Original Article / Çalışma - Araştırma

An evaluation of the results of chemoradiotherapy and surgical treatment for hypopharyngeal cancer

Hipofarenks kanserinde kemoradyoterapi ve cerrahi tedavi sonuçlarının değerlendirilmesi

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Objectives: This study aims to evaluate the efficacy chemoradiotherapy and surgical treatment in patients with hypopharyngeal cancer.

Patients and Methods: Between January 2003 and July 2009, 48 patients (31 males, 17 females; mean age 55.5±13.4 years; range 29 to 84 years) who were diagnosed with hypopharyngeal cancer were retrospectively evaluated. The patients were assigned into surgery (n=17) and chemoradiotherapy (n=31) groups.

Results: The overall survival of the patients with advanced disease in the surgery group was statistically higher than those in the chemoradiotherapy group. The recurrence rate of the patients was 35.3% in the surgery group, whereas it was 41.4% in the chemoradiotherapy group.

Conclusion: Our study results indicated that the survival rates were higher in the surgery group. On the other hand, chemoradiotherapy had the advantage of laryngeal preservation.

Key Words: Chemoradiotherapy; hypopharyngeal cancer; induction chemotherapy; radiotherapy; surgery.

Amaç: Bu çalışmada hipofarenks kanserli hastalarda kemoradyoterapinin ve cerrahi tedavinin etkinliği değerlendirildi.

Hastalar ve Yöntemler: Ocak 2003 - Temmuz 2009 tarihleri arasında hipofarenks kanseri tanısı konulan 48 hasta (31 erkek, 17 kadın; ort. yaş 55.5±13.4 yıl; dağılım 29-84 yıl) retrospektif olarak değerlendirildi. Hastalar cerrahi (n=17) ve kemoradyoterapi (n=31) gruplarına ayrıldı.

Bulgular: İleri evre hastalığı olan hastalarda genel sağkalım oranları, cerrahi grupta kemoradyoterapi grubuna göre istatistiksel olarak daha yüksekti. Hastaların nüks oranları cerrahi grupta %35.3, kemoradyoterapi grubunda ise %41.4 idi.

Sonuç: Çalışma bulgularımız sağkalım oranının cerrahi grubunda daha yüksek olduğunu göstermiştir. Diğer yönden, kemoradyoterapi larenksin korunabilmesi ile ön plana çıkmıştır.

Anahtar Sözcükler: Kemoradyoterapi; hipofarenks kanseri; indüksiyon kemoterapisi; radyoterapi; cerrahi.

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Hypopharyngeal cancer is associated with the worst prognosis among the head and neck cancers. Hypopharyngeal cancers account for 7% of 600,000 new head and neck cancer patients treated worldwide each year.[1] Due to non-specific symptoms in the early stages, the disease is usually diagnosed in advanced stages, when the five-year survival rate is poor (31-47%).[2-7]

Surgery, radiotherapy (RT), and chemotherapy (CT) have been mostly used in various protocols. Similar survival rates for each treatment option are reported in the literature, but because there are no prospective randomized studies comparing the different protocols, a common treatment method has not yet been developed. In early stages of the disease, the success rates of surgery and RT are reported to be similar, and function-preserving surgery might be possible in selected cases. In advanced-stage disease, surgical treatment may even require total laryngopharyngoesophagectomy, and almost always includes total laryngectomy as part of the procedure. Despite surgery and adjuvant RT being associated with high mortality and morbidity, they are reported to provide the best survival outcomes in advanced-stage disease.[7,8-13] On the other hand, induction CT was investigated in the 1980s to identify radiosensitive tumors[14] and later in the evolution of the treatment protocols, concomitant chemoradiotherapy (CRT) was found to be more efficient on survival outcomes compared to induction CT.[1,9,15-17]

The aim of the present study was to analyze the results of treatment in patients with hypopharyngeal cancer.

PATIENTS AND METHODS

The records of all patients with hypopharyngeal cancer seen at our institution between January 2003 and July 2009 were retrospectively reviewed. The etiological risk factors, tumor histopathology, tumor location, tumor, nodes, and metastasis (TNM) staging, treatment protocols, follow-up visits, recurrences, salvage therapies and last status of the patients were reviewed. Patients who completed a minimum of one-year of follow-up after treatment and those who were monitored until recurrence or death were included in the study. Patients whose chart information was missing were excluded from the study.

In total, 54 patients were treated for hypopharyngeal cancer, but six of them were excluded from the study (missing records in the charts and inadequate follow-up). The remaining 48 patients (31 males, 17 females; mean age 55.5±13.4 years; range 29 to 84 years) were retrospectively evaluated. As predisposing factors, while 69% (33/48) of the patients had a smoking history, 13% (6/48) were alcohol consumers.

Tumor, node and metastasis staging was performed according to the American Joint Committee for Cancer (AJCC) 2002 classification using all available data among clinical, radiological and pathological findings.[18]

Treatment approach

The treatment recommendations for the patients were made at the Head-Neck Tumor Board according to the following principles. Those with early-stage disease (stage 1-2) were offered either surgery or CRT as a single treatment modality. Those with advanced-stage disease (stage 3-4) were recommended surgery, however, induction CT was also an option for patients who required total laryngectomy. Patients who partially (more than 50%) or completely responded to induction CT continued with CRT, whereas non-responders proceeded to surgery. The patients who had advanced-stage disease and poor prognostic factors received adjuvant CRT. Considering the survival advantage of concomitant CRT over induction CT,[1,9,15-17] patients who required total laryngectomy or did not accept surgery were treated with concomitant CRT after the year 2005. The patients with bulky lymph node metastasis at presentation who received CRT underwent planned neck dissection. Salvage therapy (surgery, CRT and CT) was performed for patients who experienced recurrence with curative intention or palliation.

As the surgical treatment, total laryngopharyngectomy, bilateral neck dissection, total thyroidectomy and gastric pull up/free forearm flap/pectoralis major flap was performed in 14 patients. Partial laryngopharyngectomy and bilateral neck dissection were performed in one patient and two patients had partial pharyngectomy and ipsilateral neck dissection.

The total RT dose was 60-66 Gy at 1.8 Gy/fraction for adjuvant intent, whereas the total dose was 66-70 Gy for definitive intent. Cisplatin and/or

Table 1. Distribution of the patients according to tumor, nodes, and metastasis classification

	N_0	N_1	N_2	N_3
T_1	1	–	–	–
T_2	8	1	4	–
T_3	2	1	3	1
T_4	10	1	14	2

cisplatin-taxotere were administered during RT as a concomitant approach. Induction CT protocols consisted of cisplatin and 5-fluorouracil, or taxotere, 5-fluorouracil and cisplatin for two and three cycles. After treatment, the patients were examined monthly during the first year, every two months during the second year, every three months during the third year, every four months during the fourth year, every six months during the fifth year and once a year afterwards.

For the analysis, patients were assigned to the surgery or CRT group according to the primary definitive treatment they received. Two subgroups were formed in the CRT group as induction CT and concomitant CRT. The results of the treatments were compared by means of recurrence rates and survival.

Statistical analyses were performed using the SPSS for Windows 16.0 version statistic program (SPSS Inc., Chicago, IL. USA). Disease-specific survival (DSS) and overall survival (OS) were estimated through Kaplan Meier test. The survival differences between groups were analyzed using log-rank test. The recurrence rates of the groups were compared with chi square test. Statistical significance was accepted when $p<0.05$.

The present study was conducted with the approval of the Ethical Committee of the Uludağ University (date: 23.06.2009; issue number: 2009-12/6).

RESULTS

Ninety-eight percent of the patients were diagnosed with squamous cell carcinomas, and one with undifferentiated carcinoma. The location of the tumor was in the pyriform sinus in 43 patients (90%), in the post-cricoid region in four patients (8%), and in the posterior pharyngeal wall in one patient (2%). Nine patients (19%) had early-stage disease (stage 1 in one patient; stage 2 in eight patients), whereas 39 patients had advanced-stage disease (stage 3 in four patients; stage 4a in 28 patients; stage 4b in four patients; stage 4c in three patients) (Table 1).

Twenty-seven patients (56%) presented with lymph node metastases at the time of diagnosis. Four out of six patients with N0 disease on presentation were detected to have microscopic metastases after the surgery.

Induction CT was the initial treatment in 18 patients. According to the tumor response (≥50% vs. <50%), 13 patients (72%) who responded more than 50% to treatment continued with CRT, while the remaining 28% underwent surgery and adjuvant RT. Eighteen patients received CRT while the remaining 12 patients had surgery as an initial treatment for definitive settings. Ten out of 12 patients also required adjuvant RT (83%).

Eventually, 31 patients were included in the CRT group and 17 patients comprised the surgery group. All patients but one in the surgery group had advanced-stage disease. In the CRT group, eight patients had early-stage disease, whereas 23 patients had advanced-stage disease (Table 2). Although the variation in tumor stages between the two groups was not statistically significant ($p=0.091$), we decided to perform the analysis also by including only patients in advanced-stages.

Table 2. Distribution of the patients in the surgery and radiotherapy groups according to clinical tumor, nodes, and metastasis classification

	Surgery				Radiotherapy			
	N_0	N_1	N_2	N_3	N_0	N_1	N_2	N_3
T_1	–	–	–	–	1	–	–	–
T_2	1	–	2	–	7	1	2	–
T_3	1	–	2	1	1	1	1	–
T_4	1	–	8	1	9	1	6	1

Although completion of a minimum of one-year of follow-up examinations was required, follow-up periods ranged between one month to 89 months because some patients died without completing one-year of follow-up (average: 23.29±23.69 months).

In the surgery group, two patients died in the first month following surgery; one developed carotid artery bleeding and the other one developed electrolyte imbalance and shock. In the group that received CRT, four of the eight patients who died in the early period were due to pneumonia, pulmonary embolism, pancytopenia and myocardial infarction. The remaining patients died from pulmonary metastasis (n=2) and pneumonia (n=2).

Twelve patients presented with local recurrences, and six patients presented with regional recurrences. One patient had distant metastases and a second primary tumor. The local and/or regional recurrence rate was 38%, with no difference between the surgery (35%) and RT groups (41%) (p=0.683).

As to salvage treatment, three patients underwent surgery, while three others received CRT and one patient received CT alone. Eleven patients refused or could not receive any further treatment due to poor medical condition. Four patients that received salvage therapies were alive without disease, however, two patients still suffered from disease. Three patients died in spite of salvage therapies. Thus, 14 (78%) of the 18 patients who experienced recurrence died due to the disease.

Twenty-three (47%) of the patients were alive without any manifestation of disease symptoms, whereas two patients were alive with recurrence. The cause of death in 19 (39%) of the patients was related to disease, whereas four patients were died due to reasons other than the disease. In the light of these results, the two- and five-year OS rates of the patients were 54.5% and 45.2% respectively; and both two- and five-year DSS rates of the patients were 59%. The laryngeal preservation rate in the CRT group was 45%.

The five-year OS and DSS rates were 64.7% and 70.6% in the surgery group and 45.2% and 54.8% in the CRT group, respectively (Figure 1, 2). When all patients were analyzed, there was no significant difference in the survival rates between the CRT and surgery groups (p=0.118). However, if the only patients with advanced-stage disease were selected for the analysis, the OS rate of the surgery group was significantly better (p=0.027) (Figure 3, 4). There were no statistical comparisons available in the early-stage patients due to the small sample size.

In the subgroup analysis of patients who received induction CT and RT and concomitant CRT, we did not find any statistically significant differences in survival outcomes (p=0.556).

DISCUSSION

Hypopharyngeal cancer presents with low survival rates due to the fact that it progresses extensively with submucosal invasion and early lymph node metastasis. Another reason behind the low survival rate is that the disease is often

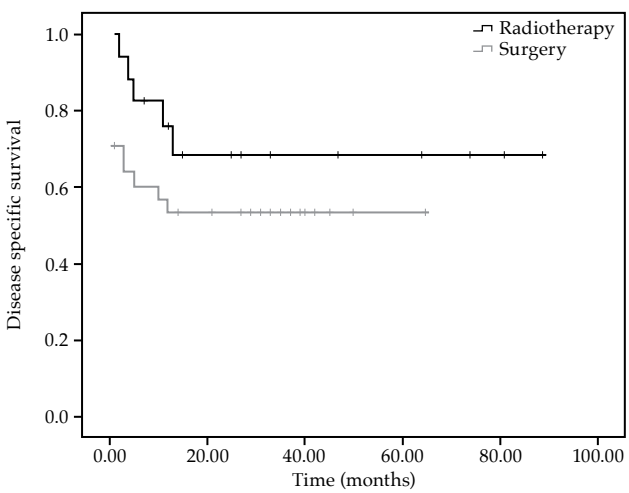

Figure 1. *Chart of five-year disease-specific survival rates of patients treated with radiotherapy and surgery.*

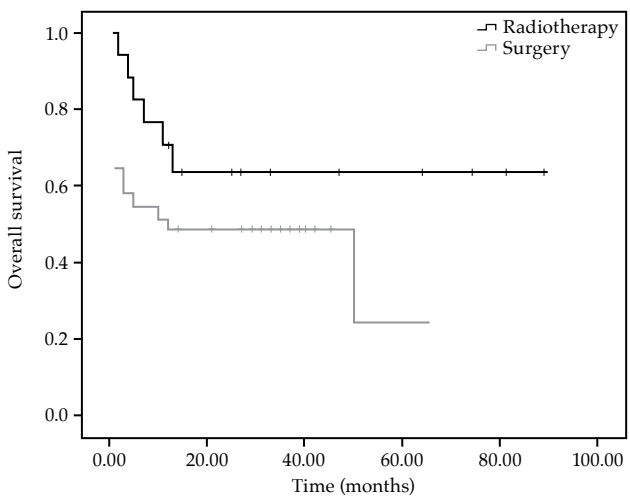

Figure 2. *Chart of five-year overall survival rates of patients treated with radiotherapy and surgery.*

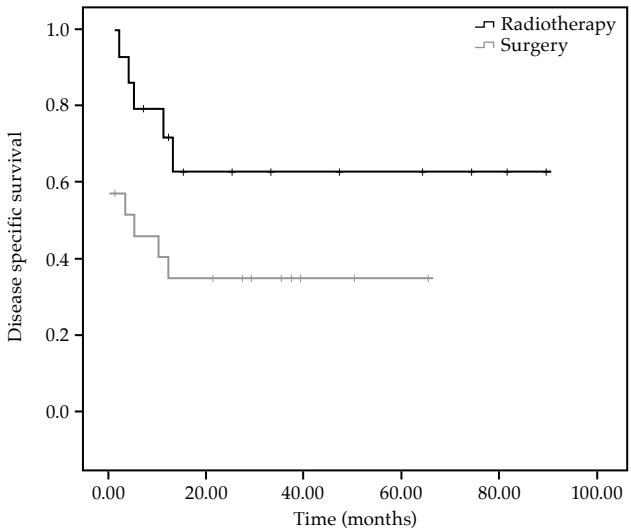

Figure 3. Chart of five-year disease-specific survival rates of advanced-stage patients treated with radiotherapy and surgery.

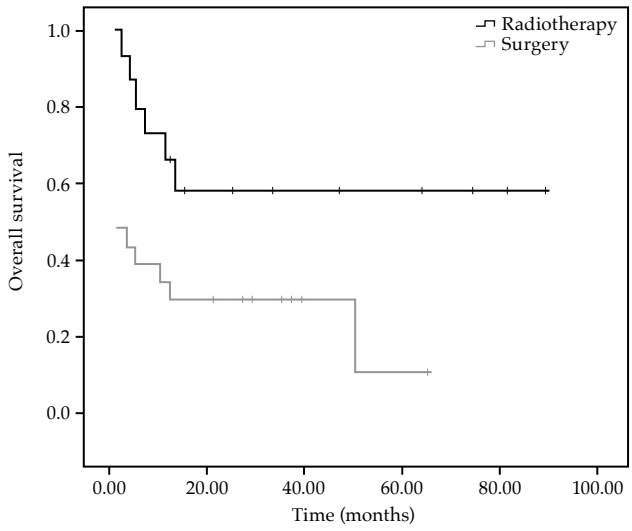

Figure 4. Chart of five-year overall survival rates of advanced-stage patients treated with radiotherapy and surgery.

diagnosed in the advanced-stage because of its subclinical progression. Many studies have demonstrated that the effectiveness of RT and surgery are similar in the treatment of early-stage tumors,[7,13,19-24] whereas the combination of both treatments is better than either alone for treatment of advanced-stage disease.[9,13,20,25-31]

Another factor that determines the prognosis of hypopharyngeal cancer is cervical lymph node metastases. In the literature, lymph node metastases was reported in 75% of cases, and 30-55% of them were found as occult metastases.[7,32-38] The rate of occult metastases in our study was 67%, which contributed to the advanced stage of the surgery group. As all clinically N_0 patients belonged to early stages which were mostly treated with RT alone, any occult metastases were not available to detect and this may have understaged the patients in the CRT group.

The rate of locoregional recurrence after treatment for hypopharyngeal cancer ranges between 17% and 32.5% in the literature.[6,8,15] The rate of recurrence in our study was consistent with these studies, and we did not find any significant correlation between treatment protocols and rate of recurrence.

The literature presents data that support the efficacy of both techniques. In a retrospective examination of 595 patients who were treated with RT and surgery, Hall et al.[39] reported no difference between these two treatments. In the multicenter study of 2,939 patients conducted by Hoffman et al.[4] five-year survival rate was reported as 50.4% for surgery; 48% for surgery and postoperative RT; and 25.8% for RT alone. However, it should be noted that the patients in the study were not randomized and treatment modalities and RT techniques were also different from current ones. In 143 patients diagnosed with postcricoid carcinoma, Axon et al.[8] reported that the five-year survival rate of patients without palpable lymph nodes in the neck was 63% in the surgery group and 25% in the RT group, whereas, five-year survival rates of patients with palpable lymph nodes in the neck was 10% in the surgery group and 0% in the RT group. The study by Lajtman and Manestar[40] conducted with 61 patients of advanced-stage pyriform sinus carcinoma reported that the five-year survival rate in patients who received surgery and adjuvant RT was 19%, which was 14% in patients who were treated with induction CT and RT. In the present study it was not possible to compare the outcomes in early-stage tumors as these almost all patients were treated with RT. On the other hand, surgery was found to have a superior oncologic outcome, especially in advanced-stage tumors.

In a multicenter study conducted by the European Organization for Research and Treatment of Cancer (EORTC), 202 patients were examined after they had been randomly assigned to either immediate surgery or induction CT.[14]

The five-year survival rates of both groups were similar, however, it was emphasized that half of the patients in the induction group had a functional larynx. This was comparable to our study with 45% larynx preservation rate.

Recent studies reported higher survival rates with improvements in RT techniques. Huang et al.[41] analyzed 47 patients with advanced-stage resectable hypopharynx carcinomas, 14 of whom were treated by surgery and 33 by intensity-modulated radiotherapy (IMRT) and CT and reported the five-year survival rates as 33% and 44%, respectively. Moreover, the five-year functional larynx preservation rate was 40%. In another study, Liu et al.[42] reported the five-year functional larynx preservation rate as 59.7% and the survival rate as 34.8% in 27 patients diagnosed with stage 2-4 hypopharynx carcinoma.

We used to start treatment with induction CT until we changed our policy to treat the patients initially with concomitant CRT in 2005, based on the reported survival advantage of concomitant CRT over induction protocol in the literature.[1,9,15-17] However, were not able to find any significant difference in survival between induction and concomitant CRT protocols in our study. This finding might be due to our small group of patients.

Conclusion, although survival was longer after surgery compared to RT, we report no statistically-significant difference between the two treatment modalities. In advanced-stage disease, longer overall survival has been associated with surgery rather than CRT. There is a need for randomized studies that compare surgery with concomitant CRT for hypopharyngeal cancer in the future.

Declaration of conflicting interests

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