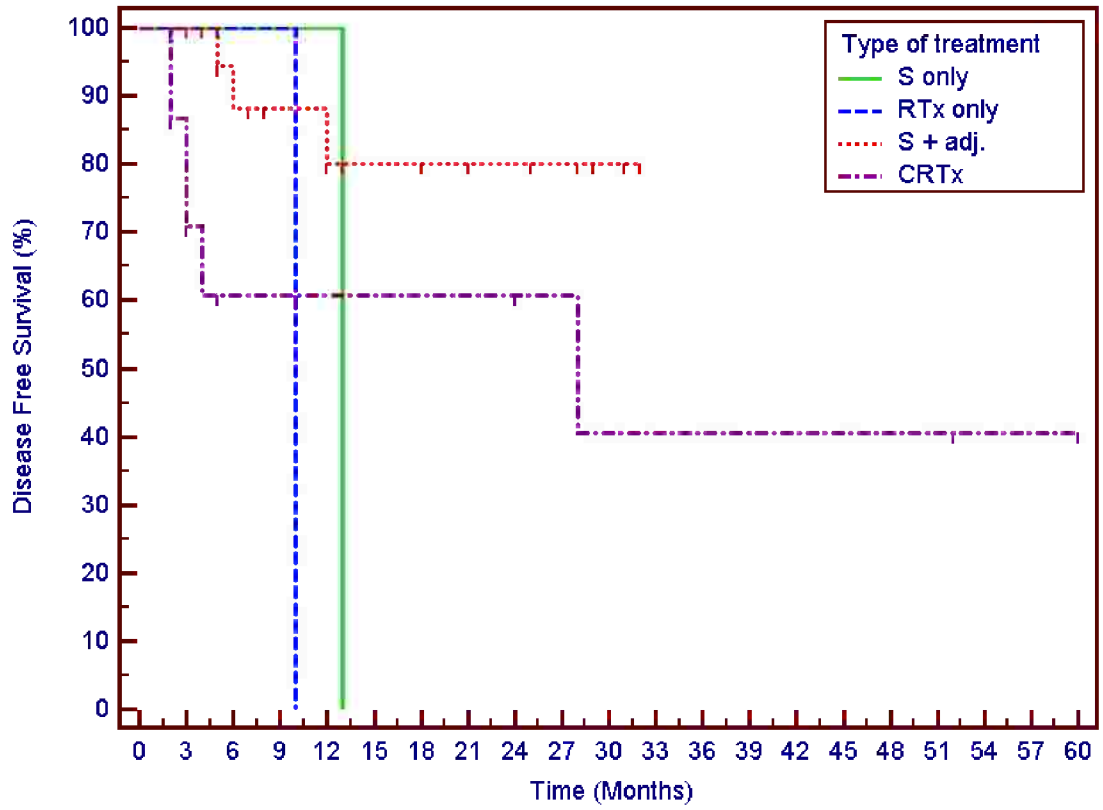

Figure (6): Kaplan Meier DFS estimates in relation to type of treatment administered to hypopharyngeal cancer patients

Type of treatment	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
S only (n = 4)	13.0	13.0	100.0	-	-	0.0	5.075	0.166
RTx only (n = 5)	10.0	10.0	0.0	-	-	0.0		
S + adj. (n = 20)	27.26	-	80.1	80.1	-	80.1		
CRTx (n = 21)	31.13	28.0	60.8	60.8	40.5	40.5		

OS and DFS were analyzed in relation to type of treatment used in management of oral and oropharyngeal cancer patients (shown in figure 7&8). This analysis revealed that combined treatment modality (surgery followed by adjuvant treatment) was associated with statistically significant better OS and DFS compared to surgery or radiotherapy only. (Log rank p value of 0.006 and 0.012 respectively)

Overall survival

Five years OS was about 58.6% for patients managed with surgery followed by adjuvant therapy, 38.9% for patients managed by chemoradiotherapy, 15% for patients managed with surgery only and 27.3% for patients managed with radiotherapy alone. Mean value for OS was about 95.47 months for surgery followed by adjuvant treatment, 35.56 months for chemoradiotherapy, 32.55 months for surgery only and 38.16 months for radiotherapy only.

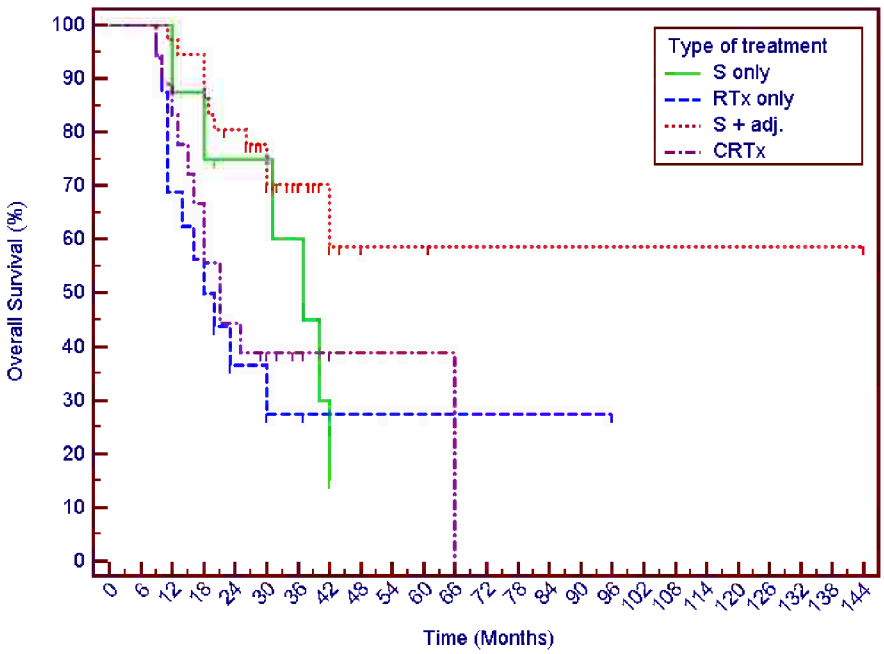

Figure (7): OS estimates in relation to type of applied treatment for oral and oropharyngeal cancer patients using Kaplan Meier method

Type of treatment	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
S only (n = 8)	32.55	37.0	87.5	75.0	60.0	15.0	12.420*	0.006*
RTx only (n = 16)	38.16	18.0	68.8	36.5	27.3	27.3		
S + adj. (n = 36)	95.47	-	100.0	80.6	70.3	58.6		
CRTx (n = 18)	35.56	21.0	83.3	44.4	38.9	0.0		

Disease free survival

Five years DFS was significantly better for patients managed with surgery followed by adjuvant therapy reaching about 72.5% compared to 70.1% for patients managed with radiotherapy alone and 31.8% for patients managed by chemoradiotherapy and 0% for surgery alone.

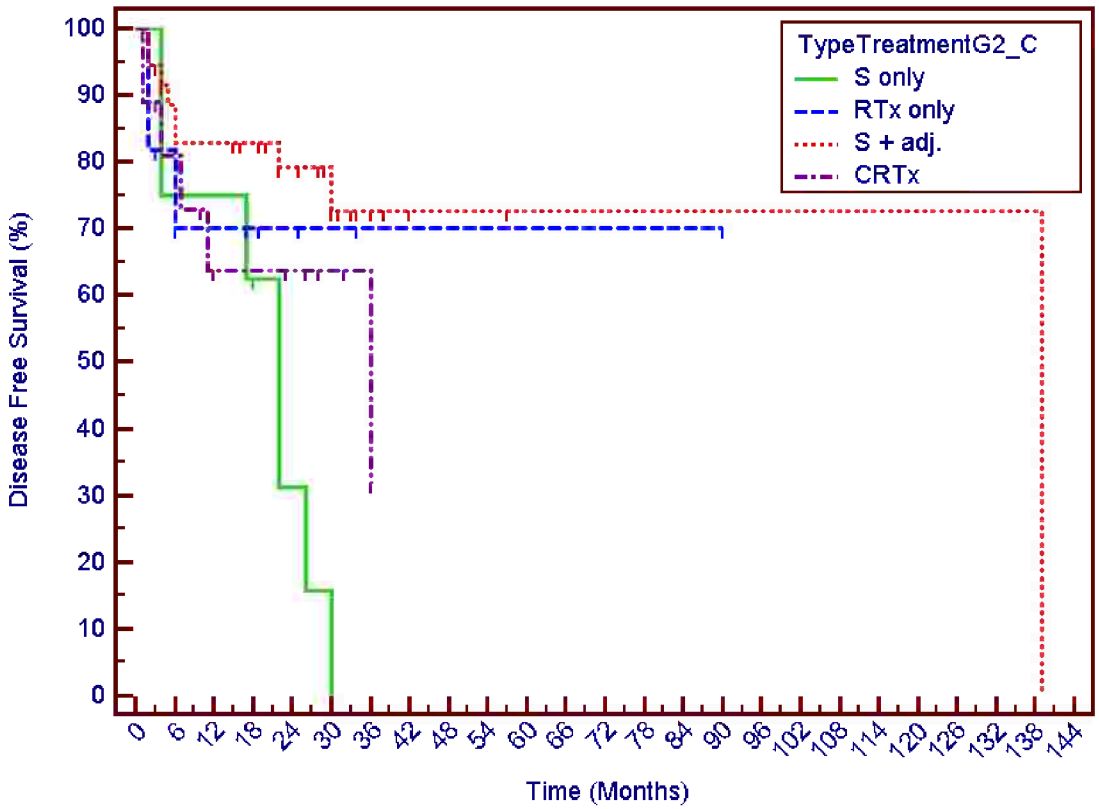

Figure (8): DFS estimates in relation to type of applied treatment for oral and oropharyngeal cancer patients using Kaplan Meier method

Type of treatment	Mean	Median	12 month (%)	24 month (%)	36 month (%)	End	Log rank	
							χ^2	(p)
S only (n = 8)	18.75	22.0	75.0	31.3	-	0.0		
RTx only (n = 16)	64.18	-	70.1	70.1	70.1	70.1		
S + adj. (n = 36)	104.31	139.0	88.6	79.1	72.5	0.0	10.862*	0.012*
CRTx (n = 18)	24.91	36.0	63.6	63.6	31.8	31.8		