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ORIGINAL ARTICLE

Factors predicting the development of distant metastases in patients with head and neck squamous cell carcinoma: A retrospective study from a single centre

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Summary

Purpose: *The presence of distant metastases (DMs) after the initial treatment of head and neck squamous cell carcinoma is associated with a poor outcome. The incidence of DMs in head and neck cancer is about 4-26%. The purpose of this study was to evaluate the prevalence of distant metastases and the factors predicting the development of DMs.*

Methods: *Between January 2000 and December 2010, 292 patients with head and neck squamous cell carcinoma were included in this study.*

Results: *Thirty three patients (11.3%) developed local recurrences, 27 patients (9.2%) developed DMs. The median post DMs survival was 23.4 months (range 1.8-229.1). The factors that significantly increased the risk of DMs were the presence of local recurrence (p=0.0001, OR:17.32, 95% CI:4.86-19.90), pathologically positive neck (p=0.008, OR:5.97, 95% CI: 3.25-10.45), and primary tumor localized in oral cavity or lip (p=0.035, OR:2.6, 95% CI:1.43-4.65).*

Conclusion: *Patients with these factors should be considered candidates for adjuvant systemic treatment and evaluated for early detection of DMs during follow-up.*

Key words: *distant metastases, head and neck cancer, predictive factors*

Introduction

Head and neck squamous cell carcinoma accounts for 3% of new cancer cases in the United States [1]. The locoregional control rate was improved over last three decades but the survival rate of patients with head and neck carcinoma has not been changed [2]. This may be due to deaths from other diseases, a second primary tumor, or development of DMs [3]. As DMs develop, the chance for cure becomes low and survival decreases. The incidence of DMs in head and neck cancer is about 4-26% [4-6]. Previous studies have indicated that survival ranges between 4.3 and 7.3 months after development of DMs [7-9]. Several studies have evaluated clinicopathological risk factors associated with the development of DMs. The most common risk factors revealed are primary site, advanced stage, younger age, locoregional control, metastatic lymph nodes and nodal sular extension [8,10].

The purpose of this study was to evaluate the prevalence of DMs and the factors predicting the development of DMs.

Methods

Study population

Between January 2000 and December 2010, 329

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Table 1. Patient and disease characteristics

Parameter	*No. of patients (%)**
Age, years	
Median (range)	55 (18-84)
Gender	
Male	228 (78.1)
Female	64 (21.9)
Primary site	
Oral cavity	55 (18.8)
Oropharynx	6 (2.1)
Hypopharynx	13 (4.5)
Larynx	129 (44.2)
Nasopharynx	89 (30.5)
T stage	
T1-2	138 (47.3)
T3	81 (27.7)
T4	65 (22.3)
N stage	
N0	112 (38.4)
N1	54 (18.5)
N2	108 (37)
N3	12 (4.1)
TNM stage	
I	20 (6.8)
II	44 (15.1)
III	88 (30.1)
IV	135 (46.2)

*Sum may be less than total number of patients because of lack of data for a given variable

patients with head and neck squamous cell carcinoma were treated at the Department of Medical Oncology, Gazi University Hospital. Thirty seven patients were excluded from the study for incomplete data, lost to follow-up, or as a result of primary tumors located on different sites such as paranasal sinuses and auditory canal; the remaining 292 patients were available for this analysis. The data used in this study were obtained retrospectively from the Hospitals' databases. Tumor location was classified as oral cavity, oropharynx, hypopharynx, nasopharynx and larynx. Tumor stage was determined according to TNM classification. Treatment modalities were not analyzed because of differences in dosage and unreliability of such data in a retrospective study. For each patient, age, sex, stage at initial diagnosis, nodal status, anatomic site, differentiation, presence of recurrence and DM were recorded. The routine follow up program consisted of medical examination and locoregional examinations at 3-month intervals in the first and second year, 4-month intervals between the third and fifth years, and annually thereafter. Magnetic resonance imaging (MRI), computerized tomography (CT), and positron emission tomography (PET) were used to detect DMs in patients who had symptoms. Distant metastasis free survival (DMFS) was defined as the time from the end of treatment till the date of detection of systemic metastases.

Statistics

All statistics were calculated using SPSS version 21 (SPSS Inc., Chicago, IL). Descriptive statistics were calculated for baseline demographic and clinicopathologic characteristics. Survival rates were calculated using the Kaplan-Meier analysis. The log rank test was used to identify the features of patients with head and neck squamous cell cancer that were predictive of DMs. We also employed the Cox proportional hazards model for multivariate analysis. Adjusted hazard ratio (HR), 95% confidence intervals (CI), and corresponding p values were calculated. The variables that reached statistical significance ($p<0.05$) in this model were then deemed to be independent predictors of DMs.

Results

Patient characteristics

Table I shows the baseline characteristics of the 292 patients included in this study. There were 228 (78.1%) males and 64 (21.9%) females with a median age of 55 years (range 18-84). The primary tumor sites were larynx in 129 patients (44.2%), nasopharynx in 89 (30.5%), oral cavity in 55 (18.8%), hypopharynx in 13 (4.5%), and oropharynx in 6 patients (2.1%). Disease stage at initial presentation was I in 20 patients (6.8%), II in 44 (15.2%), III in 88 (30.1%), and IV in 135 patients (46.2%) (Figure 1).

Among these 292 individuals, 27 (9.2%) patients were diagnosed as having DMs during the follow-up. The sites of DMs were as follows: lung (4.5%), multiple (2.9%), bone (1.7%), and brain (0.7%). The 5-year DMFS was 87.3%. Thirty three patients (11.3%) developed local recurrences, and 27 (9.3%) developed DMs. Of these, 8 patients (29.6%) with DMs had died at the end of the study. The median post DMs survival was 23.4 months (range 1.8-229.1).

Factors predicting the development of distant metastases

The development of DMs was highest in oral cavity and lip squamous cell carcinoma (19.2%). In univariate analysis, primary tumor site (p=0.003), clinical stage (p=0.004), pathologically positive neck (p=0.035), and presence of recurrence

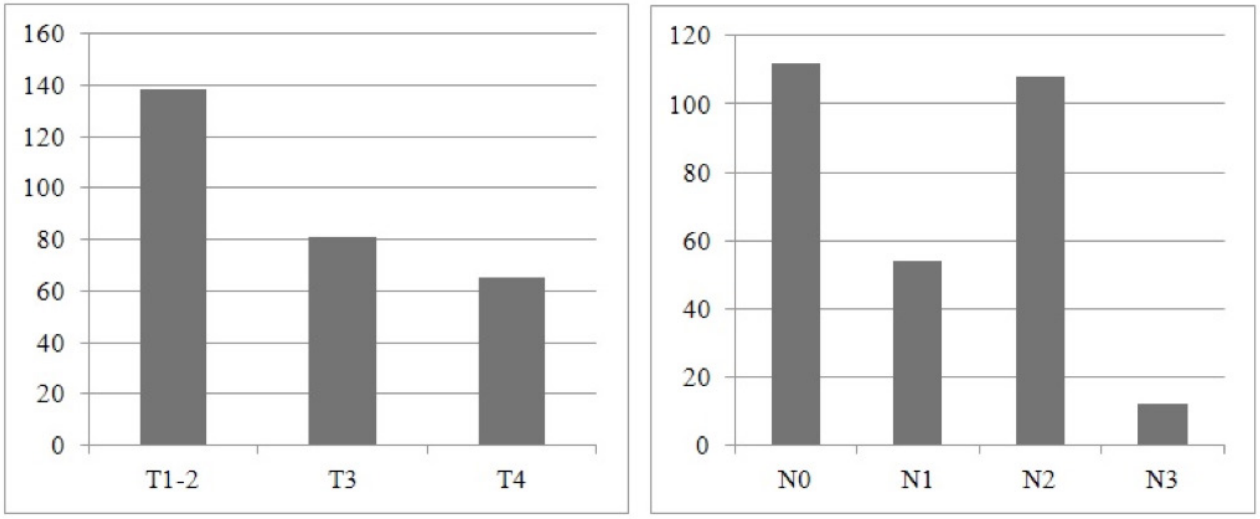

Figure 1. Clinical T and N stage of patients at initial presentation.

(p=0.0001) were significant predictive factors for DMs. In the Cox proportional hazard model, presence of local recurrence (p=0.0001, OR:17.32, 95% CI:4.86-19.90), pathologically positive neck (p=0.008, OR:5.97, 95% CI: 3.25-10.45), and primary tumor site (oral cavity and lip ; p=0.035, OR:2.6, 95% CI:1.43-4.65) remained independent predictors of DMs (Table 2).

Discussion

The presence of DMs after the initial treatment of head and neck squamous cell carcinoma is associated with poor outcome. The incidence of DMs reported in the literature is highly variable ranging from 4 to 26% [4-7]. The most common site of distant metastasis from head and neck cancer is the lung [11]. DMs were developed in 9.2% of all patients during the study period. Our data showed that the lungs were the most common site for DMs (48%). A retrospective study including 5019 upper respiratory and digestive tract squamous cell carcinomas patients analyzed the frequency of DMs between 1948 and 1973. The incidence of DMs was 11% in that study. The most common sites were lung (52%) and bone (20%) [12]. A previous study included 2550 patients with squamous cell carcinomas of the larynx and hypopharynx, and demostrated that DMs developed in 217 patients (9%) [13]. Another study revealed a distant metastatic rate of 11% [7]. Most DMs develop within 2 years from the time of initial diagnosis [14].

In our study the higher incidence of DMs was seen in oral cavity and the lip (19.2%). This data is not consistent with other studies, that reported a higher risk in hypoharyngeal and nasopharyngeal tumors [7,15]. Of note, other reports revealed that tumor site had no significant influence on the development of DMs [7,16].

Some authors reported an increased risk of DMs with T classification [14]. But in our study we couldn't find any association between T classification and the incidence of DMs.

Previous studies have revealed that extensive nodal disease was connected with increased risk of DMs for each primary site. Larger primary tumors were also more likely to develop DMs [8,17]. Our study showed that pathologically positive neck have a higher risk of DMS. A retrospective study reported that the grade of tumor differentiation, and the presence, number and site of nodal metastases were significantly associated with DMs. That study included 443 patients with surgically treated primary head and neck squamous cell carcinoma and showed that patients with bilateral lymph node metastases had a higher risk of DMs [6]. Some authors have reported that >3 lymph nodes are associated with development of DMs [6,7,18]. Extracapsular spread is also reported as a risk factor for the development of DMs [19,20]. In our study, data about extracapsular spread was incomplete so we couldn't analyze the influence of this factor. Disagreement exists on the influence of the grade of differentiation of the tumor on the appearance of DM. Some authors found that poorly differentiated tumors had greater tendency to metastasize [8,17].

Table 2. Clinicopathological factors predicting distant metastases

Factors	*Patients N (%)**	*5-year DMFS (%)*	*Univariate p value*	*Multivariate p value*
Age (years)			0.518	
<45	61 (28.8)	92.5		
45-60	126 (43.2)	89.3		
>60	103 (35.3)	86.5		
Gender			0.683	
Female	64 (21.9)	86.5		
Male	228 (78.1)	94.8		
Primary site			0.003	0.035
Oral cavity	56 (19.2)	76.5		
Hypopharynx	13 (4.5)	78.8		
Supraglottis	81 (27.7)	86.4		
Glottis	47 (16.1)	95.8		
Nasopharynx	89 (30.5)	90.2		
Clinical stage			0.004	NS
1	20 (6.8)	100.0		
2	44 (15.1)	91.4		
3	88 (30.1)	94.2		
4	135 (46.2)	87.0		
Nodal status			0.035	0.008
N0	110 (37.6)	92.7		
Unilateral metastasis	89 (30.5)	85.7		
Bilateral metastasis	93 (31.8)	81.6		
Presence of recurrence			0.0001	0.0001
Present	76 (26.1)	62.4		
Absent	216 (73.9)	97.7		
Differentiation			0.144	
Undifferentiated	44 (15.1)	95.1		
Poor	35 (11.9)	89.1		
Moderate	62 (21.2)	76.8		
Good	70 (23.9)	93.6		
Surgical margin			0.266	
Negative	77 (26.3)	78.5		
Positive	17 (5.8)	69.9		

DMFS: distant metastases free survival, NS: not significant
*Sum may be less than total number of patients because of lack of data for a given variable.

Treatment modalities for the prevention and early management of DMs are important for prolonging overall survival of these patients. In a previous study including 462 patients with head and neck squamous cancer, surgery was performed and patients received postoperative radiotherapy with or without adjuvant chemotherapy. There was no difference in the overall survival and in the locoregional control with adjuvant chemotherapy, but the incidence of DMs was decreased with adjuvant chemotherapy. In our study the patient population was heterogeneous, so the role of treatment modalities in the development of DMs was not analyzed.

There is no consensus for screening DMs in patients with head and neck squamous cell can-

cer. It is important to identify patients with DMs pretreatment to avoid unnecessarily extensive treatments. Since it is not effective to screen all patients, high risk factors should be identified to select patients. Because no effective treatment is available for DMs, timing is important [21]. A previous study dealt with the evaluation of screening for DMs with chest computed tomography (CT) in 109 patients with head and neck squamous cell carcinoma. The sensitivity of chest CT was 73%, the specificity was 80%. Chest CT failed to detect metastases to the lung in 7 of 32 (21.8%) patients, while 2 patients had developed DMs outside of the thorax [22]. There seems that the whole body screening with PET-CT may be suitable. Previous data showed that sensitivity of PET-CT was 100% with specificity 98% [23,24]. The number of patients in this study was statistically inadequate to evaluate the sensitivity of screening during follow up to detect DMs in high risk patients.

The first limitation of this study was that treatment modalities and screening techniques were not evaluated because of differences in dosages and low reliability of such data inherent in retrospective studies. Another limitation of this study includes its retrospective design, which has the usual associated issues of potential selection bias and incomplete data collection. Attempts to address these concerns were made including the use of consecutive patient sampling to reduce patient selection bias. And also several efforts were made to obtain complete patient information from medical records, provincial registries and physician offices.

Conclusion

The factors that significantly increased the risk of DMs in patients with head and neck squamous cell carcinoma were the presence of local recurrence, pathologically positive neck, and primary tumor site. Patients with these factors should be considered candidates for adjuvant systemic treatment and evaluated for early detection of DMs during follow-up.

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