Original Article

Surgical treatment of hypopharyngeal cancer

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ABSTRACT

Objectives: This study aims to evaluate our department's approach to the treatment of hypopharyngeal tumors, the features of the tumors, the survival analyses and to present our results in the light of the literature.

Patients and Methods: Eighty-one hypopharyngeal tumor patients and four patients with undefined primary origin, those patients with undefined origin have tumors that infiltrate both hypopharynx and cervical esophagus, totally 85 patients (56 males, 29 females; mean age 54.6±13.4 years; range, 23 to 81 years) who underwent surgical treatment, were included in this study. Demographic data, tumor characteristics, and treatment protocols were recorded retrospectively.

Results: Patients were classified on the primary subsite of the hypopharynx: 51% originated from the sinus piriformis, 29% from the postcricoid area, 15% from the posterior wall of the pharynx and only 5% from the cervical esophagus. The relationship between sex and hypopharyngeal subsite was statistically significant (p<0.001); postcricoid tumors were more prominent in female patients. Also, patients with a history of tobacco use had a tendency for tumors originating from the piriform sinus (p<0.001). Additionally, highly significant differences were revealed between clinical and pathological T and N staging (p<0.001). Estimated 60-month survival rate was 45%.

Conclusion: The majority of patients in the study group were not old-aged or alcohol consumers; particularly none of the female patients had any bad habit as a predisposing factor suggested in the etiology. The relationships between tumor site and smoking show that if the campaign against smoking is successful, the rate of sinus piriformis cancer will decrease. For a significant number of patients, primary surgical reconstruction was possible, which shortens postoperative recovery time and accelerates postoperative adjuvant therapy. Therefore, survival rates were found to be high.

Keywords: Esophageal reconstruction; hypopharynx cancer; organ preservation surgery; surgical treatment; survival.

Hypopharynx cancer (HC) is one of the most challenging conditions of head and neck oncology due to its low treatment success rate and high morbidity. More than 95% of this region's malignancies are squamous cell carcinomas.[1] Hypopharynx cancers are very rare malignancies and constitute 3-5% of all head and neck cancers and 7% of upper airway and digestive tract cancers.[2,3] There are many reasons why patients with HC have poor survival; most patients have a history of heavy alcohol and tobacco consumption and they have systemic comorbidities and malnutrition, depending on the addiction.[4] The symptoms of HC are extremely vague, which causes diagnosis to be delayed until an advanced stage in most patients. At the time of diagnosis, 60-80% of patients have metastatic disease, which reduces direct survival

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by 50%.[5] Among all head and neck cancers, the highest risk of distant metastasis is in HC, 20% of cases have distant metastases at diagnosis.[6] In large series, approximately 70-85% of patients had stage 3-4 disease at diagnosis and five-year survival rates were between 15% and 45%.[5,7-9]

Treatment in HC varies according to the disease stage;[10] organ preservation surgery or radiotherapy (RT) can be used in early-stage T_1-T_2 tumors. In T_2-T_3 disease in which laryngeal protection is not possible, concomitant chemoradiotherapy (CRT) after induction chemotherapy (CT), only concomitant CRT or total laryngopharyngectomy can be performed. In locally advanced T_{4a} tumors, the first choice is total laryngopharyngectomy+adjuvant RT/CRT; concomitant CRT alone can be tried if surgery is not appropriate.

If surgery is decided in HC cases, careful operation planning is required; the tendency for a high rate of submucosal spread can cause misinterpretation of the extent of disease.[11] Another aspect to be considered at the time of diagnosis is second primary cancers. Seven percent of patients have a synchronous cancer focus at the time of diagnosis.[4]

In this study, we aimed to evaluate our department's approach to the treatment of hypopharyngeal tumors, the features of the tumors, the survival analyses and to present our results in the light of the literature.

PATIENTS AND METHODS

In İstanbul University İstanbul Medical Faculty Otorhinolaryngology Department, the records of 85 patients (56 males, 29 females; mean age 54.6±13.4 years; range, 23 to 81 years) who underwent surgical treatment for HC between January 2001 and December 2011 were evaluated retrospectively. Assessment was performed in the form of file screening, on the basis of disease stage, treatment, reconstruction method, tumor site, and survival. The study protocol was approved by the İstanbul University İstanbul Medical Faculty Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Tumor staging was performed according to the seventh edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) classification. Of the 85 patients included in the study, 81 (95.3%) patients' tumor originated from hypopharynx primarily, and the remaining four patients had tumors of unknown origin that extended to the cervical esophagus, involving all subparts of the hypopharynx. All tumors were clinically resectable. Surgery was the primary treatment protocol in 81 patients (95.3%) and salvage surgery was performed in four patients after RT (n=1) and CRT (n=3). In the surgical treatment of primary tumors, total/partial laryngectomy, total/partial pharyngectomy or total pharyngolaryngectomy/cervical esophagectomy operations were performed.

In metastatic necks, radical or modified radical neck dissection was performed according to the relationship of metastatic lymphadenopathies with the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve. In the existence of clinical and radiologic N0 neck, posterolateral selective neck dissection was performed to include levels 2, 3, 4, and 5, due to the risk of possible occult metastases. In five patients with a limited lesion in the lateral wall of the piriform sinus, only ipsilateral neck dissection was performed, whereas bilateral neck dissection was performed in all other patients. Concurrent paratracheal neck dissection was performed in all patients with bilateral neck dissection.

Various reconstruction methods were performed to provide the integrity of the digestive tracts following primary tumor resection and neck dissection. In tumors above the thoracic inlet, primary closure was applied if 3 cm or more intact pharynx mucosa remained after resection; patients with less than 3 cm of remaining intact pharyngeal mucosa and those who underwent total pharyngectomy were reconstructed with free or pedicular flaps. In tumors that extended below the thoracic inlet, total esophagectomy was performed and digestive system integrity was provided with visceral pedicular flaps. Patients were followed-up for a mean 34 months (range, 1-211 months) after surgery for possible recurrent disease.

Tumor origin	Patients	
	n	%
Postcricoid	25	29
Pyriform sinus	43	51
Posterior pharynx wall	13	15
Cervical esophagus	4	5

Statistical analysis

Survival rates were graphically plotted using Kaplan-Meier survival analysis curves. Variability in survival probabilities between groups was statistically analyzed using the log-rank/chi-square test and statistical comparisons were performed using the chi-square test. The distribution of the sample according to different variables was determined using frequency calculations and presented as a graphic.

RESULTS

When patients were grouped according to the tumor region, 51% (n=43) originated from sinus piriformis, 29% (n=25) from postcricoid area, 15% (n=13) from pharyngeal wall, and 5% (n=4) from cervical esophagus (Table 1). The cervical esophagus group comprised tumors of unknown origin; the tumors invaded all subparts of the hypopharynx and extended to the esophagus.

Surgery was the primary treatment modality in all patients except for four salvage surgeries. When classified histopathologically, 83 patients (97.6%) had squamous cell carcinoma, one had fusiform cell sarcoma, and one patient had leiomyosarcoma. The two patients with sarcomas were in the CRT failure group.

According to the TNM classification (AJCC 2010), 27.1% of patients were T_1-T_2 and 72.9% were T_3-T_4, as assessed through preoperative imaging and clinical examination. In the pathologic staging, 17.7% of patients were T_1-T_2 and 82.3% were T_3-T_4; 11 (52.3%) of the 21 patients who were clinically and radiologically diagnosed as T_1-T_2 were reclassified as T_3-T_4 according to pathology reports. Six patients were excluded from the pathologic staging because postoperative pathology reports did not provide adequate information for staging. In clinical N staging, 31% of patients were clinically diagnosed as N_0-N_1, and 69% were diagnosed as N_2-N_3. One patient who could not undergo clinical neck staging was excluded from this evaluation. According to the pathology reports, the neck staging was as follows: N_0-N_1 (48.1%), N_2-N_3 (51.9%). Sixteen of the 55 patients, who were clinically evaluated as N_{2-3}, were found as N_{0-1} according to pathology
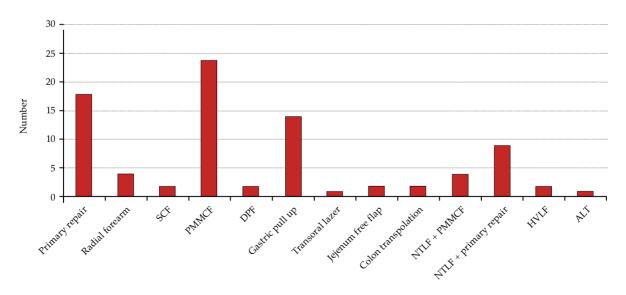

Figure 1. *Reconstruction methods.*
SCF: Cervical cutaneous flap; PMMCF: Pectoralis major flap; DPF: Deltopectoral flap; NTLF: Near-total laryngopharyngectomy; HVLF: Hemivertical laryngopharyngectomy+primary repair; Primary: Total laryngectomy partial pharyngectomy+primary repair; ALT: Anterolateral thigh flap.
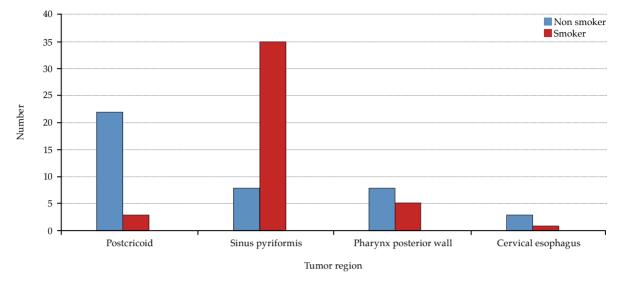
Figure 2. *Relationship between primary tumor region and tobacco use.*

results. There were statistically significant differences between clinical and pathologic evaluations at both T and N stages (p<0.001).

When the patients were evaluated according to the primary tumor excision technique, partial laryngopharyngectomy was performed in 23 patients (27.05%); partial laryngopharyngectomy (n=13), open vertical hemilaryngopharyngectomy (n=2), laser partial laryngopharyngectomy (n=1), supracricoid hemilaryngopharyngectomy (n=3), and partial pharyngectomy with larynx preservation (n=4). A total of 62 patients (72.9%) underwent total laryngectomy with pharyngectomy. The numbers of total pharyngectomies and partial pharyngectomies were 27 (31.7%) and 58 (68.3%), respectively. Total esophagectomy was performed in addition to total pharyngectomy in 16 patients (18.8%) whose tumors extended to the thoracic inlet.

Primary closure was performed after total/partial laryngectomy and partial pharyngectomy in 29 of the 85 patients (34.11%). Additionally, pectoralis major myocutaneous flaps in 28 patients (32.94%), regional cutaneous flaps in four patients (4.70%), and secondary healing in one patient (1.2%) were used for digestive system integrity after total laryngectomy partial pharyngectomy (TLPF)/partial laryngectomy partial pharyngectomy (PLPF). Visceral

flaps (gastric pull-up, jejunal free flap, colon interpolation) in 18 (21.17%), and fasciocutaneous free flaps (radial forearm free flap, anterolateral thigh free flap) in five patients (5.88%) were used after total pharyngolaryngectomy procedures for digestive system integrity. In total, seven patients (8.23%) underwent free flaps (Figure 1).

Preoperatively, 51.8% of patients (n=44) were tobacco users and 15.2% had alcohol habits (n=13). Only one patient who used alcohol did not use
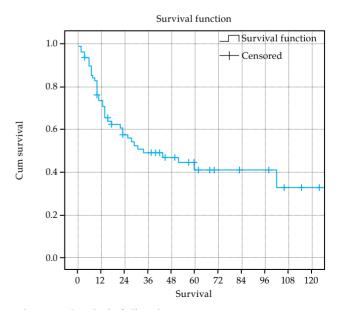

Figure 3. *Survival of all patients.*

tobacco. Patients with sinus piriformis cancer had higher rate of tobacco use and those with postcricoid tumors had the lowest rate of tobacco use. In total, tobacco consumption was 51.8% (n=44). According to the statistical evaluation, primary tumor origin and tobacco use were significantly related (p<0.001) (Figure 2).

Regarding sex, 65.8% of the patients were males and 34.2% were females. In the comparison of sex and primary tumor origin, 16 of the 29 female patients were found to have postcricoid localized tumors. There were significant differences in sex-to-region relationships in statistical evaluations performed after excluding the four female patients classified as cervical esophagus (patients with tumors of unknown origin) (p<0.001).

The mean survival time of 77 patients whose follow-up records could be reached was 89.2±13.5 months. The estimated 60 months' survival rate was 45% (Figure 3). Two patients with RT failure, two patients with RT-related sarcoma, and eight patients without follow-up records were excluded from the evaluation; 73 patients who underwent surgical treatment were evaluated for survival analysis for adjuvant treatment.

DISCUSSION

In HC, the treatment protocol varies according to the disease stage. Transoral or open surgical techniques that allow laryngeal conservation or primary RT can be used alone in early stage tumors (T_1 and selected T_2); T_2 and T_3 HC tumors requiring total laryngectomy are treated with induction CT first, followed by RT, and salvage total laryngopharyngectomy is recommended in patients who do not respond to this protocol.[10] For stage T_3 and T_{4a} tumors in which laryngeal functions cannot be preserved after CRT protocols, primary treatment is planned as total laryngopharyngectomy and adjuvant RT/CRT. According to studies that compared induction CT followed by RT administration and postoperative RT treatment, there were no differences between laryngeal preservation regimens, surgery, and adjuvant RT in terms of disease control and survival.[12] However, there are no prospective randomized clinical studies comparing treatment options.[13] In the survival evaluations of all patients in our series, the five-

year survival rate was found as 45%. Our rate was largely consistent with the literature with survival rates of 15-45%.[5,7-9,14] In the context of HCs, our surgical treatment results can be compared with organ-preservation protocols in two studies. The first of these studies was conducted by the European Organisation for Research and Treatment of Cancer (EORTC),[12] which included 202 patients with HC who could be treated with total laryngectomy+partial pharyngectomy. In that study, an HC group underwent standard treatment (surgery+RT) and the other group was given neoadjuvant CT. According to the CT response, the responsive group was treated with RT and the unresponsive group was treated with surgery+RT. In the final analysis, the mean survival time was 25 months in the standard treatment group and 44 months in the experimental group. However, there was no significant difference in five-year survival, nor was there any difference in local control and second primary malignancy formation. The larynx preservation rate remained at 50%. In another study, a group of patients with neoadjuvant CT received randomized surgery+RT and the other group received definitive RT. The surgical group was superior in five-year survival and local control.[13] As a result, organ-preservation protocols have become remarkable after cisplatin-based CT, but with 35-50% laryngeal preservation rates and with no significant difference in survival rates it remains as a treatment option and is yet open to research.[15,16] In the present study, in addition to pharyngectomy, total laryngectomy was performed in 72.9% of patients (n=62) and partial laryngeal conservation surgeries were undertaken in 27.1% (n=23). Our conservative surgery rates are compatible with the literature (15-34%).[7]

In the evaluation of postoperative pathologies, 82.1% of the patients were T_{3-4} and 53.9% were N_{2-3}, and 92.4% of the patients were found to have stage 3-4, advanced-stage tumors. Compared with the case series of Chu et al.,[17] the number of T_{3-4} patients and neck metastasis rates were similar. In addition, the positive neck ratios reported in the literature are in the range of 65-80%, and in our series, the positive neck ratio was similar at 63.4%.[18] When pathologic TNM

classifications were compared with clinical TNM classifications, it was found that 52.3% of the patients clinically evaluated as T_{1-2} were T_{3-4} in pathologic evaluations, indicating that there was a statistically significantly lower clinical staging in T staging. The lymph nodes evaluated clinically as N_{2a} were N_1 after pathologic evaluation; this situation was associated with false high clinical staging.

Thyroid invasion was detected in 31% of patients who underwent thyroidectomy. Paratracheal metastases are awaited in HC, and technically, thyroidectomy is needed to completely remove the paratracheal lymph nodes. The necessity to perform ipsilateral thyroidectomy even in the absence of thyroid invasion or extralaryngeal spread was supported by the high rate of direct invasion of the thyroid gland in our series.

In 34% of patients (n=29), the pharynx could be repaired primarily. This rate was 14% in the series of Chu et al.[17] Reconstruction with pedicled myocutaneous flaps was performed in partial pharyngeal defects that were not suitable for primary closure (32.9%, n=28). Pedicled myocutaneous flaps were not used as a tube in the presence of circular defects because the likelihood of marginal necrosis development is high and the bulk of the muscle mass is not suitable for tubing.[19] Similar to the literature, thoracic inlet invasion was present in 18.8% of the cases (n=16).[17] Reconstruction was performed with gastric pull-up (80%) or colon interpolation (20%) in patients who underwent total esophagectomy. Colon interpolation was performed in patients who could not undergo gastric pull-up owing to previous gastric surgery.

Patients who underwent total esophagectomy had the lowest survival rate. Four (30.7%) of the 13 patients who could be reached died in the postoperative sixth month and 53.8% (n=7) died in the first postoperative year; the mean survival time was 30.1±37.0 months.

The postcricoid carcinoma rate was 29.4% (n=25), and 64% (n=16) of these patients were females. However, the proportion of female patients in the study was 34.1%. Only two of the female patients smoked cigarettes and none used alcohol. It was thought that the postcricoidal region superiority, low tobacco-alcohol use, and high female sex ratio might be related to Plummer-Vinson syndrome.[3]

In HC, the tumor origins and related factors vary from country to country.[3] The highest origin in our series was sinus piriformis with 50.5%, and the rarest origin was the posterior wall with 15.3%. Tobacco smoking rate was 81.3% and alcohol consumption rate was 20.9% in sinus piriformis cancers. In contrast, the rate of cigarette smoking was 12% in postcricoid cancers, constituting one-third of the patients, and none of these patients used alcohol. In addition, the anamnesis of Calvados, Cachaça, dark rum, mate, which are thought to play a role in the etiology of hypopharyngeal cancers in some countries, was not detected.[3]

The deficits of the study include not assessing the quality of life and functional outcomes of the patients, not examining the surgical complications, mortality and morbidity, and not comparing these with the definitive RT±CT results of our clinic.

In conclusion, in addition to achieving results consistent with the literature in general, there were several remarkable points. First, unlike United States-based epidemiologic data, we found that patients were not at advanced age and heavy alcohol users, and that harmful habits did not play a role in the etiology, particularly in female patients. In addition, the significant association between tobacco and tumor origin in particular indicates that HC originating from the sinus piriformis will be reduced if the smoking cessation campaign initiated in our country is successful. In our study, the statistically significant low preoperative clinical T staging compared with postoperative staging, which affects the surgical treatment and directly determines the surgical method to be applied, is another important issue to be considered. In particular, mistakes in preoperative staging and its effect on survival should be investigated in the future because preoperative staging is an important parameter in the selection of patients who undergo function preservation surgery and in the success of treatment.

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