RESEARCH ARTICLE / *Araştırma Makalesi*

The Evaluation of Clinical Characteristics and Treatment Results of Head and Neck Cancer Patients: Single Center Experience

Baş Boyun Kanseri Hastalarının Klinik Özellikleri ve Tedavi Sonuçlarının Değerlendirilmesi: Tek Merkez Deneyimi

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Abstract

Objective	The purpose of this study was to review the general characteristics, risk factors, treatment modalities of our head and neck cancer (HNC) patients and to calculate survival of patients, to evaluate the factors affecting our treatment results and survival.
Materials and Methods	Sixty-seven eligible patients with HNC were evaluated. The study data were obtained from the files of patients diagnosed with HNC who were followed up in Sakarya University Training and Research Hospital between 2011 and 2020.
Results	The median age at diagnosis was 62 ± 11.40 (range: 19 to 82), 62 in men and 50 in women. The most common location was larynx with 55% frequency. Cigarette and alcohol use rates were 69% and 18%, respectively. Secondary malignancy was observed in 18% (n = 12) of the patients, with the most common secondary malignancy being lung cancer (9%, n = 6). The stages of the patients at the time of diagnosis were 13.45% (n = 9), 22.47% (n = 15), 50.77% (n = 34) and 11.93% (n = 8) stage 1,2,3 and 4, respectively. Forty two percent of the patients had metastases at the time of diagnosis or metastasis developed during follow-up. Metastatic sites were lung in 13 patients (19.45%), lymph node in 10 patients (15%), bone in 7 patients (10.56%), and liver in 1 (1.50%) patient. Local recurrence occurred in 27% (n = 18) of patients. Local recurrence and / or metastasis developed in 50% of 58 patients with stage 1, 2 or 3. The majority of these patients were stage 3 (n = 17 (59%)). While the median disease free survival (DFS) of stage 1-2 patients was 49 ± 29.65 months (range: 0-107 months), the median DFS of stage 3 patients was calculated as 19 ± 10.95 months (range: 0-40 months). Median Progression-free survival (PFS) after first line chemotherapy (CT) with metastatic HNC cancer was 8±3 months (range: 2-14 months). Median overall survival (OS) was calculated 192±83 months in all patients.
Conclusion	Secondary malignancy development rates were found to be slightly elevated in our study. The total dose of cisplatin concurrent with RT was slightly lower than the other similar studies. The most preferred combination of chemotherapy in metastatic patients was cisplatin/5Fluorouracil/cetuximab. Our PFS results were slightly higher than in the literature.
Keywords	Head and Neck Cancer; Chemotherapy; Treatment

Öz

Amaç	*Bu çalışmanın amacı baş boyun kanserli (BBK) hastalarımızın genel özelliklerini, risk faktörlerini, tedavi modalitelerini gözden geçirmek ve sağkalımlarını hesaplayıp sağkalımı ve tedavi sonuçlarını etkileyen faktörleri değerlendirmekti.*
Gereç ve Yöntemler	*Altmış yedi BBK tanılı hasta değerlendirildi. Çalışmanın verileri Sakarya Üniversitesi Eğitim ve Araştırma Hastanesinde 2011-2020 yılları arasında takipli hastaların dosyalarından elde edildi.*
Bulgular	*Tanı anındaki medyan yaş erkekler 62, kadınlar 50 olmak üzere tüm hastalarda 62 ± 11,42 (aralık: 19-82) idi. En sık yerleşim yeri %55 oranla larinks idi. Sigara ve alkol kullanım oranları sırasıyla %69 ve %18 idi. Sekonder malignite oranı %18 olup en sık görüleni akciğer kanseriydi (%9, n = 6). Hastaların tanı anındaki evreleri 1,2,3 ve 4 sırasıyla %13,45 (n = 9), %22,47 (n = 15), %50,77(n = 34) ve %11,93 (n = 8) idi. Hastaların tanı anında ya da takibi sırasında olmak üzere toplam %42'si metastatikti. Metastaz bölgeleri 13 hastada (%19,45) akciğer, 10 hastada (%15) lenf nodu, 7 hastada (%10,56) kemik, ve 1 hastada (%1,50) karaciğerdi. Lokal rekürrens %27 (n = 18) oranındaydı. Evre 1,2 ve 3 58 hastanın %50'sinde lokal rekürrens ve/ veya metastaz gelişmişti. Bu hastaların çoğunluğu evre 3 hastalardı (n = 17 (%59)). Evre 1-2 hastalarda medyan hastalıksız sağkalım 49 ± 29,65 ay (aralık: 0-107 ay) iken evre 3 hastalarda medyan hastalıksız sağkalım 19 ± 10,95 ay (aralık: 0-40 ay) idi. Metastatik birinci seri kemoterapi sonrası medyan progresyonsuz sağkalım 8±3 ay (aralık: 2-14 ay) ve tüm hastalarda medyan genel sağkalım 192±83 ay idi.*
Sonuç	*Çalışmamızda sekonder malignite gelişme oranı hafif yüksekti. Radyoterapi eş zamanlı sisplatin total dozları literatürdeki benzer diğer çalışmalara göre hafifçe düşüktü. En çok tercih edilen metastatik birinci seri kemoterapi kombinasyonu sisplatin/5Fluorourasil/setuximab'tı. Progresyonsuz sağkalım sonuçları literatüre göre hafif yüksekti.*
Anahtar Kelimeler	*Baş ve Boyun Kanseri; Kemoterapi; Tedavi*

INTRODUCTION

Head and neck cancers (HNC) are a heterogeneous group of malignancies with different tumor biology, prognosis, and therapeutic response, including oral and nasal cavities, pharynx, larynx, paranasal sinuses, thyroid and salivary glands.[1] HNC is the sixth most common cancer worldwide, with over half a million cases and 300,000 deaths in 2008.[2] Tobacco and alcohol consumption are the strongest risk factors for HNC, however passive smoking, human papillomavirus (HPV) infection, Ebstein-Barr virüs (EBV) infection, low body mass index, low physical activity, poor diet, low socioeconomic status, and having a family history of cancer affect the risk.[3]

The primary treatment in HNC is surgery with or without lymph node dissection, depending on the stage of the disease at the time of diagnosis.[3] Although primary treatment is surgery, other treatment modalities can be applied alone or in combination before or after surgery depending on the stage of the tumor and its anatomical location. Adjuvant radiotherapy (RT) is performed after surgery to decrease the risk of local recurrence and increase survival, especially in patients with unfavorable pathological features. Chemotherapy (CT) can be used as an adjuvant treatment after surgical resection or in combination with RT as a palliative treatment for advanced or recurrent cancers.[4]

The purpose of this study was to review the general characteristics, risk factors, treatment modalities of our HNC patients and to calculate survival of patients, to evaluate the factors affecting our treatment results and survival. Then, to compare the compatibility of our results with the literature and analyze the factors affecting mortality.

MATERIALS and METHODS

This is a cross sectional study using data from January 1, 2011 and December 31, 2019. Sixty seven patients diagnosed with HNC and followed up at Sakarya University Training and Research Hospital were included in this trial. Inclusion criteria:

1. Above 18 years of age
2. Diagnosed with HNC

Exclusion criteria

1. Sarcoma, lymphoma and melanoma subtypes
2. Thyroidal cancers
3. Under 18 years of age

Ethics Committee approval was obtained from Sakarya University Ethics Committee (13.02.2020) (Ref. No.: 71522473/050.01.04/36)

Statistical analyzes

SPSS 22 statistical package program was used to assess the data obtained in the study. Descriptive statistics, Fisher's exact test and Chi-square test and Kaplan–Meier test for survival analysis was used. The possible factors identified with univariate analysis were further entered into the Cox regression analysis, with backward selection, to determine independent predictors of survival. Among correlated factors with similar effects on survival, only those with clinical significance were included. The proportional hazards assumption and model fit was assessed by means of residual analysis. A P value <0.05 was considered to be significant.

RESULTS

In this study, 67 eligible patients with HNC who were followed up between 2011 and 2020 at Sakarya University Training and Research Hospital were evaluated. Seven patients who didn't come to the outpatient clinic follow-up were not included in some statistical calculations, since there was no recent status information.

Of the patients 84% (n = 56) of the patients were male and 16% (n = 11) were female. The median age at diagnosis in all patients was 62 ± 11.40 (range: 19 to 82), 62 in men and 50 in women. When evaluated according to localization, the most common location was larynx with 55% frequency. Distribution according to tumor localization is

summarized in Figure 1. The average age of the patients with nasopharyngeal and oral cavity-oropharyngeal tumor localization was youngest and the average age was 48. Cigarette and alcohol use rates were 69% and 18%, respectively. When evaluated according to tumor site, the highest rate of smoking was laryngeal cancer with 86.55%. The frequency of alcohol use in laryngeal cancer is 25% and the highest compared to other localizations. Sixteen percent (n = 11) of the patients had a family history of malignancy. Secondary malignancy was present in 18% (n = 12) of the patients, with the most common secondary malignancy was lung cancer (9%, n = 6). Demographic and baseline characteristics of the patients are summarized in table 1.

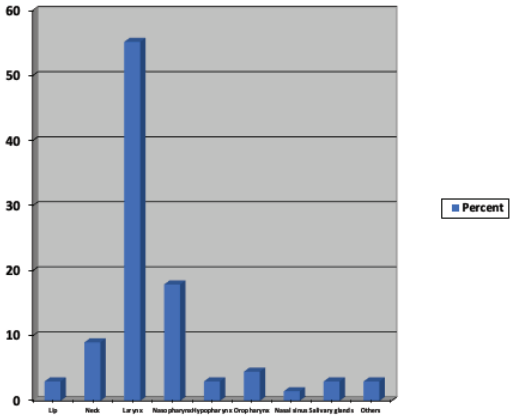

Figure 1. Distribution characteristics according to Tumor localization

Table 1. Demographic and baseline characteristics of patients (n=67)	
Sex	
Male, n (%)	56 (84)
Female, n (%)	11 (16)
Median age	62 ± 11.40 (19-82)
Stage (at the time of diagnosis), n (%)	
1	9 (13.45)
2	15 (22.47)
3	34 (50.77)
4	8 (11.93)
Metastatic patients, n (%)	28 (42)
Local recurrence, n (%)	18 (27)
Metastatic sites, n (%)	
Lung	13 (19.45)
Lymph node	10 (15)
Bone	7 (10.56)
Liver	1 (1.50)
Cigarette use, n, (%)	46 (69)
Alcohol intake, n, (%)	12 (18)
Family history of malignancy, n (%)	11 (16)
Secondary malignancy, n (%)	12 (18)

Survival analyses

Whether variables such as age, gender, disease stage, smoking, alcohol consumption, tumor localization, presence of cancer history in the family and having at least 1 cardiovascular disease risk factor (acute coronary syndrome, cerebrovascular disease, diabetes mellitus, hypertension etc.) was evaluated by proportional hazard analysis. Although some variables had effects on survival, having only stage 4 disease had a statistically significant risk of mortality than reference stage-1 disease (hazard ratio [HR]= 69.65; 95% CI =5.30-899, p=0,001). The analysis results of all variables are summarized in table 2.

Eleven patients (16.50%) received neoadjuvant / induction CT or chemoradiotherapy (CRT). 41.80% (n = 28) of the patients had an operation to primary. Five (7.50%) patients had postoperative surgical margin positivity.

Table 2. Multivariate Cox regression analysis of the factors affecting overall survival

Variables	HR(95% Cl)	P Value
Age	1.04 (0.98-1.10)	0.190
Gender	2.52 (0.48-13.18)	0.275
AJCC Stage [stage I (Ref)]		
II	1.17 (0.19-6.97)	0.850
III	1.89 (0.41-8.78)	0.415
IV	69.6 (5.3-899.8)	0.001*
Tabocco Use [None (Ref)]		
Use	0.72 (0.15-3.31)	0.672
Smoking Pack Use	1.01 (0.98-1.03)	0.285
Alcohol Use	0.18 (0.02-1.46)	0.111
Localization [Laryngeal (Ref†)]		
Nasopharyngeal	0	0.982
Others	1.28 (0.48-3.38)	0.617
Family history of malignancy (positive)	0.03 (0.00-10.75)	0.255
Cardiovascular disease (positive)	1.28 (0.45-3.66)	0.641

Abbreviations: HR, hazard ratio; 95% CI, 95%confidence intervals; AJCC, American Joint Committee on Cancer.
* Significant at p<0.050.
† Reference group

Of the patients 46.50% (n = 31) had received CRT. Four patients (6%) who received CRT were diagnosed with larynx carcinoma who received CRT due to surgical margin positivity. Although 1 patient had positive surgical margin, she didn't receive any postoperative treatment because she didn't want CRT. Weekly cisplatin, weekly carboplatin, weekly cisplatin / docetaxel and weekly setuximab were administered while receiving CRT to 27 patients (40.35%), 2 patients (3%), 1 patient (1.50%), and 1 patient (1.50%), respectively. Radiotherapy was administered simultaneously for 6 weeks and the weekly dose of cisplatin was 20 mg / m2 in 1 patient, 35 mg / m2 in 1 patient and 30 mg / m2 in other 25 patients. Of the patients 20.85% (n = 14) received RT as curative (n = 8, 12.45%) or adjuvant (n = 6, 8.42%) treatment.

Local recurrence and / or metastasis developed in 50% of 58 patients who were stage 1, 2 or 3. Local recurrence and / or metastasis developed in 50% of 58 patients, the majority of whom were stage 3 (n = 17 [59%]). Median disease free survival (DFS) of patients with stage 1,2 or 3 was 33 ± 15.45 months (2.72-63.28 months). While the median DFS of stage 1-2 patients was 49 ± 29.65 months (range: 0-107 months), stage 3 patients was 19 ± 10.95 months (range: 0-40 months) (figure 2a,b)

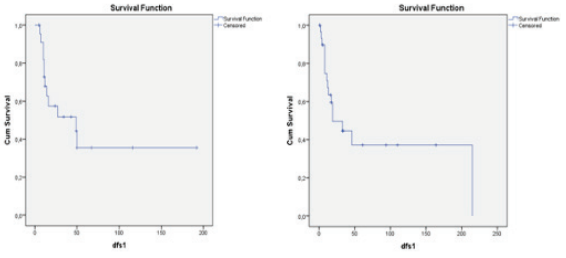

Figure 2.a: Disease free survival (DFS) curve of early-stage patients b: DFS curve of locally advanced stage patients

Chemotherapy agents administered to patients with metastatic stage is summarized in the table 3. Twenty-five of the patients who received CT as first line could be evaluated; data were not available for 3 patients because 2 patients left follow-up of outpatient and 1 patient did not accept CT. In patients with metastatic cancer median progression free

survival (PFS) after first line CT was 8±3 months (range: 2-14 months) (figure 3a), and 1 patient who received Cisplatin/5Fluorouracil (CF)/cetuximab was discontinued due to cetuximab allergy. One patient died due to sepsis whose median PFS was 6 months, while the patient had a CF-cetuximab response. One patient died after the first cycle of CT due to tracheosophageal fistula. Two patients died due to treatment-related (Docetaxel-CF and CF-cetuximab) side effects after first cycle of CT. Combinations with gemcytabine or docetaxel were often preferred as second line CT. Median OS was calculated 192±83 months in all patients (figure 3b)

Table 3: Chemotherapy agents administered to patients with metastatic stage

Treatments	Patient number (n)	Percent
CF	1	1.50
CF/Cetuximab	13	19.50
Cisplatin/Docetaxel	2	3
Cisplatin/Gemcytabin	1	1.50
Docetaxel/CF	5	7.50
Carboplatin/Paclitaxel	5	7.50
Abbreviation: CF: Cisplatin/5Fluorouracil		

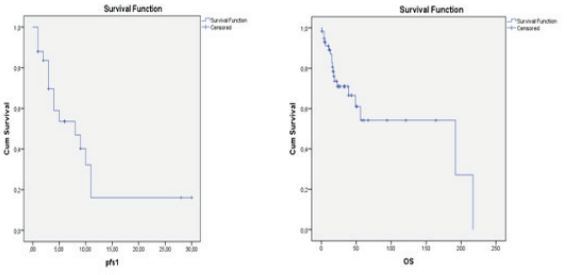

Figure 3, a: Progression free survival curve of first line treatment b: Overall survival curve of all patients

DISCUSSION

Head and neck cancers are a heterogeneous group of diseases and mostly originate from mucosal surfaces. A multidisciplinary approach is required in all stages of diagnosis and treatment, including head and neck surgeon, medical oncologist, radiation oncologist, dentist, pathologist, rehabilitation therapists, psychiatrist-psychologists and dieticians.[5]

Staging varies by region in HNC.[6] The tumor subtype is mostly squamous cell carcinoma, as in our patients. Apart from this, adenocarcinoma, lymphoma, melanoma and sarcoma types are also seen.[7] We excluded sarcoma, melanoma and lymphoma subtypes because patients with head and neck sarcoma and melanoma were evaluated separately and patients diagnosed with lymphoma are followed by hematology in our center. Head and neck squamous cell carcinomas represent approximately 3% of all human malignancies.[8]

The choice of treatment is based on the region, the stage of the tumor, and the functional, comorbid status of the patients. Approximately 30-40% of patients are stage I-II and these patients are usually treated with primary surgery or definitive RT.[7-9] Thirty six percent of our patients (n=24) were stage 1 and 2. Twelve of these patients were those who received adjuvant CT / CRT after the operation and 14 patients received definitive RT or CRT. Five-year survival in stage I-II patients usually reaches up to 70-90%.[7-9] Regularly follow-up of these patients after treatment is also very important because if there are cigarette and alcohol intake in etiology of HNC, the risk of secondary primary HNC and lung cancer are higher than others.[10] Some other studies have also shown that the risk of developing multiple primary malignancies is higher in oral cavity, pharynx, larynx, lungs, or esophagus tumors than others.[11-13] In our study, secondary malignancy was slightly higher than the other studies with the percent of 18 (n = 12) while in some studies with more patient series, the rate of secondary malignancy varies between 9% and 15.8%,[11,14] Cigarette and alcohol use rates were 69% and 18%, respectively and the highest rate of smoking and alcohol use was in laryngeal cancer patients with 86.55% and 25% respectively. So the highest rate of secondary malignancy was in laryngeal cancer. The most common secondary malignancy was lung cancer (9%, n = 6) in our study because in some patients, the distinction whether the mass in the lung is metastasis

could not be made exactly pathologically or radiologically. In other studies the most common secondary malignancy occured in the upper aerodigestive tract (40%–59%), lung (31%–37.5%), and esophagus (9%– 44%).8 Of the 12 patients with secondary malignancy were in 10 primary laryngeal carcinoma and 2 nasopharyngeal cancer.

Postoperative RT or CRT may be considered in early stage patients treated surgically if there is a surgical margin proximity or positivity, if the tumor is locally advanced, if there are risk factors such as perineural invasion, lymphovascular invasion, extranodal extension.[15] Postoperative treatments are also considered in patients who have malignant lymph node after lymph node dissection.[15-17] In our study, after surgery in early stage 8 patients received RT and 2 patients received CRT. One of these patients had surgical margin positivity and the other patients had one of the high risk factors.

In locally advanced disease, multimodal therapies are selected in which RT, CT and surgery are combined and organ preservation is aimed.[18] The rate of our locally advanced patients was 50.77 % (n=34) and was the highest. Options such as upfront surgery, then RT-CRT, induction CT, operation or only CRT are preferred according to the patient and tumor site. The majority of our locally advanced patients consisted of patients diagnosed with nasopharynx and larynx cancer. Surgical procedures were mostly performed in all but except nasopharyngeal cancer. Only one nasopharyngeal cancer patient underwent dissection to the neck lymph nodes remaining after CRT as a surgical procedure. Actually there are studies on open or endoscopic surgery in recurrent nasopharyngeal cancers.[19-20] Surgery is not preferred as the primary treatment method in nasopharengeal cancers. As concurrent CRT cisplatin is used weekly or tree weekly schedules with RT.[21] In our study none of the patients were given at a dose of 100 mg/m2 every 3 weeks of cisplatin simultaneously with RT due to potential toxicity concerns. Regardless of the primary site, the majority of our patients received 30 mg / m2 cisplatin weekly concurrent with RT. Moreover, 3-weekly cisplatin was not preferred in rural patients, considering that the risk of febrile neutropenia may increase due to their low socioeconomic level and low personal care. In a retrospective study Kose et al from Turkey, 3-weekly cisplatin and weekly cisplatin is compared in terms of survival and toxicity. While myelosuppression rates were higher in the 3-weekly cisplatin regimen, the mucositis rates were higher in the weekly regimen, but the difference was not statistically significant. Likewise, the majority of patients were in the weekly cisplatin regimen in Kose et al study.[22] Although 3 weekly 100 mg / m2 cisplatin is recommended as preferred regimen in our guidelines, it has been shown in other studies that it cannot be given due to increased myelotoxicity concerns in Turkey. In a meta-analysis comparing RT concurrent weekly and 3-weekly cisplatin regimens, the results of patients were evaluated according to who received definitive CRT and postoperative CRT.[21] In definitive treatment CRT setting, myelosuppression, nausea, vomiting and nephrotoxicity were found to be statistically significantly less in the weekly regimen compared to the 3-weekly regimen. However in the postoperative setting the two approaches were more equal with less differences in the cisplatin-induced toxicities, the weekly cisplatin induced more grade 3-4 dysphagia and weight loss.[21] Another noteworthy issue in our study was that patients received cisplatin at a maximum total dose of 180 mg from 30 mg /m2 weekly as a definitive or postoperative setting. This dose was lower than the total doses in other similar studies.[23-24]

Treatment options in recurrent and metastatic disease are cytotoxic CT, immunotherapy and molecular targeted agents.[25] Cisplatin-based chemotherapies are recommended as single agent or combination.[26-28] The KEYNOTE-048 study determined the use of pembrolizumab with or without CT as a first-line regimen metastatic or recurrent squamous cell carcinoma of head and neck.[29] This study showed that adding pembrolizumab to a combination of platinum and fluorouracil increases OS compared to a combination

of cetuximab plus a platinum and fluorouracil. Even for those with high PD-L1 expression (CPS ≥20), single agent pembrolizumab increases overall survival compared to a combination of cetuximab plus a platinum and fluorouracil.[29] There are studies in the literature with nivolumab as immunotherapy agent in metastatic HNC subsequent line, and a study with tremelimumab is also ongoing.[29-30] In our country since the reimbursement of immunotherapy drugs is not yet possible in HNC, none of our patients could be given immunotherapy agents. The majority of our patients received cisplatin-based chemotherapies. Cisplatin/Fluorouracil/Cetuximab combination was the most preferred agent, the other preferred regimens were cisplatin/fluorouracil/docetaxel, cisplatin/fluorouracil, carboplatin/paclitaxel and cisplatin/docetaxel. Median PFS was 8 ±3 months after first line treatment in metastatic HNC patients. In the EXTREME study, CF and CF-cetuximab chemotherapies were compared and median PFSs were found to be 3.30 and 5.60 months, respectively.[28] In KEYNOTE 048 trial pembrolizumab chemotherapy and cetuximab with chemotherapy were compared and median PFSs were 5.80 versus 5.20 months.[29] The reason we obtained higher results in terms of PFS is that our analyses includes nasopharyngeal and non-nasopharyngeal patients.

The most important limitations of our study; This study is single center study and the number of cases are low. Larger studies are needed on this subject

CONCLUSION

In conclusion, when we evaluated all our patients diagnosed with HNC, the most common histopathological subtype was squamous cell cancer as in the literature. Secondary malignancy development rates were found to be slightly elevated compared to other similar studies. Cisplatin was the most preferred CT agent at a weekly dose of 30 mg / m2 concurrent with RT. The total dose of cisplatin concurrent with RT was slightly lower. The most preferred combination of chemotherapy in metastatic patients was CF-cetuximab. Our PFS results were slightly higher than in the literature. We didn't have any patients receiving immunotherapy due to our health policies.

There is no conflict of interest between authors. No relationship has been established with pharmaceutical companies, biomedical device manufacturers or other companies that have a service or product related to the subject of the article.

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