

DISCUSSION

Oral cavity squamous cell carcinoma is the most frequent neoplasm in head and neck, comprising nearly 30% of all malignant tumors in this region.^(5, 22, 155, 156) Several prognostic factors can influence treatment decisions and survival of patients. However, Survival rates of both oral and oropharyngeal tumors induced by tobacco and alcohol have not improved for decades except in few major treatment centers. Treatment failures remain a frequent event despite advances in diagnostic and therapeutic modalities.

Although squamous cell carcinoma of the hypopharynx is relatively uncommon malignancy,^(22, 102, 110) patients with hypopharyngeal carcinoma have the worst survival rates among all other patients with head and neck cancer.^(157, 158)

Several clinical trials have been conducted to investigate different treatment approaches aiming to improve local control and survival of hypopharyngeal cancer patients. The European Organization for Research and Treatment of Cancer (EORTC 24891) study demonstrated that organ preserving induction chemotherapy and definitive radiotherapy (RT) is an alternative treatment approach with comparable outcomes to laryngopharyngectomy.⁽¹²¹⁾ Organ preservation in hypopharyngeal SqCC using concurrent chemoradiation therapy (CRT) is extrapolated from the Radiation Therapy Oncology Group (RTOG 91-11) advanced laryngeal SCC study, which showed higher rates of laryngeal preservation with concurrent CRT compared to induction chemotherapy followed by RT alone.^(159, 160) So far, an ideal treatment strategy of hypopharyngeal cancer is still unclear, and no improvement of survival rates, regardless of the chosen therapeutic regimen.^(157, 161)

In this study, our aim was to review medical records of all patients diagnosed with oral, oropharyngeal, or hypopharyngeal cancer and to identify the incidence of cases presenting to Alexandria main university hospital, stand on treatment modalities applied and survival outcomes.

At our hospital, malignant tumors of the oral cavity, oropharynx, and hypopharynx constitute nearly 29.2% of all head & neck cancers excluding thyroid cancer, and about 1.22% of all body tumors. A slightly higher incidence was reported in the US national cancer data report on head and neck cancer as oral cavity cancer alone accounts for nearly 30% and hypopharyngeal cancer accounts for approximately 3% to 5% of all head and neck squamous cell carcinomas.^(22, 102) Also those cancers accounts for a relatively higher percentage about 3% of all cancers worldwide in 2012.⁽¹⁾ This might be because our study is a single institution study and Egypt is not considered one of the high prevalence regions of oral cancer in the world.

Of the 255 patients included in the clinicopathological analysis of our study, 104 patients were diagnosed with hypopharyngeal cancer, and 151 patients were diagnosed with oral or oropharyngeal cancer.

In hypopharyngeal cancer cases, the most commonly involved subsite at presentation was the postcricoid region constituting about 76% of cases. This may be because most of those patients presented with advanced stage disease at diagnosis, and hence subsite of origin could not be detected accurately. In oral and oropharyngeal cancer, the most commonly involved primary site was the tongue representing about 57.6% of cases.

Sex distribution of our patients showed a relatively higher incidence of hypopharyngeal cancer in females than males (female to male ratio of 1.21). While in oral and oropharyngeal cancer female to male ratio is 0.75. Collectively, female to male ratio of all studied cases is 0.91. This goes with some predictions of a reduction in gender difference in the incidence of head and neck cancers, possibly suggesting changes in exposure to tobacco and other risk factors.^(18, 162) In contrast, incidence rates in the US were more than twice in men as in women.⁽²⁾

Clinically, most of patients presented with more than one symptom at diagnosis. 59.2% of all patients presented with clinically apparent regional LNs involvement. That was comparable with reported values for patients who have clinically involved regional lymph nodes at presentation, nearly 60% to 80% of hypopharyngeal cancer patients,^(106, 133) 45% of oral cavity cancer patients and up to 75% of patients with oropharyngeal cancer.^(32, 163) Among hypopharyngeal cancer patients, 85.6%, 43.3% presented with dysphagia and weight loss respectively. While in oral and oropharyngeal cancer patients, 68.2%, 53% presented with ulcer and pain respectively. Other symptoms included hoarseness, sore throat, Odynophagia, Stridor, Hemoptysis, and otalgia

Squamous cell carcinoma was the most common histopathological type constituting about 92% of all cases. This is slightly higher than the figure reported by the US national cancer data report on head and neck cancer constituting about 90% of all cases.⁽²²⁾ Other uncommon histopathological types were lymphoma, adenocarcinoma and anaplastic carcinoma. Among squamous cell carcinoma, moderately differentiated tumors were the most common variant representing nearly 54.1% of all cases followed by well and poorly differentiated tumors in 20% and 11.8 % of all cases respectively.

Majority of cases reviewed in our study were at advanced stage disease at diagnosis. Nearly 90% of hypopharyngeal cancer patients and 70% of oral and oropharyngeal cancer patients were classified as stage III-IV disease at presentation. This is somewhat higher than the reported figures in large studies that approximately 70% to 85% of patients with hypopharyngeal cancer were in stage III or IV disease at presentation.^(22, 102-105, 158) This may be because of unawareness of some of patients, in addition to unavailability of a suitable and accessible health care facility in some regions. For oral and oropharyngeal cancer, determining stage at presentation depends mainly on the primary site involved. As indicated by regional LNs involvement 30% to 75% of oral and oropharyngeal cancer respectively present at late stage.^(32, 163)

A total of 57 patients diagnosed with hypopharyngeal cancer and 86 patients diagnosed with oral or oropharyngeal carcinoma treated at our department between January 2003 and December 2011 were analyzed for survival outcomes.

The median overall survival (OS) and disease free survival (DFS) of all hypopharyngeal cancer patients was 18.0 months and 6.5 months respectively. Our study showed that 1, 3 and 5-years OS rates were about 75.4%, 32.8%, and 17.5% respectively. Whereas, 1, 3, and 5 years DFS rates were about 70.8%, 56.3%, and 56.3% respectively. Highlighting that highest relapse rate occurred in the 1st 12 months post treatment. It is of note that these reported OS rates are not cause specific. Causes other than disease relapse, such as treatment toxicities, or associated co morbidities could strongly affect the OS rates.

Similar retrospective studies targeting hypopharyngeal cancer patients reported varying OS and DFS rates. In a retrospective review of patients with hypopharyngeal cancer at Wayne State University, Paximadis et al. reported that the median OS and DFS for all patients were 28.3 months and 17.6 months respectively.⁽¹⁶¹⁾ Our study median survival values are apparently poorer if compared with these reported survivals. However, 5-year OS in our study can be considered reasonable if compared with reported figures in various studies with rates ranging between 15% and 45%.^(22, 102-106, 158) In another recent retrospective cohort study on 3,958 adult patients with hypopharyngeal cancer identified in the Surveillance, Epidemiology, and End Results (SEER) database, the 5-year overall survival rate was 25.5% which is relatively higher than our survival rate.⁽⁹⁹⁾ However, metastatic patients were excluded from the survival analysis in that study. Similarly to our DFS results, in an epidemiologic study of 595 hypopharyngeal cancer patients in Ontario, Canada, Hall et al.⁽¹⁰²⁾ reported that almost 50% of the patients had recurrences, most of them were within 12 months after finishing treatment.

While interpreting survival results of our study we must take into consideration that cancer survival rates tends to be worse in developing countries, most likely because of a combination of a late stage presentation and limited access to treatment centers.

When survival outcomes of hypopharyngeal cancer patients were analyzed with respect to disease stage, 5- years OS was about 60.0% for early stage disease patients and 16.5% for advanced stage disease patients with a mean value of 31.40 months and 28.43 months respectively. One year DFS was about 80% and 69% for early and advanced stage disease respectively. Both OS and DFS were better in early stage disease than in advanced disease patients, but not statistically significant. This may be due to relative scarcity of early stage disease patients compared to advanced stage disease (5 compared to 52 patients).

Age, tumor differentiation, T stage and N stage were tested in relation to survival. Analysis revealed that age of less than 50 years was significantly associated with better survival relative to patient between 50 and 70 years and those with more than 70 years of age (Log rank p value <0.001). 5-years overall survival was about 28.1% for patients younger than 50 years compared with 0% for patients older than 50 years. Patients' age was not statistically significant in relation to DFS (Log rank p value 0.604).

Well differentiated squamous cell carcinoma was not significantly associated with a better overall survival compared to moderately and poorly differentiated tumors (Log rank p value 0.057), but it was significantly associated with better DFS (Log rank p value 0.004). 5-year OS was about 20.0% and 22.5% for well and moderately differentiated tumors compared to 0% for poorly differentiated tumors. The one year DFS rates were about 100.0% and 82.5% for well and moderately differentiated tumors and 38.1% for poorly differentiated tumors.

T-stage (T1, T2 relative to T3 or T4) and N-stage (N0, N1 relative to N2 or N3) were both significantly associated with better overall survival (Log rank p value 0.016 and 0.030 respectively). T-stage analysis in relation to OS indicated worsening of median OS from 27 months for T2, 19 months for T3 to 6 months for T4. Similarly N-stage analysis in relation to OS deteriorated from median OS of 23 for N0, N1 to 14 months for N2 disease.

In accordance with our results, Mok et al. reported that T and N classification were significantly associated with OS in a recently published study that was discussing if IMRT was associated with improved outcome in comparison to 3DCRT.⁽¹⁶⁰⁾ Age of less than 54 years, early T- stage and N-stage were all also found to be significantly associated with better survival in a large retrospective cohort study conducted on patients with hypopharyngeal cancer in the United States between 1988 and 2010.⁽⁹⁹⁾

With regards to treatment modality applied, both overall survival and disease free survival showed no statistically significant association (Log rank p value 0.149 and 0.166 respectively). OS mean value was about 20.25 month for patients treated with surgery only, 16.60 months for patients treated with radiotherapy only, 29.19 months for patients treated with chemoradiotherapy (either induction chemotherapy or concomitant chemotherapy were used), and 30.70 months for patients treated with surgery followed by adjuvant therapy. Also the mean value of DFS was about 13 month for patients treated with surgery only, 10 months for patients treated with radiotherapy only, 31.13 months for patients treated with chemo radiotherapy and 27.26 months for patients managed by surgery followed by adjuvant therapy.

In literature, the reported 5-year survival rates have ranged from 24% to 33% for surgery alone^(164, 165) and 35 to 52% for combined surgery and radiation.^(111, 166) Comparing combined surgery and radiotherapy to surgery alone, El-Badawi et al. reported better outcomes for combination therapy, with 5-year survival of 40% for surgery with radiation versus 25% for surgery alone.⁽¹⁶⁷⁾ Kuo et al, reported that the best 5-year overall survival rate was seen with combined surgery and radiotherapy about 34.5%, followed by 22.6% for radiotherapy alone and 18.9% for surgery alone.⁽¹⁶⁸⁾ Furthermore, P. Paximadis et al showed that the addition of concurrent CRT as a part of hypopharyngeal cancer treatment (either as definitive or adjuvant treatment) improves OS in all disease stages. The median OS of patients who received CRT was 36.7 months compared 14 months for those who did not. The addition of CRT also improved the median DFS from 8 months to 17.6 months.⁽¹⁶¹⁾ If we compared our survival rates with respect to treatment modality to some of these literature figures, it indicates apparently worse outcomes. 3-year OS was about 0% for surgery alone, 38.7% for radiotherapy alone, 28.6% for CRT and 6.7% for combined surgery and radiotherapy.

Of notice that data about therapeutic regimens applied to hypopharyngeal cancer patients in our hospital were most of time interrupted. For example 92.3% of patients experienced treatment interruption either due to radiation therapy technical problems, or due to poor compliance & unawareness of some patients.

Regarding patients with oral or oropharyngeal cancer, median OS and DFS for all stages were about 37 months and 139 months respectively. 5-years OS and DFS were about 36% and 52.2% respectively. By the end of the study (144months) 24.3% of patients were still alive but 0% of patients were disease free.

In stage stratified survival analysis, early stage was significantly association with better OS (log rank p value of 0.003). 5-years OS was about 56.8% and 31% for patients with early stage and advanced stage disease, respectively. While, 5- years DFS was about 65.9% for patients with early stage and 43.4% for patients with advanced stage disease. Median DFS was longer in patients with early stage disease about 139 months compared to

36 months for patients with advanced stage disease, but not statistically significant (log rank p value of 0.243).

In most published series, the chances of surviving 5-years following treatment for oral squamous cell carcinoma are around 50%. Based on data analysis from 30 hospitals stored in the tumor registry of the German–Austrian–Swiss Working Group for Maxillary and Facial Tumors (DÖSAK),⁽¹⁶⁹⁾ 5-years survival rates varied from 40.2% to 70.6% (averaging to 52.4%) on Kaplan–Meier analysis. The figure for overall recurrence-free survival after 5 years was 43.9%.⁽¹⁷⁰⁾ These values are slightly higher than our study survival outcomes. It must be noted that oral cavity and oropharyngeal cancer patients were analyzed for OS and DFS rates together. Other cohort study of patients with previously resected oral cavity squamous cell carcinoma reported that the 5-year overall survival rates were 85% for stage I–II disease, 65% for stage III disease, and 45% for stage IV disease.⁽¹⁷¹⁾ This is higher than stage stratified OS rates of our study, which is most likely because surgery followed by adjuvant therapy if indicated were administered to all patients included in analysis of that study.⁽¹⁷²⁾

Patients' age (< 50 years relative to 50-70 and >70 years), tumor differentiation (well and moderately differentiated tumors relative to poorly differentiated tumors), T-stage (T1, T2 relative to T3 or T4) and N-stage (N0, N1 relative to N2 or N3) were all significantly associated with better OS, but not DFS. The recorded OS mean value was about 101.44, 37.05 and 15.89 months for patients with <50 years, 50-70 years and more than 70 years of age respectively (log rank p value of 0.001). Mean DFS values were also better for younger age group, but it was not statistically significant. OS mean value was about 45.18 months for well differentiated tumors, 58.54 months for moderately differentiated tumors, and 17.80 months for poorly differentiated tumors with 5 years OS of about 64.3%, 36%, and 0% respectively (log rank p value of 0.010).

Regarding T-stage, 5-years OS rates were about 100%, 47%, 42.8% and 0% for T1, T2, T3 and T4 disease respectively (log rank p value of < 0.001). While for N0, N1, N2 and N3, 5-years OS rates were about 63.4%, 11.7% and 0% respectively (log rank p value of < 0.001).

Therapeutic approaches were tested in relation to survival. This analysis showed that 5-years OS rates were higher for patients treated primarily with combined surgery and adjuvant therapy compared to other regimens and it was a statistically significant association (log rank p value of 0.006). 5-years OS was about 15% for patients treated with surgery only, 27.3% for patients treated with radiotherapy only, 38.9% for patients treated with chemo radiotherapy (either induction chemotherapy or concomitant chemotherapy was used) and 58.6% for patients treated with surgery followed by adjuvant therapy. A statistically significant association was also found with DFS in favor of combined treatment approach relative to surgery only or radiotherapy only (log rank p value of 0.012), with 5 years DFS of about 0% for patients treated with surgery only, 70.1 % for patients treated with radiotherapy only, 31.8 % for patients treated with chemo radiotherapy, and 72.5% for patients treated with surgery followed by adjuvant therapy.

In accordance with these results, young age patients (under the age of 45 years) were found to have better survival.⁽¹⁷³⁾ Poorly differentiated tumors, higher T and N-category have also indicated worse prognosis.⁽¹⁷⁴⁾ Liao et al. revealed that the presence of T3–4 disease and poor differentiation were independent predictors of the 5-year disease specific

survival in a multivariate analysis of 270 patients with N2 oral cavity squamous cell carcinoma.⁽¹⁷²⁾ A more recent study indicated that N2 disease and poor differentiation were independent risk factors for T4b tumors. In that study, T4 oral cavity cancer patients with N2 disease had a poorer survival rate than the N0-1 patients. This was more obvious in the T4b group of patients.⁽¹⁷⁵⁾

In addition, another large retrospective study was conducted on 426 patients with T4a oropharyngeal carcinoma treated between 1980 and 2010 aiming to investigate different treatment approaches and identify predictors of poor prognosis. It showed a significant difference in disease specific survival between N0 and N+ (57.1% versus 26.9%, $P < 0.001$), primary surgical and primary nonsurgical treatment (52.7% versus 31.4%, $P < 0.001$). N-stage was identified as the most important prognostic factor affecting survival of T4a oropharyngeal cancer patients.⁽¹⁷⁶⁾

Howaldt et al reported similar results regarding treatment modality for oral cavity cancer patients. The 5-year survival rate was 59% for the patients who underwent surgery with radical intent and 18% for those who were treated non operatively.⁽¹⁷⁰⁾ Alternatively, Stenson et al⁽³⁸⁾ have reported that the difference between OS and PFS for patients underwent surgery-first and those received primary concomitant CRT was not significant. This study reviewed data from 15 CRT clinical trials from the year 1994 through 2008. It recommended the use of primary CRT as a treatment option achieving high survival and satisfactory functions for patients with advanced oral cavity cancer.

SUMMARY

Oral, oropharyngeal, and hypopharyngeal cancers are relatively uncommon malignancies constituting approximately 3% of all cancers worldwide. Oral cavity squamous cell carcinoma is the most frequent neoplasm in head and neck comprising nearly 30% of all malignant tumors in this region. Carcinoma of the hypopharynx is considered an uncommon malignancy and it has the worst survival rates among all other head and neck cancers. The present work was carried out to review medical records of all patients diagnosed with oral, oropharyngeal, or hypopharyngeal cancer and to identify the incidence of cases presenting to Alexandria main university hospital, stand on treatment modalities applied and survival outcome.

To achieve this aim, the present study included 255 patients diagnosed with oral, oropharyngeal or hypopharyngeal cancer. Those patients presented to Clinical Oncology and Nuclear Medicine Department, Alexandria Main University Hospital between January 2003 and December 2012. Medical records of the included patients were reviewed. Epidemiological data, clinicopathological data and details of various administered treatment regimens were retrieved and tabulated. Overall survival (OS) and disease free survival (DFS) of patients who were managed at our department were estimated using Kaplan-meier method.

In our study, oral, oropharyngeal, and hypopharyngeal cancers constitute about 29.2% of head and neck cancers excluding thyroid cancer, and about 1.22% of all body tumors. 104 patients (40.8% of studied patients) were diagnosed with hypopharyngeal cancer, 53 patients (20.8% of studied patients) were diagnosed with oropharyngeal cancer, and 98 patients (38.4% of studied patients) were diagnosed with oral cavity cancer. The postcricoid region and the tongue were the most commonly involved primary subsites.

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. 54.8% of hypopharyngeal cancer patients were females, and 43.0% of oral and oropharyngeal cancer patients were females. Positive history of smoking was found in 40% of all patients.

The most frequent signs and symptoms at presentation were regional LNs enlargement, dysphagia, ulcer, pain and weight loss. Squamous cell carcinoma (Sq.CC) was the most common histopathologic type among all studied patients constituting about 92.6%. Other types included lymphoma, adenocarcinoma and anaplastic carcinoma. Most of patients presented to our hospital were at advanced stage disease at diagnosis. 90.3% of hypopharyngeal cancer patients and 71.3% of oral and oropharyngeal cancer patients were at stage III, IV disease at presentation.

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 (32.5%) patients with hypopharyngeal cancer and in 21 (16.8%) patients with oral or oropharyngeal cancer.

A total of 57 hypopharyngeal cancer patients were included in survival outcome analysis. For hypopharyngeal cancer patients, Median OS was about 18 month and median DFS was about 6.5 month, while five years OS and DFS were about 17.5% and 56.3%

Summary

respectively. Both OS and DFS were better in early stage disease than in advanced stage disease patients, but not statistically significant.

Age, tumor differentiation, T stage and N stage were tested in relation to survival. Analysis revealed that age of less than 50 years was significantly associated with better overall survival relative to patient between 50 and 70 years and those with more than 70 years of age (Log rank p value <0.001), but not significantly associated with better DFS (Log rank p value 0.604). Well differentiated squamous cell carcinoma was not significantly associated with a better overall survival compared to moderately and poorly differentiated tumors (Log rank p value 0.057), but it was significantly associated with better DFS (Log rank p value 0.004). T-stage (T1, T2 relative to T3 or T4) and N-stage (N0, N1 relative to N2 or N3) were both significantly associated with better overall survival (Log rank p value 0.016 and 0.030 respectively), but not disease free survival.

Type of treatment administered to hypopharyngeal cancer patients was not a statistically significant factor affecting either OS or DFS (Log rank p value 0.149 and 0.166 respectively)

Regarding oral and oropharyngeal cancer patients, a total of 86 were included in survival analysis. Median OS and DFS were about 37 months and 139 month respectively. Five years OS was about 36%, while five years DFS was about 52.2%. Early stage disease was associated with statistically significant better OS (log rank p value of 0.003), but was not significantly associated with better DFS (log rank p value of 0.243).

Patients' age (< 50 years relative to 50-70 and >70 years), tumor differentiation (well and moderately differentiated tumors relative to poorly differentiated tumors), T-stage (T1, T2 relative to T3 or T4) and N-stage (N0, N1 relative to N2 or N3) were all significantly associated with better OS, but not DFS.

Analysis of OS and DFS in relation to treatment modality used in management of oral and oropharyngeal cancer patients 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).