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Definitive Radiotherapy with or without Concomitant or Induction Chemotherapy in Patients with Hypopharyngeal Squamous Cell Carcinoma: A Single Center Study in Iran

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Abstract

Background: Hypopharyngeal carcinoma (HPC) is a rare head and neck cancer which poses many therapeutic challenges. There is limited evidence regarding the outcomes of HPC treatment in Iran.

Method: In this retrospective cohort study, we evaluated patients treated with chemoradiation or radiation alone, between 2007 and 2016 in the radiation oncology ward of the cancer institute affiliated to Tehran University of Medical Sciences. The design of the study was reviewed and approved by the local institutional review board (code: 86100142). All patients underwent definitive radiotherapy with or without concurrent or sequential chemotherapy. We assessed the two-year overall survival (OS) as the primary outcome. The progression-free survival (PFS) was our secondary outcome.

Results: We studied 40 patients whose median age was 58 years. 37 patients were stage 3 or 4, while the most common stage was T3N1-2, observed in 35% of the cases. The most common site of involvement was pyriform sinus (47.5%). The two-year OS rate was 29%. The two-year PFS was 22%. In the univariate analysis, N0-1 vs. N 2-3 and stage 2 vs. stage 3-4 were significant predictors of OS. In addition, distant metastasis had almost a significant association with lower OS.

Conclusion: The outcome of locally advanced HPC was not promising using 3DCRT alone. It is necessary to implement dramatic changes in the management of these patients to achieve better outcomes.

Keywords: Hypopharyngeal neoplasms, Head and neck cancer, Radiotherapy, Concurrent chemotherapy, Squamous cell carcinoma

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Introduction

The distribution of hypopharyngeal cancer (HPC) varies worldwide. The annual incidence is estimated at 1:100,000 in the world population. HPC is more common in the 5th to 7th decades of age, occurring in males more than in females.[1] HPCs account for 3%-5% of all head and neck cancers.[2] In Iran, 25,952 cases of head and neck cancer were diagnosed between 2003 and 2009. However, there are no robust data for HPC in Iran.[3] The most common pathology is squamous cell carcinoma (SCC).[1]

Exposure to coal dust, iron compounds, steel dust, and foams can increase the risk of hypopharyngeal cancers. Consuming alcohol and smoking, as may increase the risk of SCC in other parts of the head and neck, is a risk factor for HPC.[4] Some studies have also demonstrated the relationship between hypopharyngeal cancer and HPV.[5]

About 10%-20% of HPC patients have distant metastasis at presentation, which is among the highest rates in the head and neck SCCs.[6] The survival rates associated with this cancer are about 30% at five years.[7] The five-year overall survival (OS) rates for stage I and II, III, IVa, and IVb are 57% and 61%, 41%, 29%, and 25%, respectively.[8] Traditionally, surgery has been the main treatment for HPC. However, chemoradiation for organ preservation is receiving more attention.[2] Treatment with radiation alone or voice preservation surgery is the standard treatment for stages I and II. With functional laryngopharynx, treatment using concurrent chemoradiation with or without subsequent selective lymph node, dissection can be done in stages III and IV. In these stages, with a dysfunctional laryngopharynx, laryngo-pharyngectomy (LP) with probable adjuvant radiation or chemoradiation is recommended.[5] The oncological outcomes of these two alternatives are similar but larynx preservation was reported to be superior in the definitive chemoradiation group.[2]

Organ preservation capability makes chemoradiation interesting. Surgery might entail complications in breathing, swallowing, and speaking that can severely affect the patients' quality of life.[5]

There is a scarcity of data regarding the outcome of this cancer in Iran; therefore, we aimed to assess the OS and disease-free survival (DFS) among patients undergoing definitive chemoradiation in our center. We assumed that the outcome was not promising based on our observations in the clinic.

Materials and Methods

Study design

In this retrospective cohort study, we evaluated patients with biopsy-proven SCC of the hypopharynx and treated with chemoradiation or radiation alone; this was done between 2007 and 2016 in the radiation oncology ward of Iran Cancer Institute affiliated to Tehran University of Medical Sciences. The study design was reviewed by the institutional review board of Tehran University of Medical Sciences and approved by the Ethics Committee for Research of Imam Khomeini Hospital (ethics code: IR.TUMS.IKHC.REC.1399.102). Upon admission, all participants provided written informed consent that the data in their medical archive would be used for research purposes.

Inclusion and exclusion criteria

The exclusion criteria consisted of non-curative intention of treatment and recurrent or second primary disease, de novo distant metastasis, and history of previous radiation to the head and neck.

Pretreatment evaluation

Pretreatment staging work-up included history taking, physical examination, laryngopharyngeal axis evaluation with laryngoscopy and esophagoscopy, computed tomography (CT) scan or magnetic resonance imaging (MRI) with contrast to assess the extent of primary tumor, and regional adenopathy. Neck ultrasonography (US) may be used to confirm the disease in the neck lymph nodes. The chest x-ray (CXR) was utilized to rule out pulmonary metastasis. The positron emission tomography (PET) scan was not used due to unavailability. Evaluation of nutritional status, swallow and speech mechanism, and mouth hygiene was mandatory before commencing the treatment. We used the 7th edition of AJCC for TNM staging.

Treatment description

The planned regimen for 3D conformal radiation therapy was 70 Gray (Gy) in 35 fractions, five fractions per week for seven weeks. Due to the high risk of cervical metastasis even in N0 clinical patients, it was necessary to carry out a comprehensive radiation of cervical lymph nodes from the base of the skull to clavicle. The main photon energy used for the treatment was 6 megavoltage (MV).

Simulation and immobilization and treatment planning of patients for 3D conformal radiation therapy were done according to our department's policy. For planning, the patient had to be in a supine position with head hyperextension to provide an adequate separation of the primary tumor and neck nodes from adjacent structure such as oral cavity and upper jaw. The patient was immobilized with a thermoplastic mask covering the head, and a marker was placed on the chin. The spiral CT scan without contrast was then obtained at 3 mm intervals. We did not utilize image-guided radiotherapy in this cohort.

Target volumes were delineated with respect to the information acquired by endoscopy, CT scan, MRI, and physical examination. Gross tumor volume (GTV) and CTV70 consisted of gross disease on imaging, and all nodes with short-axis diameter (SAD) larger than 1 cm. CTV60 was defined as CTV70 plus at least 1 cm margin including the entire hypopharyngeal subsite that is involved by tumor and the whole larynx. It also included the involved cervical lymph node levels. For N0 disease, the elective radiation dose was 46Gy, and it included levels II-IV and retropharyngeal lymph nodes. However, if the neck was positive, we treated levels Ib-V and retrostyloid nodes up to 60 Gy for the involved side and 46 Gy on the contralateral side based on the site of involvement in the neck. The geometrical margin for planning target volume (PTV) was based on proximity to the critical structures, usually falling in the range of 0-1cm.

For stage III and IV patients, we added chemotherapy to radiation in two settings. The induction chemotherapy was prescribed at the discretion of the treating physician using TPF (docetaxel 75mg/m^2, 5FU 425mg/m^2 bolus and maximum 750 mg per day, d1 to d4, and cisplatin 35mg/m^2 d1 to d3) or PF (5FU and cisplatin with same doses as in TPF). The concurrent chemotherapy consisted of either cisplatin 30-35 mg/m^2 weekly or 30-35 mg/m^2 d1 to d3 every three weeks. Carboplatin or cetuximab are not commonly used for concurrent chemotherapy in our institution. In the present study, sufficient chemotherapy was defined as receiving at least six weekly or two tri-weekly cycles of cisplatin.

Table 1. Characteristics of the patients (n=40)

Variable	Number (%)
Age(y)	
≤ 40	6 (15)
41-60	16 (42.5)
> 60	16 (42.5)
TNM[1] Stage (AJCC 7th ed.[2])	
II	3 (7.5)
III	14 (35)
IV	23 (57.5)
Site of involvement	
Pyriform sinus	19 (47.5)
Post-cricoid	10 (25)
Posterior wall	4 (10)
More than one site	6 (15)
Non-specified	1 (2.5)
Grade	
I	11 (27.5)
II	7 (17.5)
III	5 (12.5)
IV	1 (2.5)
Non-specified	16 (40%)

[1]Tumor node metastasis; [2]American Joint Committee on Cancer 7th edition

Patient evaluation during treatment

During induction chemotherapy, we assessed patients for any changes in the performance status, treatment toxicities, and abnormalities in laboratory tests. We also palpated neck nodes and observed primary tumor, if visible during physical examination between chemotherapy cycles. Afterwards, the patients were visited every week during radiation for the assessment of treatment compliance and incident toxicities through physical examination and laboratory tests.

Post-treatment follow-up

After treatment, we followed the patients every 4-6 weeks during the first six months with a physical examination by laryngoscopy; this

Table 2. Tumor and node stage of the patients

		Lymph Node				Total
		N0	N1	N2	N3	
T* Staging	T1	0 (0)**	0 (0)	1 (2.5)	0 (0)	1 (2.5)
	T2	3 (7.5)	1 (2.5)	2 (5)	0 (0)	6 (15)
	T3	6 (15)	7 (17.5)	7 (17.5)	2 (5)	22 (55)
	T4	7 (17.5)	2 (5)	2 (5)	0 (0)	11 (27.5)
	Total	16 (40)	10 (25)	12 (30)	2 (5)	40 (100)

*Tumor; **N= Number (%)

procedure was done every 1-3 months during the first year, every 2-4 months for the second year, every 4-6 month during years three to five, and every 6-12 months thereafter. CT scan or MRI was requested every 3-6 months during the first two years or as indicated by clinical findings. If recurrence or residue was suspected, it had to be confirmed by biopsy. Complete restaging was further done. Because the primary treatment was radiation, surgery was recommended for salvage therapy in recurrent or resistance cases.

Statistical analysis

We did not calculate the sample size for this study and included all the consecutive patients. The collected data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows Version 21 (SPSS Inc; Chicago, IL, USA). In all analytical tests, P <0.05 was considered as statistically significant. We used Kaplan-Meyer survival analysis to estimate actuarial OS and progression-free survival (PFS). OS was defined as the period between the start of radiotherapy to the last follow-up or censorship. PFS was defined as the period between the start of the radiation therapy and the recurrence, last uneventful follow-up, death, or censorship. We selected Cox hazards test to define the predictors of OS and PFS.

Results

Patients' characteristics

We analyzed the data of 40 patients in this study. The median age of the patients was 58 years (IQR: 50-68). 47.5% of the patients were females. The majority of our patients had a locally-advanced disease (stage III and IV) (Table 1). The tumor and node stages are shown in table 2.

Treatment characteristics

50% of the patients underwent induction chemotherapy for a median of two cycles. Of these, 60%, 25%, and 15% received TPF, PF, and other regimens, respectively. During radiation, 10% of the patients did not receive concurrent chemotherapy. However, among the patients receiving concurrent chemotherapy, 65% received cisplatin weekly (median six cycles), and 25% had cisplatin tri-weekly (median two cycles). Among the patients, 14 (35%) and 26 (65%) received <70 Gy and ≥70Gy, respectively. The median duration of radiation was 51 days (IQR=45-56).

The nutritional access (percutaneous gastrostomy or jejunostomy) was used for 7.5% and tracheostomy for 5% of patients to support feeding and airway, respectively.

Disease outcomes

In our study, the median follow-up time was 12 months (range:3-127). Local recurrence took place in 16 patients (40%) during the study period. In addition, four patients (10%) had distant metastasis. During this time, 17 (42.5%) patients died. Thus, the actuarial two-year OS rate was 29% (CI 95%=7.5-51.5) (Figure 1), and the two-year PFS rate was 22% (CI 95%=2.5-41.5). Large effect sizes were observed among the analyzed subcategories of the variables; however, we only found a statistically significant relationship between OS and the overall stage as well as the node status (Table 3). Occurrence of distant metastases had an almost significant relationship with OS. In the multivariate analysis, the node status significantly predicted the OS (P for multivariate Cox regression=0.042).

Discussion

In this retrospective cohort study, we observed a non-promising survival rate of 29% after two years in patients with hypopharyngeal carcinoma. The PFS rate was 22% at two years. The only variable that predicted OS was clinical node status at the time of treatment.

According to previous studies, hypopharyngeal cancer has a poor survival compared with other head and neck SCCs. In one study conducted in 1997, five-year OS was 33.4%.[9] In another report, which compared surgery followed by post-op radiation with definitive chemoradiation, 5-year DFS and OS were 22% and 42% for the former, while those were 15% and 30% for the latter.[10] In one study (2005), the two- and five-year disease-specific survival (DSS) were 72% and 52% in locally-advanced HPC patients undergoing LP.[11] In another study, the five-year actual survival rate was 60.3% in patients with T1 and T2 HPC treated by subglottic hemi-pharyngolaryngectomy with post-op radiation.[12] One study carried out in 2009 showed that hypopharyngeal cancer patients receiving definitive radiation therapy had a three-year DFS of 40.9%.[13] In a study performed on locally-advanced HPC treated by definitive chemoradiotherapy, the two-year OS and DFS were 32.8% and 29.3%, respectively.[14] One study (2016) compared surgery with definitive radiation in advanced HPC, reporting that oncological outcomes and OS were similar between the two groups. However, complications were more frequent in the surgery group, while the organ preservation was higher in the radiation group. The two- and five-year survival rates were 64% and 40%, respectively.

In our study, the two-year OS was 29%, which is lower than other studies. Such a poor OS may be attributed to the following reasons: due to unavailability, we were not able to use intensity-modulated radiation therapy (IMRT) in our center. With this technique patients can have a better disease control and swallowing function;[15] in some studies, patients treated with IMRT showed higher local control but with identical OS in comparison with 3DCRT.[16] The next reason is

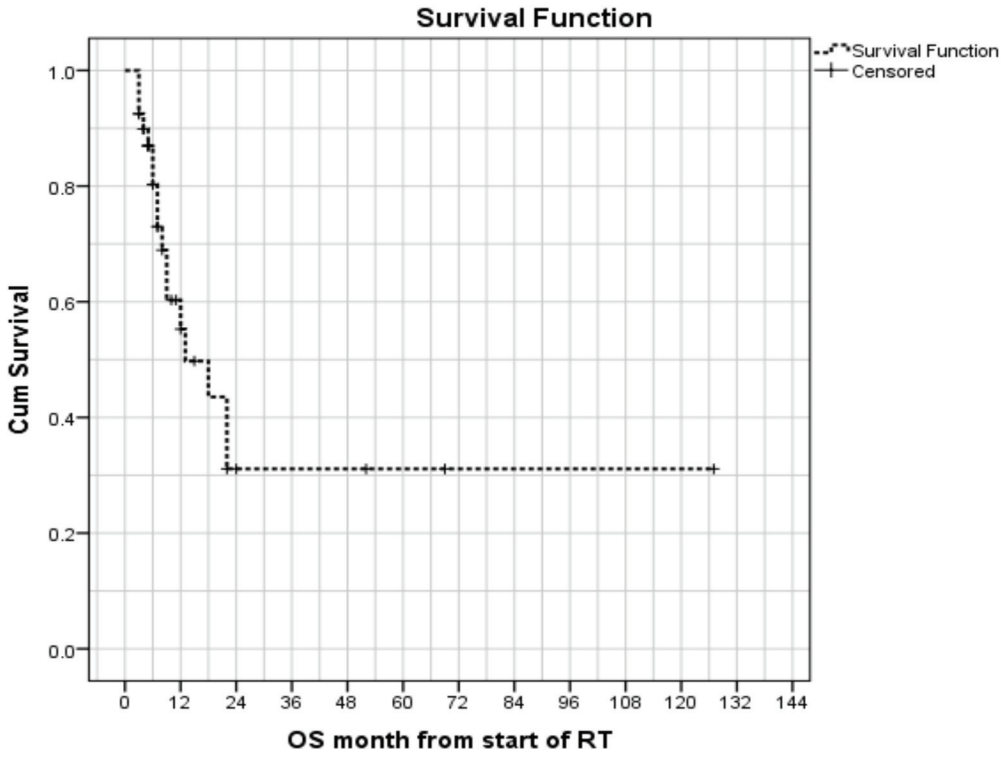

Figure 1. The Kaplan-Meyer curve is shown for the OS from the start of the RT in our cohort.
OS: Overall survival; RT: Radiation therapy; Cum: Cumulative

Table 3. Predictors of overall survival (Cox-hazard test)

		2-year OS	*P* for univariate Analysis	Hazard ratio (CI 95%)
Age	< 60	33%	0.442	Ref.[6]
	≥60	29%		1.46 (0.55-3.85)
Sex	Male	19%	0.439	Ref
	Female	41%		0.68 (0.26-1.80)
T status	T1-T2	34%	0.894	Ref
	T3-4	27%		1.08 (0.34-3.83)
N status	N0-1	50%	0.047	Ref
	N2-3	0%		2.68 (1.01-7.08)
TNM Stage	2-3	69%	0.029	Ref.
	4	0%		3.59 (1.14-11.30)
Tumor site	Pyriform sinus	33%	0.637	Ref.
	Other sites	25%		1.25 (0.48-3.25)
Induction CT	No	23%	0.895	Ref.
	Yes	44%		0.93 (0.34-2.58)
RT completed	No	28%	0.481	Ref.
	Yes	33%		0.7 (0.25-1.93)
Enough concurrent	No	30%	0.629	Ref.
chemotherapy	Yes	31%		0.79 (0.30-2.08)
Feeding tube	No	23%	0.121	Ref.
	Yes	100%		0.04 (0.0-33.84)
Tracheostomy	No	25%	0.220	Ref.
	Yes	100%		0.04 (0.0-122.87)
Locoregional	No	45%	0.669	Ref
Recurrence	Yes	8%		1.21 (0.47-3.19)
Distant Metastasis	No	37%	0.095	Ref
	Yes	0%		2.7 (0.84-8.71)

OS: Overall survival; T: Tumor; N: Node; CT: Chemotherapy; RT: Radiotherapy; Ref: Reference; CI: Confidence interval

that we did not accurately assess patients for nutritional support prior to radiation. As a result, some of the patients did not complete the treatment due to severe weight loss. This was due to the excessive load of patients referring to our center; thus, providing nutritional access necessitated a relatively long waiting list that would cause unacceptable delays or interruptions in treatment. During radiation, the incidence of pharyngeal dysphagia in hypopharyngeal cancer is higher than other sites of head and neck cancer; this can lead to weight loss, malnutrition, and aspiration, hence the necessity of nutritional support in these patients.[17] In some centers, a feeding tube is prophylactically provided for patients before the radiation therapy. However, only about one third of patients need nutritional access during treatment. It was shown that the feeding tube affected weight loss and the complications of treatment but not the OS.[18]

Our results showed the large effect size of feeding tube in terms of the two-year OS rate; however, due to the limited sample size, it was not significant. Another reason for our poor results is that approximately one third of our patients could not receive the planned dose of radiation therapy or concurrent chemotherapy. The final reason is that the management fear associated with the surgical complications of LP made most of the surgeons in our center refuse to carry out this procedure in the primary treatment of patients with locally-advanced HPC. As mentioned earlier, by implementing surgery, the outcome of locally-advanced HPC patients could be more promising.

Our study had some limitations. The design was retrospective and we were not able to accurately evaluate the complications. In some patients, the follow-up was not complete because our center was a referral; therefore, many patients from other regions did not return for routine follow-up. We could not obtain enough information from some of our deceased patients

as their families were not cooperative. Despite the rarity of hypopharyngeal cancer, our sample size was large and our treatment protocol was similar among all patients, which was the strength of the present study.

As shown, in our center, the outcome of definitive radiation therapy for HPC patients was poor compared with other studies. Thus, we need to implement a new protocol to improve the treatment results. We should try different strategies such as using more novel techniques for radiation with less toxicity, combining radiation with surgery, and providing early nutritional support for a better treatment tolerance.

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Conflict of Interest

None declared.

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