ORIGINAL ARTICLE

THE PATIENTS' CHARACTERISTICS AND NON-SURGICAL TREATMENT RESULTS FOR HYPOPHARYNGEAL CANCER IN SOUTHEAST OF IRAN: A 13-YEAR STUDY

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Background: Various modalities have been used to treat hypopharyngeal cancer. Non- surgical modalities include radiotherapy alone, sequential chemoradiation and concomitant chemoradiation or bio radiation. This study was conducted to evaluate the primary non-surgical treatment. **Methods:** A total number of 67 patients treated from March 2009 to January 2022 were enrolled in this study. The 2-year and 5-year survival rates were estimated using the Kaplan-Meier method. Log-rank test was used to compare the survival outcomes according to various factors. To define independent prognostic factors, we used Cox regression analysis. **Results:** The mean age of the patients was 56.2 years, and 55.2% of them were male. These patients were treated by radiation alone (9 patients) or induction chemotherapy followed by either radiation (4 patients), chemoradiation (33 patients), or bio-radiation (21 patients). The mean follow-up time was 18.12 months. The 2-year and 5-year overall survival rates were estimated to be 43% and 18%, respectively. Multivariate analysis showed that T stage, N stage, and treatment modality had a statically significant relationship with overall survival. **Conclusion:** The results of non-surgical treatment for hypopharyngeal cancer are not satisfactory. More studies are needed to investigate the role of salvage surgery.

Keywords: Hypopharyngeal neoplasm; Chemoradiotherapy; Survival analysis

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INTRODUCTION

Hypopharyngeal cancer is rare and its prognosis is poor.[1,2] Its global incidence rate was estimated to be 0.8 per 100,000.[3] According to a previous study, hypopharyngeal cancer accounts for 1.8% of all head and neck cancers in the southeast of Iran.[4] The poor prognosis of hypopharyngeal cancer is related to several factors such as diagnosis in advanced stages, predisposition to develop secondary cancers, alcohol abuse, associated comorbidities and malnutrition.[5] Considering the anatomical location of this cancer, it is important to preserve organ function in choosing the treatment modality.[6]

There are different modalities for the treatment of hypopharyngeal cancers.[5] Multi-modality approaches including surgery and adjuvant radiation or chemoradiation are the basis of treatment in locally advanced patients.[6] However, many patients are not suitable for surgery due to poor performance, so non-surgical modalities are chosen for them.[7] Non-surgical treatments include radiotherapy alone, concomitant chemoradiation and induction chemotherapy, followed by chemoradiation or bioradiation.[5] In recent years, adding cetuximab to chemotherapy regimens in the head and neck cancers has been proposed. Cetuximab has been investigated both in the induction phase and concomitant phase (bioradiation) of non-surgical approaches.[8,9] To the best of our knowledge, the results of non-surgical treatment in hypopharyngeal cancer are rarely reported. No study has been conducted on hypopharyngeal cancer in the southeast of Iran. Therefore, in this prospective study (from 2009 to 2020) an attempt was made to describe the demographic characteristics of the patients with hypopharyngeal cancer and to estimate the 2-year and 5-year overall survival rates following non-surgical treatments (radiotherapy alone and induction chemotherapy followed by chemoradiation or bioradiation). Also, an attempt was made to investigate the role of different prognostic factors in survival.

MATERIAL AND METHODS

This research was approved by the Ethics Committee of the Kerman University of Medical Science (Code: IR.KMU.REC.1401.236)

In this prospective study, the characteristics of the hypopharyngeal squamous cell cancer patients and their treatment information were recorded. These

patients were treated in the radiation referral centers of Kerman University of Medical Sciences from March 2009 to January 2022. The patients were enrolled in the study consecutively based on the census method. Exclusion criteria included the presence of metastasis, inadequate follow-up, insufficient recorded data and incomplete treatment. A phone call with the patient was used to complete the information.

The patients were assigned to receive radiotherapy alone (T_1-T_2N_0 patients) or radiotherapy plus systemic therapy (T_3-T_4 or N positive patients). Treatment modality was selected base on the oncology guidelines and physician choice and no randomization was performed. Clinical staging (based on physical examination, endoscopic examination, CT scan, and/or MRI) was used to do the analysis. Systemic treatment consisted of 3 cycles of induction chemotherapy with cisplatin (100 mg/m^2, on the first day), docetaxel (75 mg/m^2, on the first day), and 5-fu (750 mg/m^2, for 3 days) repeated every 3 weeks. After induction chemotherapy, those with a complete response received radiation therapy alone, and the rest received concomitant chemoradiation (carboplatin, weekly, AUC 1.5) or bioradiation (weekly cetuximab, 400mg/m2 in the first week and 250 mg/m2 in the following weeks). The choice between bioradiation and chemoradiation was based on changes in treatment methods over time, and no randomization was done. For radiotherapy, a total dose of 66 to 70 Gy was used by conventional method and 3D technique in all patients.

The main purpose was to estimate the 2- year and 5-year overall survival (OS). An attempt was made to investigate the role of different variables in OS. Tumour subsite (pyriformis versus other sub sites), T stage, N stage and treatment modality were considered as prognostic factors. Age and gender were considered as confounding factors. SPSS version 19 was used for analysis. The 2-year and 5-year survival rates were estimated by Kaplan- Meier method. For this purpose, the date of the first visit and the last visit were used. Lo g-Rank test was used to determine the difference in survival rates based on variable factors. To define various factors influencing the outcome, we used Cox Regression test. A *p*-value <0.05 was defined as the statistically significant level. The American Joint Committee on Cancer (AJCC) staging, version 8, was used for staging.

RESULTS

Patient characteristics and treatment information are shown in table-1. A total of 67 patients who met the inclusion criteria were analysed. The mean follow-up time was 18.12 months (from 1 to 90 months, standard deviation: 15.27). 13.5% (9 patients) were in stages I and II (T_1/T_2N_0). These patients had undergone radiotherapy alone. The remainder received induction chemotherapy first. Following induction chemotherapy, complete responders (4 patients) received radiotherapy and incomplete responders received chemoradiation (33 patients) or bioradiation (21 patients).

Figure-1 shows the survival rate curves in all patients, based on variable factors. Two-year and 5-year survival rates were calculated as 43% and 18%, respectively. Log-rank test revealed advanced T stage (higher than T_3, p<0.005), higher N stage (N_2-N_3, p=0.01), older age (≥61 years, p=0.04) as poor prognostic factors. However, gender (p=0.32), tumour sub-site (pyriformis subsite versus other subsites, p=0.06) and treatment modality (chemoradiation versus bioradiation, p=0.09) had no significant relationship with survival (Table-2). Multivariate analysis revealed that advanced T stage (hazard ratio:2.4, p=0.01), higher N stage (hazard ratio: 2, p=0.04) and bioradiation modality (hazard ratio: 4.3, p=0.008) were independent factors associated with poor survival. The relationship of gender (p=0.54), subsite (p=0.25), age (p=0.37) and group stage (p=0.99) with overall survival was not statically significant (Table-3).

Metastasis occurred in 37.3% of the patients (n=25) during the follow-up period. The sites of metastasis were the lung (16.4% of the patients, n=11), liver (6% of the patients, n=4), bone (7.5% of the patients, n=5), brain (3% of the patients, n=2), and multiple sites (4.4% of the patients, n=3). Salvage surgery was done in 3 patients after local recurrence. No mortality was seen after salvage surgery.

Table-1: The patients' characteristics and treatment modality

Parameter	Finding
Age	Mean: 56.2 years (range:27 - 77, SD:± 11.7)
Gender Number (%)	Male: 37 (55.2) Female:30 (44.8)
Sub site: Number (%)	Pyriformis sinus: 42 (62.7) Pharyngeal wall: 7 (10.4) Post-cricoid: 6 (9) Unknown: 12 (17.9)
Clinical T stage Number (%)	T_1: 12 (17.9) T_2: 37 (55.2) T_3: 15 (22.4) T_4: 3 (4.5)
Clinical N stage Number (%)	N_0: 11 (16.4) N_1: 27 (40.3) N_2: 23 (34.3) N_3: 6 (9)
Group stage Number (%)	I: 6 (9) II: 3 (4.5) III: 29 (43.3) IV: 29 (43.3)
Treatment modality: Number (%)	RT*: 9 (13.5) IND/RT~: 4 (6) CT/RT§: 33 (49.2) BT/RT$^{£}$: 21 (31.3)

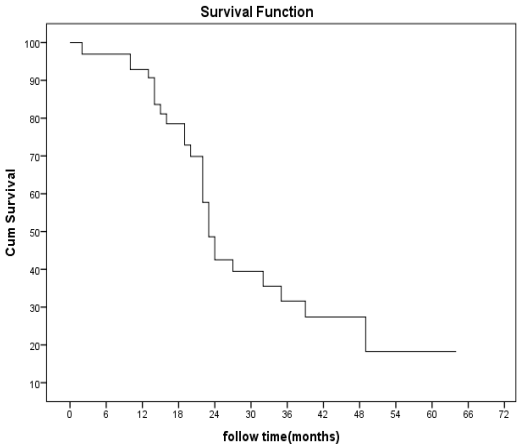
*: Radiotherapy alone, ~: Chemotherapy followed by radiation alone,$^{\S:}$ chemotherapy followed by chemoradiation, $^{£:}$ chemotherapy followed by bioradiation

Table-2: The mean survival time according to various factors

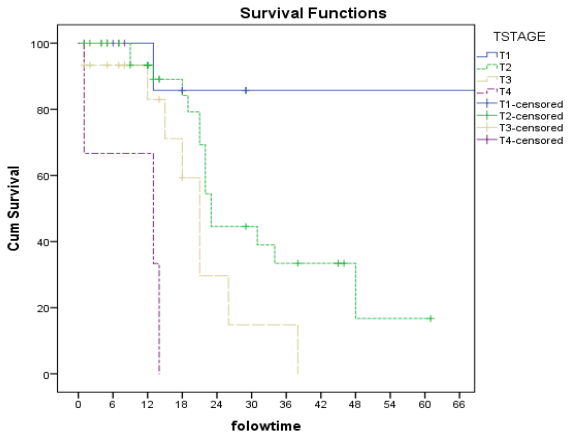
Variable	Mean survival (SD, Range)	*p*-value
All patients	35.9 (5.5,25.1-46.7)	-
Age		
<61 years	42.1(7.2,27.9-56.3)	0.04
≥61 years	19.8 (1.4,17-22.7)	
Gender		
Male	27.7 (3.6, 20.5-34.8)	0.32
Female	47.3 (8.7, 30.2-64.4)	
T stage		
T1	79 (10.18,59-98.9)	<0.005
T2	32.4 (3,9,24.7-40.1)	
T3	20.9 (3,29, 14.4-17.3)	
T4	9.3 (4.1,1.1-17.5)	
N stage		
N0	69.4 (12.5,44.9-93.6)	0.01
N1	29.9 (4, 21.9-38)	
N2	27.4 (4.1, 19.2-35.5)	
N3	14.9 (3.7, 7.5-22.38)	
Sub site		
Pyriformis	49.6 (9.8, 30.3-68.8)	0.06
other	24.6 (3, 18.7-30.6)	
Treatment		
Chemoradiation	30.3 (3.6,23.1-37.4)	0.09
Bioradiation	20.3 (3.3, 13.7-26.9)	

Table-3: Adjusted hazard ratio for OS according to the variables

Variables	Adjusted hazard ratio (95% CI)	*p*-value
Clinical T stage (Reference: T1-T2)	2.4 (1.2-4.8)	0.01
Clinical N stage (Reference: N0-N1)	2 (1-4.2)	0.04
Treatment modality (Reference: chemoradiation)	4.3 (1.4-13.1)	0.008
Gender (Reference: male)	0.7(0.2-1.9)	0.54
Sub site (Reference: pyriformis)	1.6 (0.6-4.1)	0.25
Age (Reference: <61 years)	1.5 (0.5-4.3)	0.37
Group stage: (Reference: stage I&II)	1 (0.1-8.5)	0.99



(A)



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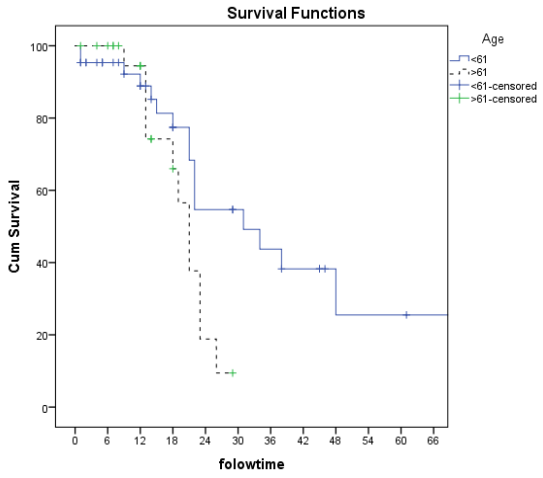

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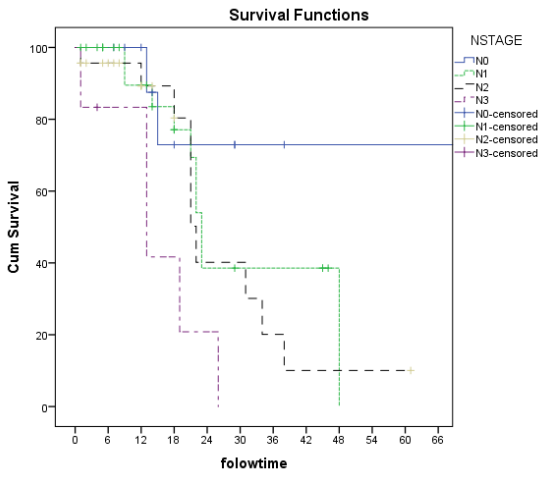

(D)

Figure-1: Survival curves according to various factors. A: all patients, B: according to T stage, C: according to age, D: according to N stage.

DISCUSSION

The ratio of hypopharyngeal cancer to all head and neck cancers varies widely in different regions.

According to WHO report, the highest ratio is in the South-Central Asia region (17.3%) and the lowest ratio is in Sub-Saharan Africa (3.7%).[3] The prevalence and prognosis of hypopharyngeal cancer in Iran are not clearly known. Usually, this cancer is studied together with other sub sites of the pharynx.[10–12]

The mean age of our patients was 56.2 years, which is consistent with previous studies.[5–7, 13] 45.8% of the patients were women. The male to female incidence rate of hypopharyngeal cancer varies in different countries. However, on average, this ratio is 5:1 all over the world.[14] It seems that the incidence of this cancer in Iran among women is higher compared to other countries. This issue needs further investigation. Similar to other studies, the Pyriformis sinus region was the most commonly involved sub-site.[4,15]

The best treatment for hypopharyngeal cancer is still unclear.[6] More than 20% of hypopharyngeal cancer patients come in advanced stages, and few of them live more than 2 years.[16] The rarity of this cancer and its poor prognosis have made it difficult to analyze treatment modalities. Attention to the preservation of the larynx has raised non-surgical methods in recent years.[17] In most of the definitive chemoradiation studies, hypopharyngeal cancers have been studied along with laryngeal cancers.[5]

Different survival rates have been reported in different studies.[18] Differences in treatment methods, chemotherapy protocols, radiotherapy techniques and patients' characteristics can justify this issue.[19] Based on one retrospective study (40 patients) conducted in Iran, the 2-year OS following non-surgical treatment was 29%.[20] A study was conducted by Chung EJ, *et al*. to compare induction chemotherapy followed by chemoradiation (ICT) or definitive chemoradiation (CRT) with primary surgery (SRT). In this study, overall survival for ICT, CRT and SRT groups were 44.6, 39.6, and 45.3%, respectively (p=0.1). In this study, three different cisplatin-based regimens were used in the induction phase.[7] In a retrospective study on 60 locoregionally advanced patients, the 3-year overall survival after surgery and chemoradiation was 38% and 43%, respectively (p>0.05).[21] In another study, the 5-year survival for primary surgery (14 patients) and chemoradiation with IMRT technique (33 patients) was estimated to be 44% and 33%, respectively (p=0.7).[22] Also, the analysis of retrospective (11 studies) and randomized (2 studies) studies showed that there was no difference in survival between surgical and non-surgical treatments.[5]

In the present study, the 2-year and 5-year overall survival rates were estimated to be 43% and 18%, respectively. Only 13.5% of our patients were in stages I and II. This issue can be effective in poor treatment results. In the present study, only 3 patients underwent salvage surgery after chemoradiation failure. In Chung EJ study 45% of the patients underwent salvage surgery after chemoradiation recurrence.[7] Salvage surgery improves the results of non-surgical treatments.[5] The difference between our results and the previous study may be due to the positive effect of salvage surgery. Also, all our patients were treated with 3-dimentional technique and IMRT was not used due to its unavailability in our center. IMRT may improve locoregional control.[20]

Various prognostic factors have been proposed in hypopharyngeal cancers. N stage, T stage, the number of involved nodes, and lymphatic invasion are among the most important factors.[15,23] In the present study, multivariate analysis showed that higher T and N stage and concomitant bioradiation in comparison with chemoradiation are independently associated with worse prognosis, which is consistent with previous studies.[21–23] Unpredictably, group staging had no significant relationship with survival. It may be due to lower number of our patients in early stages.

One limitation of this study was that some patients did not have proper follow-up. Also, some patients did not complete the treatment protocol. These patients were excluded from the study. This may affect the results.

CONCLUSION

The prognoses of hypopharyngeal cancer is poor. The overall survival rate for both surgical and non-surgical modalities is reported to be less than 50%. The role of salvage surgery after non-surgical treatments with the aim of improving results needs further investigation.

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AUTHORS' CONTRIBUTION

MHL: Study design, literature search, data collection, writing and analysis. AAM, HE: Patient's preparation, staging and treatment evaluation.

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