Original Article

A New Approach to Survival Analysis of Head and Neck Squamous Cell Carcinoma

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Abstract

Background: Squamous cell carcinoma is the most common histological subtype of head and neck cancers.

Methods: In a retrospective longitudinal study, we assessed the risk of local or metastatic recurrence and death in 140 patients with head and neck squamous cell carcinoma (HNSCC). Multivariate and shared frailty models were used for survival analysis with sex, primary tumor site, grade and stage of the tumor, and treatment modalities as contributing factors.

Results: The most frequent site for HNSCC was the oral cavity (30%), followed by the tongue (26.4%). For most primary sites, men were at nearly 2-fold higher risk of local recurrence than women, but there was no difference by sex in the risk of metastatic recurrence. Undifferentiated HNSCC was associated with a higher risk of local recurrence (nearly 4-fold) and metastasis (6–15-fold based on the primary site) than well-differentiated tumors. In early months after surgical resection alone, the risk of local recurrence was higher compared to other treatment modalities. There was a strong dependency between the risk of local and metastatic recurrence.

Conclusion: In conclusion, men diagnosed with HNSCC, those with higher grade or advanced state tumor, and those treated by surgery alone are at higher risk of unfavorable outcomes than others and may need more frequent follow-up visits.

Keywords: Head and neck cancer, metastasis, recurrences, squamous cell carcinoma, survival

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Introduction

Head and neck cancers (HNC) involve related anatomical regions: the oral cavity, pharynx (oropharynx, nasopharynx, and hypopharynx), and larynx with an estimated incidence of nearly 700,000.[1] While different regions of the world represent different anatomical regions as the primary location of the tumor,[2,3] the most common type is squamous cell carcinoma (SCC) in all anatomical regions.[4,5]

On the one hand, the survival rates of these cancers are increasing due to advances in treatments and lifestyle modification, e.g. smoking cessation.[6,7] On the other, this increase might correlate with secondary outcomes: recurrence of the primary cancer, development of metastasis, or even a second primary malignancy.[8,9]

Recurrence rate has been reported to be 10%-48% based on site and stage of the primary tumor.[8,9] Older studies had assessed the HNC regardless of the anatomical regions involved. Boysen *et al*. showed that 76% and 87% of malignancies recurred in the first 2 and 3 years after the primary treatment, respectively.[10] Similar results were reported by de Visscher and Manni.[11] As the primary site of the tumor might affect the prognosis, more recent studies have been conducted to explore this effect. Lester and Wight concluded that 95% of recurrences or second primary tumors were found in the first 2.7, 2.3, and 4.7 years for oropharyngeal, hypopharyngeal, and laryngeal primary tumors, respectively.[12] Another study evaluated both the primary site and type of the tumor and showed that 83% of oral cavity SCCs recur within 2 years following treatment.[13] Unfortunately, due to the heterogeneity of individual risk factors and among continents, as well as different approaches to post-treatment follow-up among different healthcare providers,[14–16] an optimal follow-up plan after the primary treatment has yet to be fully designed and implemented.[17] Such a regular follow-up plan should consider the type and site of the cancer as well as the primary treatment.[18,19] However, current guidelines do not consider geographical differences and individual risk differences.

To the best of our knowledge, many of the current studies have evaluated only the first outcome after the first treatment, namely a recurrence, second primary tumor, or distant metastasis.[23–26] A recurrent tumor is not independent of its previous occurrence(s). Also, there might be more than two outcomes that interact with each other.[20,21] In these situations, previous survival analyses, such as Cox proportional hazards model, might be inaccurate. Therefore, we aimed to investigate the natural disease history and outcomes of patients with head and neck SCC. We have used advanced statistical methods, i.e. frailty models, in a retrospective cohort of patients with HNSCC to assess all the outcomes for a median follow-up of 20 months (local recurrences, metastasis and death) for each patient at a referral center in Tehran, Iran.

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Materials and Methods

Subjects

This retrospective longitudinal study was carried out by collecting data from a database of 140 patients with HNSCC treated at Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, between April 1, 2004 and August 31, 2013. Of this dataset, subjects with squamous cell carcinoma of the head and neck area were included in this study. The presence of metastatic tumor in the head and neck area was the absolute exclusion criterion.

The study design and protocol were approved by the Medical Ethics Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Definitions

The definition of HNSCC was squamous cell carcinoma that developed in para-nasal sinuses, tongue, oropharynx, hypopharynx, nasopharynx, larynx, and oral cavity (except tongue). Metastasis definition included both cervical lymph node (regional) and distant metastases. Recurrent interval was defined as the duration from the end of initial treatment to the day of local recurrence confirmed by pathological examination.

Overall survival duration was defined as the duration from the end of initial treatment to the date of death or the end of the study.

Tumor staging was done according to the 6th edition Tumor-Node-Metastasis (TNM) staging criteria.[22] Patient delay was defined as the time interval between the appearance of first symptoms and the first visit to a physician. Due to public health promotion literature, the delay was dichotomized as greater or smaller than 30 day.[23]

Treatment modalities in this study were surgical resection, radiotherapy, and chemotherapy. The drug combination for chemotherapy consists of cisplatin, fluorouracil and docetaxel. Sequential combined modalities were as follows: surgical resection alone, chemotherapy + radiotherapy, surgical resection followed by chemoradiotherapy, and surgical resection followed by radiotherapy.

Statistical analyses

Survival analyses are statistical methods to assess data when the outcome is a time-to-event one. The event is a binary outcome such as incidence of a disease, recurrence of a tumor, or patient's death. The event, in turn, could occur only once (death), or multiple times for each subject (recurrent event model). Moreover, there might be situations where some risk factors (competing risks model) exist concurrently to cause an outcome.

In order to explore the relationship between risk factors and survival time, some mathematical models have been introduced. The first one was Cox proportional hazards model. The primitive assumption in this model is that the hazard ratio must be either constant throughout the study or independent of time.[24] Unfortunately, this model could not analyze immeasurable prognostic factors that might alter the survival rate. Moreover, these models could not help researchers when the hazard ratio did not meet the mentioned criteria.

Frailty models, therefore, have been introduced to calculate these unknown or immeasurable risk factors for each subject in survival analyses.[25] These models are extensions of Cox proportional hazard models that could consider unknown risk factors and heterogeneity among different subjects, which are not assumed in Cox models.

In this study, two frailty models were used: a multivariate and a shared frailty model. In the first model, hazard ratios were calculated with two types of recurrent events, and a dependent final event. The former consisted of local recurrence of the primary tumor and metastases and the latter was death. The time-varying effects, i.e., tumor stage and treatment modalities, were calculated in the second model.

The relationship between local recurrence and metastasis with death was assessed using random effects— i.e., frailties. The random effects θ and α_1 account for local recurrence, α_2 and η for metastasis, and ρ accounts for the correlation of local recurrence with metastasis. If α_1 and θ are both significantly different from 0, the local recurrence and death are significantly associated; the sign of the association is the sign of α_1. Similarly, if α_2 and η are both significantly different from 0, the metastases recurrence and death are significantly associated; the sign of α_2 determines the type of association. If ρ (the correlation between the two random effects) is significantly different from 0, the local recurrence and the metastases recurrence are significantly associated; the sign of the association is the sign of ρ.

All statistical analyses were done using the R Project for Statistical Computing, Version 3.0.1.[26]

Results

Eighty-four men (60%) and 56 women were in the study. The median age and follow-up of the subjects were 55 years and 19.5 months, respectively. As shown in Table 1, the most frequent site for squamous cell carcinoma tumor was the oral cavity (30%) and tongue (26.5%). More than 78% of the primary tumors were in advanced stages III and IV. Well-differentiated tumor grade was the most common grade in tumors of known grade; however, nearly 40% of all tumors had unknown grades.

The rates of recurrence and metastasis were 41.4% and 29.3%, respectively (Table 1).

Multivariate frailty model

Table 2 shows the multivariate frailty models. Hazard ratios (HRs) for local recurrence of SCC in larynx (2.10), hypopharynx (2.07), nasopharynx (1.95), and oropharynx (1.84) were significantly higher in men than women. No significant differences were seen between the two sexes in hazard ratios for local recurrence of SCC in other regions. Likewise, the HRs for metastases did not differ significantly between men and women.

Undifferentiated SCC tumor had significant HRs for local recurrence and metastasis compared to well-differentiated SCC tumors in all regions. The values for local recurrence were 4.42 (hypopharynx), 4.33 (paranasal sinuses), 4.72 (oral cavity), 4.58 (tongue), 4.17 (larynx), 3.68 (nasopharynx), and 4.79 (oropharynx). HRs of undifferentiated SCCs for metastases were: 11.04 (hypopharynx), 15.32 (paranasal sinuses), 5.85 (oral cavity), 14.11 (tongue), 14.05 (larynx), 6.41 (nasopharynx), and 13.13 (oropharynx). No significant differences were seen in HRs for either local recurrence or metastases of poorly- or moderately differentiated SCCs compared to well-differentiated ones.

The sites of the primary tumor had no significant HRs for developing local recurrences. HRs for metastases were 4.2 and 4.61, if the primary sites of the tumor were hypopharynx and

Table 1. Baseline characteristics by sex.

Variables		Male	Female	Total
		N (%)	N (%)	N (%)
Primary Site	Oral Cavity except Tongue	28(33.3%)	14(25.0%)	42(30.0%)
	Hypopharynx	4(4.8%)	8(14.3%)	12(8.6%)
	Nasopharynx	12(14.3%)	9(16.1%)	21(15.0%)
	Oropharynx	3(3.6%)	2(3.1%)	5(3.6%)
	Tongue	17(20.2%)	20(35.7%)	37(26.4%)
	Paranasal Sinuses	7(8.3%)	3(5.3%)	10(7.1%)
	Larynx	13(15.5%)	0(0.0%)	13(9.3%)
Primary tumor Stage	II	18 (21.4%)	12 (21.4%)	30 (21.4%)
	III	48 (57.1%)	32 (14.6%)	80 (57.1%)
	IV	18 (21.4%)	12 (21.4%)	30 (21.4%)
Grade	Well differentiated	19 (22.6%)	16 (28.6%)	35 (25.0%)
	Moderately differentiated	19 (22.6%)	5 (8.9%)	24 (17.1%)
	Poorly differentiated	3 (3.6%)	5 (8.9%)	8 (5.7%)
	Undifferentiated	14 (16.7%)	4 (7.1%)	18 (12.9%)
	Unknown	29 (34.5%)	26 (46.4%)	55 (39.3%)
Initial Treatment	Surgery	38 (45.2%)	21 (37.5%)	59(42.1%)
	RT†+ CT‡	16 (19.1%)	8 (14.3%)	24(17.1%)
	Surgery+RT	13 (15.5%)	13 (23.2%)	26(18.6%)
	Surgery+RT+CT	17 (20.2%)	14 (25.0%)	31(22.1%)
Outcome	Local	38(65.5%)	20(34.5%)	58(41.4%)
	Metastases	23(56.1%)	18(43.9%)	41(29.3%)
	Death	11(61.1%)	7(38.9%)	18(12.8%)
Age	Mean ± SD (year)	52 ± 18	50 ± 17	-
Patient Delay	Median (day)	60	90	-

† Radiotherapy
‡chemotherapy

nasopharynx, respectively. When the primary tumor was located in the oral cavity, the HR for metastasis was the lowest (0.09). Hypopharynx and nasopharynx had HRs of 5.42 and 3.92 for death, respectively.

Patient delay equal to or above 30 days was significantly associated with lower HRs for local recurrence in hypopharynx (0.57), paranasal sinuses (0.53), tongue (0.50), nasopharynx (0.57), and oropharynx (0.58). When a patient was diagnosed with oral cavity SCC, his/her delay was correlated with lower HR of metastasis (0.47). Patient delay was not significantly associated with metastasis in other sites of the primary tumor.

Table 3 shows the dependency of local recurrence on death, metastasis on death, and local recurrence on metastasis. The parameters θ and α_1 were both significantly different from zero in all sites of primary tumors. In other words, a positive and moderate dependency exists between local recurrence and death. Likewise, as both η and α_2 were both high and significantly different from zero for all primary sites, the risk of death was increased after a metastatic recurrence. The correlation coefficient ρ was also high and significantly different from zero, illustrating that after local recurrences, the risk of metastasis was increased.

Shared frailty model

Time-varying effects of primary stage of the HNSCC leading to local recurrence during follow-up are depicted in Figure 1. In the first month after the end of treatment, higher stages of primary tumors correlated with more local recurrence rates. This trend decreased in the 9th month after treatment, and then increased again. In other words, the higher the stage of the primary tumor, the higher the HR of local recurrence by time.

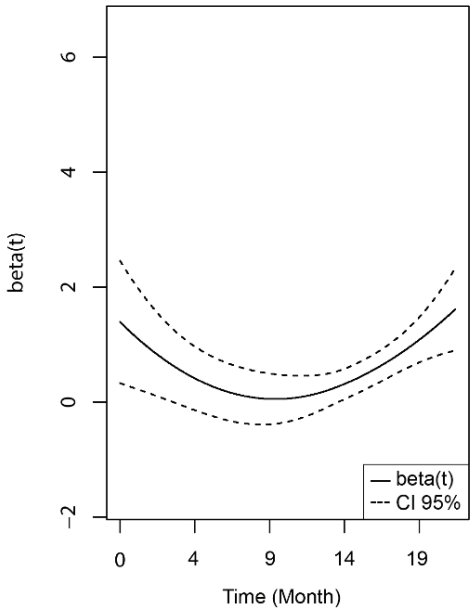

Figure 1. Time-varying effects of stage of the primary tumor (all sites) on local recurrence during follow-up time. Dashed lines indicate 95% confidence interval.

Table 2. Analysis with multivariate frailty model[a] of local recurrence, metastases and death, controlling for primary sites.

		Primary sites						
		Hypopharynx	**Paranasal sinuses**	**Oral cavity**	**Tongue**	**Larynx**	**Nasopharynx**	**Oropharynx**
Variables	**Modalities**	**HR[b] 95% CI[c]**	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**	**HR 95% CI**
				Local Recurrences				
Sex (ref: Female)	Male	2.07* (1.08 - 3.97)	1.71 (0.95 - 3.10)	1.59 (0.87 - 3.91)	1.99 (0.99 - 3.73)	2.10* (1.07 - 4.11)	1.95* (1.17 - 3.26)	1.84* (1.13 - 2.99)
Grade (ref: Well diff)	Moderate	0.94 (0.38 - 2.31)	0.76 (0.33 - 1.75)	0.82 (0.35 - 1.90)	0.77 (0.32 - 1.84)	1.13 (0.43 - 2.97)	1.20 (0.63 - 2.30)	1.26 (0.66 - 2.42)
	Poor	0.57 (0.14 - 2.38)	0.61 (0.16 - 2.24)	0.61 (0.16 - 2.13)	0.54 (0.14 - 2.01)	0.70 (0.18 - 2.97)	1.19 (0.45 - 3.11)	1.14 (0.44 - 2.94)
	Undiff	4.42* (1.61 - 12.12)	4.33* (1.70 - 11.04)	4.72* (1.78 - 12.52)	4.58* (1.71 - 12.52)	4.17* (1.58 - 11.02)	3.68* (1.63 - 8.31)	4.79 * (2.14 -10.71)
	Unknown	2.69* (1.25 - 5.79)	2.17* (1.07 - 4.43)	2.37* (1.15 - 4.90)	2.22* (1.03 - 4.80)	2.48* (1.17 - 5.25)	2.33* (1.25 - 4.36)	2.59* (1.37 - 4.89)
Local recurrence risk by Primary Site (ref: other sites)		1.59 (0.53 - 4.75)	0.60 (0.21 - 1.73)	1.40 (0.75 - 2.61)	1.70 (0.76 - 3.37)	0.34 (0.11 - 1.04)	1.83 (0.90 - 3.74)	0.42 (0.14 - 1.23)
Patient Delay (ref: <30days)	≥30days	0.57* (0.40 - 0.82)	0.53* (0.29 - 0.95)	0.55 (0.30 - 1.01)	0.50* (0.27 - 0.94)	0.55 (0.30 - 1.01)	0.57* (0.40 - 0.83)	0.58* (0.40 - 0.83)
				Metastatic Recurrence				
Sex (ref: Female)	Male	0.91 (0.42 - 1.96)	0.82 (0.34 - 1.95)	0.94 (0.46 - 1.93)	0.85 (0.37 - 1.97)	0.91 (0.38 - 2.14)	0.91 (0.42 - 1.97)	0.79 (0.36 - 1.76)
Grade (ref: Well diff)	Moderate	0.51 (0.14 - 1.92)	0.52 (0.11 - 2.37)	0.35 (0.09 - 1.32)	0.46 (0.11 - 1.89)	0.57 (0.13 - 2.58)	0.43 (0.11 - 1.64)	0.46 (0.12 - 1.79)
	Poor	1.92 (0.48 - 7.73)	2.85 (0.38 - 21.17)	1.39 (0.36 - 5.36)	2.51 (0.43 - 14.53)	2.75 (0.47 - 16.03)	2.52 (0.51 - 12.46)	2.34 (0.45 -12.00)
	Undiff	11.04* (2.60 - 46.89)	15.32* (2.13 - 80.97)	5.85* (1.62 - 21.12)	14.11* (2.81 - 76.97)	14.05* (2.71 - 70.78)	6.41* (1.38 - 29.68)	13.13* (3.07 -56.17)
	Unknown	1.05 (0.39 - 2.81)	1.26 (0.33 - 4.72)	0.74 (0.28 - 1.92)	1.06 (0.34 - 3.28)	1.16 (0.38 - 3.57)	0.82 (0.30 - 2.27)	1.14 (0.40 - 3.26)
Metastatic recurrence risk by Primary Site (ref: other sites)		4.20* (1.30 - 13.59)	1.65 (0.40 - 6.11)	0.09* (0.02 - 0.4)	1.27 (0.49 - 3.32)	0.54 (0.09 - 3.36)	4.61* (1.65 - 12.89)	0.25 (0.02 - 3.13)
Patient Delay (ref: <30days)	≥30days	0.54 (0.25 - 1.17)	0.55 (0.23 - 1.32)	0.47* (0.23 - 0.94)	0.53 (0.23 - 1.22)	0.55 (0.24 - 1.27)	0.47 (0.22 - 1.02)	0.50 (0.22 - 1.09)
				Death				
Death risk by Primary Site (ref: other sites)		5.42* (1.05 - 27.95)	1.60 (0.37 - 7.02)	0.91 (0.32 - 2.56)	0.48 (0.14 - 1.67)	0.70 (0.15 - 3.23)	3.94* (1.04 - 14.93)	1.07 (0.14 - 8.32)

[a] Multivariate frailty model included sex, stage, treatment modalities, grade, patient delay, primary tumor site for local recurrence, included sex, grade, patient delay, primary tumor site for metastatic recurrence and included primary tumor site for death. Effect of stage and treatment modalities are shown in figures because these variables have time-varying effects on local recurrence.
[b] Hazard ratio
[c] Confidence Interval
* *P*-value < 0.05

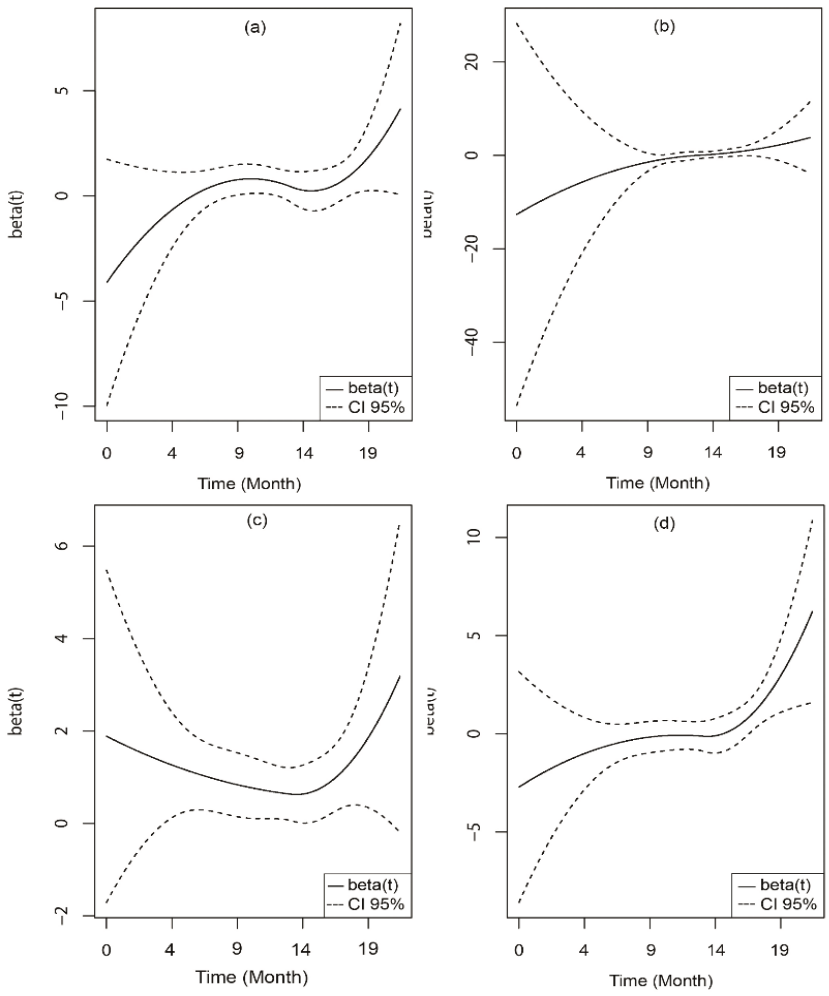

Figure 2. Time-varying effects of treatment modalities (in all sites) on local recurrence during follow-up time. Dashed lines indicate 95% confidence interval.) **(a)** Surgical resection followed by chemoradiotherapy, **(b)** Surgical resection followed by radiotherapy, **(c)** Surgical resection alone and (d) Chemotherapy in sequence with radiotherapy.

Figure 2 depicts the time-varying effects of treatment modalities on local recurrence during follow-up. In the early months after surgical resection alone, the risk of local recurrence was higher than that of other treatment modalities. Then, this risk decreased until 14 months of follow-up and increased again in later months. Other treatment modalities, which approximately followed a similar trend, showed a low risk in the first few months after treatment. Then, the risk went up as the duration of follow-up increased (Figure 2).

Discussion

The most important causes of morbidity and mortality in patients with head and neck cancers (HNC) are loco-regional recurrence and metastasis. It has been shown that the most common type of HNC is head and neck squamous cell carcinoma (HNSCC).[27] In this hospital-based study, we analyzed the association of sex, site of the primary tumor, grade and stage of the tumor, treatment modalities, and patient delay with the risk of local recurrence of the tumor, metastasis, and death. Needless to say, prevention and control of these risks could significantly improve the local recurrence, metastasis, and survival rate of patients with HNSCC.[28–33]

Male sex was significantly associated with higher hazard ratios for local recurrence and metastasis of the pharyngeal and laryngeal SCCs. However, there were no significant differences in the risk of these outcomes in other tumors of the oral cavity. Although it has been shown that male sex is a significant risk for developing HNSCCs, its effect on local recurrence and metastasis has yet to be fully known.[34,35] In a prospective cohort study of 444 patients with HNSCC, Duffy *et al.* reported no differences in recurrence events between the two sexes with HNSCC.[36] This was contrary to the results of Holsinger FC *et al.* who reported that about 84% of patients failing treatment for primary laryngeal cancer were men.[37]

In this study, the risk of death was strongly correlated with the risk of local recurrence and metastasis, which in turn was dependent on the site of the primary tumor. We found that SCCs in naso- and hypopharynx tended to metastatize more frequently than those in other sites. Also, SCCs of oral cavity were associated

Table 3. Dependency parameters of multivariate frailty mode.

Dependency parameters	Primary sites						
	Hypopharynx	Paranasal sinuses	Oral cavity	Tongue	Larynx	Nasopharynx	Oropharynx
θ (SE$^+$)	2.38(1.34)*	2.55(1.39)*	2.60(1.47)*	2.54(1.39)*	2.54(1.39)*	0.99(0.78)*	2.01(1.66)*
η (SE)	5.79(2.08)*	5.68(2.05)*	4.98(2.20)*	5.66(2.04)*	5.79(2.08)*	4.88 (1.43)*	4.71(1.08)*
α1 (SE)	0.55(0.21)*	0.53(0.21)*	0.56(0.21)*	0.58(0.21)*	0.58(0.21)*	0.73 (0.16)*	0.48(0.11)*
α2 (SE)	0.69(0.20)*	0.70(0.20)*	0.82(0.20)*	0.68(0.20)*	0.70(0.20)*	0.69 (0.26)*	0.76(0.23)*
rho (SE)	0.83(0.22)*	0.82(0.22)*	0.84(0.22)*	0.82(0.22)*	0.82(0.23)*	0.95 (0.20)*	0.89(0.33)*

* *P*-value < 0.05

with lower local recurrence than other HNSCCs. In line with our results, Forastiere *et al.* reported that tumors in hypopharynx have a higher probability of metastasis compared to tumors in the oral cavity or larynx.[38] Moreover, Khuri *et al.* indicated that the rate of recurrence was higher in SCC patients with oral cavity site when compared with larynx.[39]

We also concluded that higher grades of HNSCCs, especially undifferentiated SCCs, were more likely to result in local recurrence and metastasis than lower grade tumors. These higher risks were different in various primary sites of the tumor; an effect that was independent of the abovementioned association between site of the primary tumor and risk of local recurrence and metastasis. Among them, patients with undifferentiated SCCs of paranasal sinuses had higher HR for metastasis than other sites of the primary tumor.

The TNM staging system is important in clinical decision making and prognosis of HNSCC patients.[40] We evaluated the time-varying effect of tumor stage on the risk of local recurrence in patients with HNSCC against follow-up time. The main advantage of this type of analysis is planning for intervals between follow-up care visits, as it helps with the prevention or early detection of local recurrence or metastasis.[19] As shown in figure 1, the effect of tumor stage on the risk of local recurrence was significant and did not remain stable through follow-up. However some studies did not find any significant association between tumor stage and the risk of local recurrence.[41,42]

The appropriate treatment modality is of great importance in patients with HNSCC, as it affects a region with vital structures and functions.[43,44] In our study, patients treated with surgical resection and adjuvant radiotherapy were at lower risk of local recurrence compared to other modalities. Local recurrence risk tended to increase with time in all treatment plans except surgical resection alone. After about one year from the end of initial treatment, treatment modalities, except those which included either chemo- or radiotherapy, were more likely to have a high-risk of local recurrence. A phase III trial testing two approaches of radiotherapy documented a 10% to 15% improvement in local and regional tumor control in patients with early and advanced-stage disease, but without a significant improvement in the overall survival rate.[45] In another study, adjuvant chemo-radiotherapy could reduce the risk of local recurrence compared to radiotherapy alone in patients with advanced stages of HNSCC.[46] In most studies, the risk of local recurrence has been evaluated by mean of the risk over follow-up time, whereas the local recurrence risk actually changes over time.

A different finding was that the risk of local recurrence was lower in HNSCC patients (paranasal sinuses, pharynx and tongue) with longer delays to visit their physician. Usually, if diagnosis is delayed from the onset of cancer, the patient will present at more advanced stages and poorer prognosis. However, McGurk *et al*. assessed two cohorts of patients with mouth and throat SCC and showed that when symptoms start, the delay in diagnosing the related cancer might not be associated with either the cancer stage or patient's survival.[47] They reported that the symptoms are neither associated with size nor stage of the tumor in mouth and throat SCC. Similar findings were reported for survival, prognosis, and stage of the cancer.[48–51] A cohort by Tromp *et al.* concluded that the patient delay was mainly due to absence of symptoms that results from less aggressive tumors, i.e. lower stages.[52] Also, Hsu and Chen reported that patient delay was directly associated with a higher risk of distant metastasis compared to other patients.[53] Similar studies showed that patient delay was directly associated with higher risk of local recurrence and distant metastasis as well as lower survival rates.[54–57] This disparity might be due to the fact that as the HNSCC becomes more severe, it develops symptoms that obligate the patients to visit their physicians. Moreover, the aggressiveness of a tumor is not only a result of its size, but a consequence of lymph node involvement.[52] Also, different sample sizes, study designs, ethnicities, and definition/duration of delay might play important roles in the mentioned discrepancy.

Our study has a number of limitations: we did not have data on second primary tumors in our patients, which could impact the survival rate of our patients. Moreover, about 32% of all our patients were followed up for more than 2 years. Also, if we had had a larger sample size, our results would have been more robust. Moreover, as our patients were negative for human papilloma virus infection, we could not analyze the relationship between this viral infection and outcomes. Finally, the results of the study are subject to sparse-data bias as the number of events was low and some HR estimates in Table 3 were huge (e.g., 15.32 with an upper 95% CI of 80.97) with very wide 95% CIs, e.g., 2 to 81.[58]

However, we used an advanced statistical method to analyze various risk factors related to local recurrence, metastasis, and death in HNSCC patients. This method allowed us to consider more than one outcome, unlike most of the studies which used Cox proportional hazard ratios.

In conclusion, male patients with high grades and advanced stages of hypopharynx SCC are associated with higher risk of local recurrence, metastasis, and death. Also, some treatment modalities like surgery alone might warrant more frequent follow-

up visits. Overall, we could say that any of the above risks do not occur independently of each other, so controlling any of these risks should be done cautiously in each patient diagnosed with HNSCC. Further studies with larger sample size and longer follow-up are needed to explore these relationships more deeply.

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