



Research

A Comprehensive Analysis of Prognostic Factors in Head and Neck Squamous Cell Carcinoma: Experience from a Single-center

Baş ve Boyun Skuamöz Hücreli Kanserlerinde Prognostik Faktörlerin Kapsamlı Analizi: Tek Merkez Deneyimi

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ABSTRACT

Objective: The aim of this study is to evaluate the prognostic factors of adjuvant or definitive radiotherapy (RT) and/or chemoradiotherapy (CRT) in patients with squamous cell head and neck (HN) tumor treated in our clinic.

Methods: The prognostic factors in the patients who were treated between February 2017 and May 2021 were retrospectively evaluated. A total of 78 patients diagnosed with HN cancer were included in the study. RT was applied to tumor/tumor lodge $\pm$ lymphatics at a dose of 54-70 gray. The prognostic factors, side effects, and overall survival in patients were noted and evaluated.

Results: Of a total of 78 patients, 15 (19.2%) were female and 63 (80.8%) were male. The most common tumor location in the patients was larynx (53.8%), followed by oral cavity (24.4%), and oropharynx (15.4%). Twenty-seven (34.6%) patients were in the T2 stage. Additionally, most of the patients were N0 (39 patients, 50%), and 29 (37.2%) patients were N2. Forty-three (55.1%) patients underwent surgery. Forty-three (55.1%) patients received adjuvant RT. Concomitant chemotherapy with RT was administered to 46 (59%) patients. In all groups, significant differences were found in hemoglobin and platelets before and after RT. Borderline significant in white blood cells. N stage of the tumor, smoking habit, and tumor localization were found to be significant for survival.

Conclusion: In the treatment of HN cancers, disease-free survival and a functional life in which organs at risk are protected as much as possible are aimed. RT/CRT is a highly toxic, long-term, and organ-preserving therapy. One of the main goals is to provide a survival advantage by increasing local control and protecting patients from side effects.

Keywords: Head and neck tumors, squamous cell cancer, concurrent chemoradiotherapy, prognostic factors

ÖZ

Amaç: Bu çalışmanın amacı, kliniğimizde skuamöz hücreli baş ve boyun (BB) tümörü tanısı ile tedavi edilen hastalarda adjuvan veya definitif radyoterapi (RT) ve/veya kemoradyoterapinin (KRT) prognostik faktörlerini değerlendirmektir.

Gereç ve Yöntem: Şubat 2017-Mayıs 2021 tarihleri arasında tedavi edilen hastalarda prognostik faktörler geriye dönük olarak değerlendirildi. Çalışmaya BB kanserli toplam 78 hasta dahil edildi. Tümör/tümör loju $\pm$ lenfatiklere 54-70 gray dozda radyasyon tedavisi uygulandı. Hastalardaki prognostik faktörler, yan etkiler ve genel sağkalım not edildi ve değerlendirildi.

Bulgular: Toplam 78 hastanın 15'i (%19,2) kadın, 63'ü (%80,8) erkekti. Hastalarda en sık tümör yerleşimi larinks (%53,8) iken, bunu oral kavite (%24,4) ve orofarenks (%15,4) izlemekteydi. Yirmi yedi (%34,6) hasta T2 evresindeydi ve hastaların çoğu N0 (39 hasta, %50) ve 29 (%37,2) hasta N2 idi. Kırk üç (%55,1) hasta ameliyat edildi. Kırk üç (%55,1) hastaya adjuvan RT uygulandı. Kırk altı (%59) hastada RT ile eş zamanlı kemoterapi uygulandı. Tüm gruplarda RT öncesi ve sonrası hemoglobin ve trombositlerde anlamlı farklılıklar bulundu. Beyaz kan hücrelerinde sınırda anlamlılık bulundu. Tümörün N evresi, sigara içme alışkanlığı ve tümör lokalizasyonu sağkalım için önemli bulundu.

Sonuç: BB kanserlerinin tedavisinde hastalısız sağkalım ve risk altındaki organların mümkün olduğunca korunduğu fonksiyonel bir yaşam amaçlanmaktadır. RT/KRT oldukça toksik, uzun süreli, organ koruyucu bir tedavidir. Ana hedeflerden biri yan etkilerle lokal kontrolü artırarak sağkalım avantajı sağlamak ve hastaları yan etkilerden korumaktır.

Anahtar Kelimeler: Baş ve boyun tümörleri, skuamöz hücreli kanser, kemoradyoterapi, prognostik faktörler

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INTRODUCTION

Head and neck (HN) squamous cell carcinoma (SCC) is the seventh most common malignancy (1). There are 550,000 patients diagnosed with HN tumors (HNTs) worldwide each year; 300,000 of these patients lose their lives. Around 90% of all HNTs are SCC (2). The disease most commonly occurs as SCC that spreads from the mucosal lining of the upper respiratory-digestive tract, typically in the oral cavity, larynx, or pharynx (3). The disease is highly correlated with standard of living. The incidence increases as alcohol and/or cigarette consumption increases. Sixty percent of patients with HNT test positive for human papilloma virus (4).

A multidisciplinary approach is important to decide on treatment. The choice of treatment is based on histopathological features, tumor localization, and patient-related factors. Especially in its early stages, radiotherapy (RT) and surgery, alone or in combination, can eliminate regional disease (3). In terms of survival, there is no difference between these two methods (5).

SCC HNT with stage 3-4 are at high risk for regional recurrence and distant metastasis. Usually, combined treatment modalities are used. Treatment modalities include surgery, RT and chemotherapy (CT). Generally, RT is used after surgery or definitively, with or without CT. CT can be used as an induction. Surgery and/or RT following induction CT, definitive chemoradiotherapy (CRT), or postoperative therapy have been shown to improve local control and survival (6,7).

In this study, we aimed to evaluate the prognostic factors of squamous cell HN cancers, which were treated with adjuvant or definitive RT and/or CRT in our clinic.

METHODS

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2022-09, date: 09.05.2022).

A total of 78 patients diagnosed with HN cancer, who were treated in our clinic between February 2017 and May 2021, were included in the study. This is a retrospective study, and all participants provided written informed consent.

Patient inclusion criteria were as follows: oriented and cooperative patients aged 18-80 years diagnosed with HNT. In the study, the criteria for administering adjuvant RT and/or CT, determining CT schemes, assessing lymph node involvement, evaluating extracapsular extension (ECE), surgical margin positivity/proximity, and addressing

other histopathological risk factors [such as lymphatic vessel invasion (LVI), perineural invasion (PNI), and blood vessel invasion] were examined.

During the pre-RT evaluation process, history and physical examinations of the patients were performed. Positron emission tomography (PET) images, magnetic resonance imaging (MRI), and/or computed tomography images were taken. Complete blood count and blood biochemistry were evaluated for all patients before treatment. Laboratory tests were repeated weekly during treatment.

To create a RT plan, each patient underwent a special thermoplastic mask fixation in the supine position. The section thickness was taken as 2.5 mm for tomography images. Patients' planning computed tomography images were fused with pretreatment MRI and/or PET-computed tomography images for tumor localization and nodal involvement. Lymphatic areas were determined according to the disease indication in the Radiation Therapy Oncology Group (RTOG) HN atlas.

Monte Carlo planning analysis with 6 megavolt photon energy was used. Volumetric arc therapy plans were made on a linear accelerator device for RT. In a total of five fractions per week from Monday to Friday, with a daily fraction dose of 2 gray (Gy), an RT dose of 54 Gy was administered to prophylactic neck lymphatics, 60 Gy to involved neck lymphatics, and 66-70 Gy to tumor and/or tumor lodge. The patients were included in the treatment by performing cone-beam computed tomography every other day.

Concomitant CT with RT was given weekly or every 3 weeks. Cisplatin, carboplatin or cetuximab was used as CT agents. Cisplatin CT was administered at a dose of 75-100 mg/m² every 3 weeks, or 40 mg/m² per week.

Patients were checked weekly during RT and subsequently every 3 months following the first 6 weeks after RT. Side effects observed within 90 days from the start of RT were considered as early side effects. Those observed 90 days after RT were considered late side effects. Side effects were scored according to the American RTOG criteria (https://en.wikibooks.org/wiki/Radiation_Oncology/Toxicity_grading/RTOG).

Statistical Analysis

Statistical analyses were performed using SPSS software, version 15.0 (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether they are normally distributed. In our study, RT and CT treatments, as well

as descriptive analyses, were presented using means and standard deviations for normally distributed variables (hematological toxicity variables). Paired Student's t-test was used to compare the measurements at two time points (pre-treatment and post-treatment) for hematological variables (lymphocyte, hemoglobin, thrombocyte, white blood cell, neutrophil). The statistical significance value of $p < 0.05$ was accepted as significant. The effect of tumor stage (T, N), age, gender, smoking history, RT technique, and tumor location on the survival of squamous cell HN cancer was investigated using the log-rank test. The general characteristics of patients were noted. Frequency percentages were calculated for categorical variables.

RESULTS

Of a total of 78 patients, 15 (19.2%) were female and 63 (80.8%) male. The mean age of all patients is 60 years. The most common tumor location in the patients was larynx (53.8%) followed by oral cavity (24.4%) and oropharynx (15.4%). Twenty-seven (34.6%) patients were in the T2 stage, 18 (23.1%) patients were in T4, 17 (21.8%) patients were in T1, and 16 (20.5%) patients were in T3 stage. Most of the patients were N0 (39 patients, 50%) and 29 (%) patients were N2. Most of the patients were smokers (70 patients, 89.7%). 43 (55.1%) patients underwent surgery. Forty-three (55.1%) patients received adjuvant RT; 35 (44.9%) patients received definitive RT. In the evaluation of pathological findings of the operated patients, it was observed that 16 (20.5%) of patients had ECE. 27 (34.6%) patients had no ECE and 35 (44.9%) were unknown. Twenty-eight (35.9%) patients were PNI-negative and 12 (15.4%) patients were PNI-positive. Twenty-one (26.9%) patients were LVI negative and 14 (17.9%) patients were LVI-positive. Surgical margins were close or positive in 7 (8.9%) patients. Recurrence was seen in 11 (14.1%) of the patients. Metastasis was seen in 5 (6.4%) of the patients. 10 (12.8%) patients developed the need for hospitalization during the treatment. Characteristics of all patients are shown in Table 1.

Radiation therapy at a dose of 54-70 Gy was applied to the tumor/tumor lodgewith or without lymphatics. Ten (12.8%) patients underwent three-dimensional conformal RT and 68 (87.2%) patients underwent intensity-modulated RT. Concomitant CT with RT was performed in 46 (59%) patients. Thirty-eight (48.8%) patients received cisplatin, 3 (3.8%) received carboplatin and 5 (6.4%) received cetuximab. Twenty-five (32.1%) patients underwent cisplatin CT at a dose of 75-100 mg/m² every 3 weeks, and 21 (26.9%) patients received cisplatin CT at a dose of 40 mg/m² per week.

Table 1. Patient properties

		n	%
Gender	Female	15	19.2
	Male	63	80.8
Comorbidity	Yes	33	42.3
	No	34	43.6
	Unknown	11	14.1
Tumor location	Larynx	42	53.8
	Oral cavity	19	24.4
	Hipopharynx	5	6.4
	Orofarenks	12	15.4
T stage	T1	17	21.8
	T2	27	34.6
	T3	16	20.5
	T4	18	23.1
N stage	N0	39	50
	N1	10	12.8
	N2	29	37.2
Smoke	No	8	10.3
	Smoker	70	89.7
Operation	Yes	43	55.1
	No	35	44.9
Surgical margins	Positive	7	8.9
	Negative	36	46.2
ECE	Yes	16	20.5
	No	27	34.6
	Unknown	35	44.9
BVI	Yes	9	11.5
	No	15	19.2
	Unknown	54	69.2
LVI	Yes	14	17.9
	No	21	26.9
	Unknown	43	55.1
PNI	Yes	12	15.4
	No	28	35.9
	Unknown	38	48.7
RT technique	3DCRT	10	12.8
	IMRT	68	87.2
RT status	Adjuvant	43	55.1
	Definitive	35	44.9
Concomitant CT	Yes	46	59
	No	32	41
CT agent	Cisplatin	38	48.8
	Carboplatin	3	3.8
	Cetuximab	5	6.4
CT plan	Triweekly	25	32.1
	Weekly	21	26.9

Table 1. Continued

		n	%
Recurrence	Yes	11	14.1
	No	67	85.9
Metastasis	Yes	5	6.4
	No	73	93.6
Hospitalization	Yes	10	12.8
	No	68	87.2
TPN	Yes	5	6.4
	No	73	93.6
ONS	Yes	59	75.6
	No	19	24.4
IV support	Yes	22	28.2
	No	56	71.8

CT: Chemotherapy, RT: Radiotherapy, ECE: Extracapsular extension, BVI: Blood vessel invasion, LVI: Lymphatic vessel invasion, PNI: Perineural invasion, 3DCRT: Three-dimensional conformal radiotherapy, IMRT: Intensity modulated radiotherapy, TPN: Total parenteral nutrition, ONS: Oral nutrition solution, IV: Intravenous

The overall survival rate for three years is 59% in all data. The side effects on skin, oral mucosa, and esophagus were noted. 48.7% of the patients had grade 3 skin reaction; 80.8% of the patients had grade 3 mucositis; 14.1% had grade 2 mucositis; and 71.8% had grade 3 esophagitis, and 21.8% had grade 2 esophagitis. A complete blood count was performed to assess the patients' hematological toxicity. 84.6% of patients had grade 1 hematological toxicity and 15.4% of patients had grade 2 toxicity. The distribution of side effects is given in Table 2.

When hematological toxicity was compared in all groups, significant differences in hemoglobin and platelets were found before and after RT. Borderline significant in white blood cells (Table 3). A significant difference was found in hemoglobin and platelets when hematologic toxicity was compared between groups in those who received CRT alone (Table 4).

When survival analysis was performed according to patient characteristics, N stage of the tumor, smoking habit, and tumor localization were found to be significant. T stage of the tumor was found to be borderline significant (Table 5).

DISCUSSION

Local treatment methods such as surgery and or RT may be preferred alone for definitive treatment in early-stage diseases (8). In addition, concomitant CRT may be the most appropriate approach in cases where surgical intervention is restricted due to the anatomical location of the tumor (9). For locally advanced resectable diseases, surgery and adjuvant RT with or without CT are accepted as a standard treatment.

Table 2. Side effect

	Grade	n (%)
Skin reaction	0	2 (2.6)
	2	38 (48.7)
	3	38 (48.7)
Mucositis	0	2 (2.6)
	2	11 (14.1)
	3	63 (80.8)
	4	2 (2.6)
Esophagitis	0	3 (3.8)
	1	2 (2.6)
	2	17 (21.8)
	3	56 (71.8)
Haematological toxicity	0	0 (0%)
	1	66 (84.6%)
	2	12 (15.4%)
	3	0 (0%)

Table 3. Hematological toxicity in all groups

	Mean	SD	Number of patient	p-value
Pre-RT hemoglobin	12.8995	1.29388	78	0.000
Post-RT hemoglobin	12.2022	1.19837	78	
Pre-RT neutrophil	5.6335	3.09142	78	0.098
Post-RT neutrophil	4.5286	2.23554	78	
Pre-RT white blood cell	8.4519	3.36864	78	0.052
Post-RT white blood cell	6.2701	2.47090	78	
Pre-RT lymphocyte	1.9150	0.67887	78	0.102
Post-RT lymphocyte	1.0968	1.73616	78	
Pre-RT platelet	302.2758	85.68495	78	0.000
Post-RT platelet	266.8949	69.36562	78	

T-test paired samples statistical. RT: Radiotherapy, SD: Standard deviation

Meta-analyses have shown increased locoregional disease control and survival rates with CRT (10,11). For patients with inoperable locally advanced HN cancer, high-dose cisplatin-based concomitant CRT remains standard of care (12). In our study, 20.5% of patients were T3, 23.1% were T4, 12.8% were N1, and 37.2% were N2.

It is known that CRT treatment modality is associated with increased toxicity and is less tolerated in patients with poorer performance (12). Also, it increases the risk of mucositis, hematological suppression, and dermatitis (13). Cisplatin-based concomitant CRT improved patient survival but also increased toxicities such as gastrointestinal, haematological,

Table 4. Hematological toxicity only in CRT patients

	Mean	SD	Number of patient	p-value
Pre-RT hemoglobin	12.7524	1.11535	46	0.000
Post-RT hemoglobin	11.9822	1.17008	46	
Pre-RT neutrophil	5.8370	3.63124	46	0.108
Post-RT neutrophil	4.2220	2.24300	46	
Pre-RT white blood cell	8.6226	3.79959	46	0.066
Post-RT white blood cell	5.8461	2.47285	46	
Pre-RT lymphocyte	1.8354	.56599	46	0.498
Post-RT lymphocyte	0.8022	.32004	46	
Pre-RT platelet	299.7546	83.82116	46	0.005
Post-RT platelet	251.1913	72.39278	46	

T-test paired samples statistical. CRT: Chemoradiotherapy, RT: Radiotherapy, Std: Standard deviation

Table 5. Univariate analysis of patient characteristics

	3-year survival (%)	p-value
Age		
<50 (11)	52%	0.575
≥50 (67)	60%	
Gender		
Male (63)	58%	0.89
Female (15)	57%	
T stage		
1 (17)	75%	0.065
2 (27)	70%	
3 (16)	74%	
4 (18)	19%	
N stage		
N0 (39)	83%	0.009
N1 (10)	50%	
N2 (29)	23%	
Smoking history		
Yes (70)	46%	0.023
No (8)	100%	
RT technique		
3DRT (10)	37%	0.148
ARC/IMRT (68)	64%	
Tumor location		
Larynx (42)	82%	0.000
Oral cavity (19)	43%	
Oropharynx (12)	0	
Hypopharynx (5)	0	
3DRT: Three-dimensional radiotherapy, RT: Radiotherapy, ARC/IMRT: Arc therapy/intensity-modulated radiotherapy		

and renal (14-16). Adelstein et al. (14) reported that the rate of side effects of grade 3 and above was 89% in their study. In our study, 80.8% of patients had grade 3 mucositis, 14.1%

had grade 2 mucositis, 71.8% had grade 3 esophagitis and 21.8% had grade 2 esophagitis. Also, 48.7% of patients had grade 3 skin reactions, and 48.7% had grade 2 skin reactions. 15.4% had grade 2 hematological toxicity, and 84.6% had grade 1 hematological toxicity.

The study by Wu et al. (12) showed that CT causes hematological damage. In our study, hemoglobin and platelets significantly decreased in patients receiving CRT (p=0.000 for hemoglobin and p=0.005 for platelets).

In the study of Alterio et al. (1), the tumor located in the larynx and nasopharynx was shown to be a positive prognostic factor compared to other localizations. They also identified tumors located in the hypopharynx and other median regions as a poor prognostic factor. In our study, tumor location was found to be significant for survival. Three-year survival rates: larynx 83%; oral cavity 19%; hypopharynx and oropharynx 0%. The p-value was found to be significant (p=0.000). The study by Riaz et al. (17) reported that having T3-T4 tumors was a poorer prognostic factor than T1-T2 tumors. In our study, 3 years' survival for T4 tumors was 19%. The p-value was found to be borderline significant (p=0.065). Also, in our study, N stage and smoking history were found to be significant for survival. The p-values are 0.009 for N stage and 0.023 for smokers.

Study Limitations

This analysis has some limitations. First, its retrospective and single-center nature limits the generalizability of the information obtained. The relatively small sample sizes provide potentially significant prognostic value in proportion to the overall power distribution. Furthermore, some pathological and clinical data, such as human papillomavirus status and p16 expression, may be relevant for predicting survival and treatment response in each patient.

CONCLUSION

In conclusion, the treatment of HN cancers aims to achieve disease-free survival and a functional life, in which organs at risk are protected as much as possible. RT/CRT is a highly toxic, long-term, organ-preserving therapy. One of the main goals is to provide survival advantage by increasing local control with and to protect patients from side effects.

ETHICS

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2022-09, date: 09.05.2022).

Informed Consent: This is a retrospective study, and all participants provided written informed consent.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: G.P.S., Concept: G.P.S., E.E.Ö., M.K.B., M.F., E.K.Ü., Design: G.P.S., Data Collection or Processing: G.P.S., M.K.B., M.F., Analysis or Interpretation: G.P.S., M.K.B., E.K.Ü., Literature Search: G.P.S., E.E.Ö., M.K.B., M.F., Writing: G.P.S., E.E.Ö., M.F., E.K.Ü.

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