The Journal of Laryngology & Otology

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Distant metastasis at the time of presentation of head and neck squamous cell carcinoma: a retrospective chart review from a tertiary cancer care centre

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Main Article

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Cite this article: Majitha CS, Nayak DR, Shetty S, Devaraja K, Basheer JI. Distant metastasis at the time of presentation of head and neck squamous cell carcinoma: a retrospective chart review from a tertiary cancer care centre. *J Laryngol Otol* 2024;**138**:661–666. https://doi.org/10.1017/S0022215123002323

Received: 7 September 2023
Revised: 20 November 2023
Accepted: 26 November 2023
First published online: 22 December 2023

Keywords:
Head and neck cancer; hypopharyngeal cancer; extranodal extension; metastasis; oral cancer

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Abstract

Objective. To evaluate the rates and patterns of distant metastasis in head and neck SCC at the time of presentation and to study the association between distant metastasis with pre-treatment, clinical, and pathological predictors of outcomes.

Method. This is a retrospective study conducted in a tertiary care hospital. All patients with primary head and neck squamous cell carcinoma that had been evaluated at our institute between October 2018 and December 2020 were included in the study. Various clinical data were analysed and pattern of metastasis was studied.

Result. Ten per cent (50 cases) of 501 studied patients had distant metastasis. The most common site of distant metastasis was lung. The rate of distant metastasis was high in patients with poorly differentiated cancers. By Kaplan–Meier analysis, the median survival duration after diagnosis of metastasis was four months.

Conclusion. The rate of distant metastasis was 10 per cent in the study. Patients with poorly differentiated tumours, locally advanced primary lesions, higher nodal stage, particularly with extra nodal extension, and hypopharyngeal primary, tend to exhibit increased risk for distant metastasis at the time of presentation.

Introduction

Head and neck squamous cell carcinoma (SCC) is one of the leading cancers in low and medium-income countries and exhibits poor prognosis due to advanced stage at the presentation.[1] One of the common causes of mortality in head and neck SCC is the occurrence of distant metastasis, which could be present at the time of diagnosis of the primary disease in head and neck, or more often, it develops after treating an aggressive primary tumor.[2]

Approximately 4–15 per cent of cases of head and neck SCC eventually tend to develop distant metastasis despite curative intent multimodal therapeutic intervention.[3–8] Most cases that develop distant metastasis tend to do so within the first 12–36 months, with a median time of 15 months following primary tumour treatment.[7,8] Although there is a bit of controversy in this regard, two of the well-known risk factors for the development of distant metastasis in head and neck SCC are a gross extranodal extension of the nodal disease and loco-regional failure of primary treatment.[3–11] The lung is the most common site of distant metastasis in head and neck SCC.[3,10] Although several research studies also have identified the clinicopathological predictors of distant metastasis after the distant metastasis, there is limited information in the literature about the actual incidence of distant metastasis at the presentation of head and neck SCC itself. Moreover, there is no clarity on the association of pre-treatment clinical and pathological risk factors with distant metastasis in such scenarios.

To address these issues, this retrospective study was conducted in a tertiary care hospital, wherein the data of head and neck SCC managed over approximately 25 months was analysed. The objective of the study was to evaluate the rates and patterns of distant metastasis in head and neck SCC at the time of presentation and to study the association between distant metastasis with pre-treatment, clinical, and pathological predictors of outcomes.

Materials and methods

Study setting

This retrospective study was conducted by the Department of Otolaryngology and Head and Neck Surgery of a tertiary care hospital in South India. All the patients evaluated at

our institute between October 2018 and December 2020 were considered for possible inclusion in the study.

Study population

Medical records of all the patients of head and neck SCC registered at our hospital were reviewed for the selection of the study population. Those patients with a previous history of head and neck malignancy (recurrent cancers), other site malignancy, carcinoma of unknown primary, carcinoma in situ, and histological types other than squamous cell carcinoma were excluded from the study.

Data collection

The various clinicopathological factors that were noted in each of the eligible patients were: (1) age at diagnosis, (2) gender, (3) primary tumour site, (4) histopathological grading, (5) tumour–node–metastasis (TNM) stage (as per the eighth edition of the American Joint Committee on Cancer TNM staging manual),[12] and (6) radiological investigations done and their corresponding findings. The managment principles and the survival durations of these patients were also noted whenever available.

Outcome analysis

The primary outcomes were the rate and sites of distant metastases and site-specific distribution of these distant metastases. The secondary outcome was to study the association between the pattern of distant metastasis with each of the other variables, such as the histological grade of the primary tumour, T stage, N stage, and status of extranodal extension. Lastly, the survival analyses of the included cohort with distant metastasis were also carried out to check if there were any differences in the survival of these patients as per their clinicopathological determinants.

Statistical analysis

The data were imported into Microsoft Excel (version 2007 , Microsoft Corporation, Redmond, USA), and the analysis was carried out with SPSS (version 21.0, IBM SPSS Statistics, New York, USA). The data were reported as means and standard deviations for continuous variables, and reported as percentages for categorical variables. The chi-square test or the Fisher's exact test was used to assess the relationships between the category variables. Statistical significance was defined as a p value of less than 0.05. Kaplan–Meier analysis was done to calculate the survival rate. The median survival rate was also calculated.

Ethical approval

The study was approved by the institute's ethical committee (IEC number – 928-2020).

Results

In all, 751 patients were registered and managed at our institute during the study period, of which 501 met the eligibility criteria and were included for further analysis. Only the cases of primary head and neck SCC were included in the study. Those patients with previous history of any other malignancy or radiation, T0/Tis, recurrent cases and other histological types were excluded. The mean age of the study population was 58 years (range 22–90 years old). The male-to-female ratio in our study cohort was 4.3:1. The most common site of malignancy in the included patients was the oral cavity (49.5 per cent), followed by pharynx (28.8 per cent) and laryngeal cancers (18.4 per cent), as depicted in Table 1.

Histologically, the majority of the SCCs had a moderately differentiated picture (59.1 per cent), followed by those with a well-differentiated picture (27.9 per cent). Poorly differentiated cancers were seen in 12.8 per cent and 0.2 per cent had basaloid variety. As per the eighth edition of American Joint Committee on Cancer -TNM staging manual,[12] the T stage was dispersed mostly among stages T3 (31.1. per cent), T2 (27.3 per cent) and T4 (30.9 per cent), with 10.6 per cent being diagnosed with stage T1 disease. Most of the included patients had no cervical nodal metastasis (50.3 per cent). Amongst the remaining included patients, N1 nodal disease was seen in 17.7 per cent, N2 in 22 per cent and N3 in 10 per cent.

The investigations for metastatic work-up were done as deemed appropriate to the clinical context, as decided by the treating unit or multidisciplinary tumour board, and in accordance with our institutional practice.[13] While all the included patients had undergone plain radiograph of the chest, the cases that had very advanced primary and exhibited high risk for distant metastasis had also undergone either computed tomography of the thorax, or ^{18}F-fluoro-deoxy-glucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) ($n = 31$). Most of the patients ($n = 494$) also had been subjected to ultrasound abdomen and liver function tests as a part of the metastatic work-up.

Table 1. Site-specific distribution of distant metastases in head and neck squamous cell carcinoma

Site (alphabetical order)	Total cases ($n = 501$)	Distant metastasis ($n = 50$)	Metastatic sites (with numbers)
External ear	7	1	Liver
Hypopharynx	69	12	Lung (9), Liver (1), Bone (1), Multisite (1)
Larynx	92	15	Lung (12), Liver (1), Bone (1), Multisite (1)
Nasopharynx	8	0	N/A
Oral cavity	248	16	Lung (14), Bone (1), Multisite (1)
Oropharynx	67	5	Lung (5)
Scalp	2	0	N/A
Sinonasal	8	1	Lung

https://doi.org/10.1017/S0022215123002323 Published online by Cambridge University Press

Fifty of the included patients exhibited distant metastasis (10 per cent) at the time of diagnosis, all of whom were further managed by palliative-intent treatment policies. Among those with metastasis, the majority were 50 years of age and above ($n = 41$; 82 per cent) and were men ($n = 44$; 88 per cent). Table 1 summarises the frequency and pattern of distant metastasis seen in our cohort, as per the different sites of head and neck SCC.

As for the site distribution, oral-cavity ($n = 16$; 32 per cent) and laryngeal ($n = 15$; 30 per cent) cancers had the highest number of distant metastases, followed by the hypopharynx ($n = 12$; 24 per cent) and oropharynx ($n = 5$; 10 per cent) cancers. We had only eight cases of nasopharyngeal cancer and no distant metastasis. However, when the proportional incidence of distant metastasis rates (percentage of metastatic cases with a total number of malignancies of that site) was analysed, the highest metastatic rates were found for the tumours arising from the hypopharynx (12/69; 17.4 per cent) and larynx (15/92; 16.3 per cent), followed by tumours arising from the external auditory canal (1/7; 14.2 per cent) and sinonasal region (1/8; 12.5 per cent), as compared to tumours involving the oral cavity (16/248; 6.5 per cent) and oropharynx (5/67; 7.5 per cent).

Most of the patients had distant metastasis involving one organ at the time of diagnosis of metastasis ($n = 47$; 94 per cent). The common sites of isolated distant metastasis were lung ($n = 41$), followed by liver ($n = 3$) and bone ($n = 3$), and three patients had sites of isolated distant metastasis in more than one of these sites at the time of diagnosis. Most of the distant metastasis was picked up by ^{18}F-FDG-PET/CT ($n = 25$), and the rest were picked up by ultrasound of the abdomen, plain radiography of the chest, and computed tomography. Interestingly, among those patients who had altered liver function tests ($n = 7$) and suspicious ultrasound ($n = 6$), five patients had metastatic lesion(s) in the liver (three isolated lesions in liver and 2 multi-site disease). On analysing the status of distant metastasis with the other predictive factors (as depicted in Table 2) there were statistically significant associations of distant metastasis with the poor differentiation of tumours ($p = 0.000$), advanced tumour (T) stage ($p = 0.033$), and advanced nodal (N) stage ($p = 0.007$), but not with age ($p = 0.315$) or gender ($p = 0.195$) of the patient.

Using Kaplan–Meier analysis, the median survival duration after the diagnosis of metastasis was four months in our study cohort, as shown in Figure 1. Further, as depicted in Figure 1, sub-group analyses using the Mantel–Cox (log-rank) test showed that survival rates among the patients with metastasis did not demonstrate any statistically significant differences with the age at diagnosis ($p = 0.192$), site of the primary tumour ($p = 0.630$), T stage ($p = 0.567$), N stage ($p = 0.925$), or numbers of metastatic sites ($p = 0.942$).

Discussion

The rate of distant metastasis at the time of presentation of head and neck SCC was ten per cent in our study cohort, which is comparable to literature-reported rates (3.1–16.5 per cent).[14–16] Interestingly, most of our patients with distant metastasis were men and 50 years old or older.

Table 2. Association of distant metastasis with clinical and pathological variables

Variable	Categories	Total numbers (n=501)	Frequency of metastasis (percentage per category)	*p* value (Pearson chi-square tests)
Age	21–30	4	1 (25%)	0.315
	31–40	44	3 (6.8%)	
	41–50	92	5 (5.4%)	
	51–60	144	14 (9.7%)	
	61–70	146	21 (14.5%)	
	71–80	59	5 (8.5%)	
	81–90	12	1 (8.3%)	
Gender	Male	407	44 (10.8%)	0.195
	Female	94	6 (6.4%)	
Differentiation	Well	140	15 (10.7%)	0.000*
	Moderate	296	21 (7.1%)	
	Poor	65	13 (20%)	
**Tumour stage	T1	53	2 (3.7%)	0.033*
	T2	137	2 (1.5%)	
	T3	156	19 (12.2%)	
	T4	155	24 (15.5%)	
**Nodal stage	N0	252	11 (4.4%)	0.007*
	N1	89	12 (13.5%)	
	N2	110	20 (18.2.1%)	
	N3a	16	3 (18.7%)	
	N3b	34	4 (11.8%)	

*Statistically significant; **as per the eighth edition of the American Joint Committee on Cancer TNM staging manual[12]

https://doi.org/10.1017/S0022215123002323 Published online by Cambridge University Press

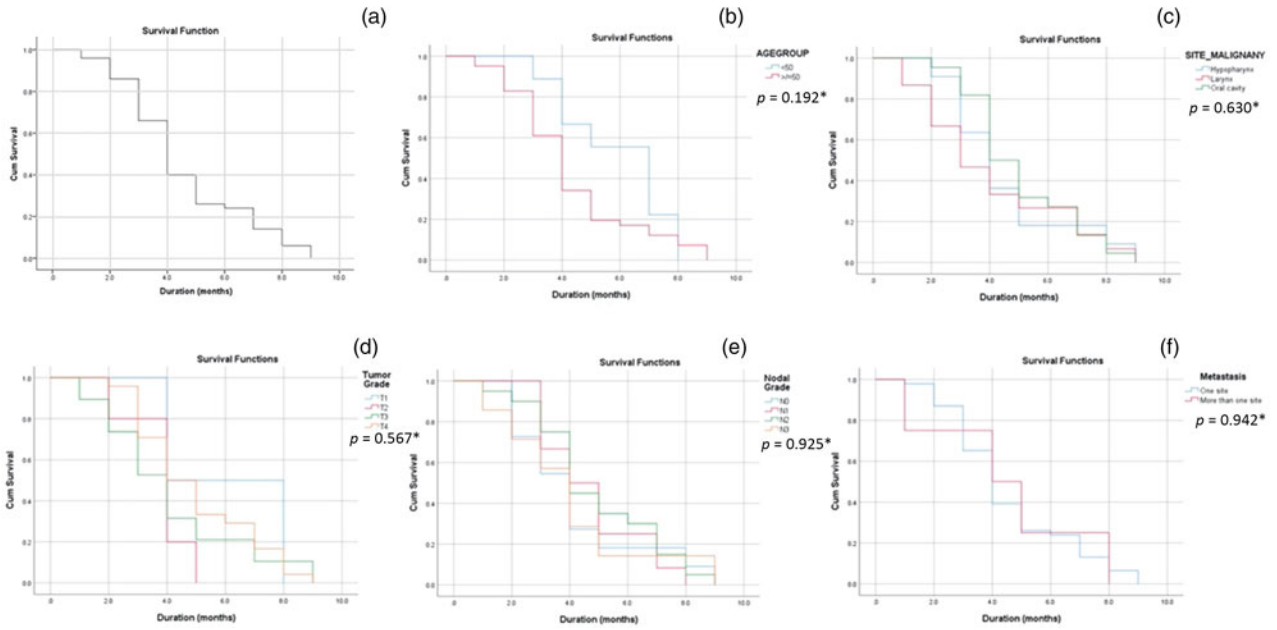

Figure 1. Kaplan–Meier curves showing the overall survival of the study cohort (a), and survival differences as per the age group (b), primary site of malignancy (c), tumour grade (d), nodal grade (e) and number of sites of distant metastasis (f). Tumour grade and nodal grade as per the eighth edition of the American Joint Committee on Cancer TNM staging manual[12]

Neither age nor gender showed any statistically significant association with the presence of distant metastasis at the time of diagnosis. Oral cavity, laryngeal, and hypopharyngeal tumours exhibited a greater rate of distant metastasis in our group. However, this study had large number of patients in oral-cavity and laryngeal malignancy groups. When the pattern of distant metastasis was considered with the proportional distrubtion of cases in each site, it was shown that the hypopharyngeal tumours have a greater incidence of distant metastasis than the laryngeal cancers, although this link was not statistically significant. A recent United States population-based study using the American College of Surgeons National Cancer Data Base reported that distant metastasis was seen more often in nasopharyngeal cancers followed by hypopharynx cancers.[14] Our study included a smaller number of nasopharyngeal cancers, so this variation in the distribution of nasopharyngeal cancer between United States and southern part of India could be attributed to differential rates of distant metastasis reported in nasopharyngeal cancers.[17]

Factors such as poor differentiation of the tumour, advanced T stage and advanced N stage exhibited significant association with distant metastasis at the time of presentation of head and neck SCC. The results of the present study echo the conclusions of the National Cancer Data Base study from United States, in which, the advanced T stage, positive N stage and N3 status were predictive of the presence of distant metastasis at the time of presentation of head and neck SCC, both by univariate and multivariate analyses.[14]

Of the various subsites of the head and neck, even though oral cancers are much more common than pharyngeal and laryngeal tumours in our study, the hypopharyngeal and laryngeal cancers had the highest propensity to have distant metastasis at the time of presentation (almost three times more than that of oral and oropharyngeal cancers). This is also reflected by other reports in the literature, suggesting a vigorous pre-treatment workup for distant metastasis in hypopharyngeal cancers.[14,18] Although the exact reasons for the higher propensity of distant metastasis among hypopharynx and larynx cancers are not well understood, the rich lymph–vascular supply of these regions might have a role to play in this regard.[19] Nevertheless, since these above-mentioned clinical and histopathological risk factors are also the established risk factors for the occurrence of distant metastasis after curative therapy of head and neck SCC, the presence of these factors should prompt a strict post-therapy surveillance.[18,20]

The lung is by far the most common site of distant metastasis, even at the time of presentation of head and neck SCC, as seen in our report as well as in previous studies.[14,18] The other common sites of distant metastasis include the liver and bone, but rarely does head and neck SCC also present with isolated metastatic lesions in the stomach, duodenum, or peritoneum.[14,21–23]

There are several challenges concerning the choice of investigation that is sensitive as well as cost-effective for detecting the distant metastasis in head and neck SCC.[13–15] The routine use of computed tomography of the thorax to screen for the most likely site of distant metastasis is not cost-effective in all cases of head and neck SCC, particularly in low- and medium-income countries.[13,24] Similarly, although ^{18}F-FDG-PET/CT could have higher chances of detecting distant metastases compared to chest radiograph or computed tomography, their use as a routine investigation to diagnose distant metastasis at the time of presentation of head and neck SCC is not justifiable in all cases.[14,15] Our findings, which are similar to previous studies, highlight the utility of multiple imaging modalities for examining the pattern of distant metastases.[15,16]

One of the solutions to detecting distant metastases could be the development of novel and reliable models based on the known clinical and pathological risk factors that could predict the risk of distant metastasis at the time of presentation. In fact, attempts are already being made to develop and validate novel nomogram prediction models for determining the patients who are at high risk of distant metastasis after curative treatment.[8,20] Similarly, cellular ratios, such as neutrophil-to-lymphocyte ratio, and molecular markers, such as loss of E-cadherin, have

https://doi.org/10.1017/S0022215123002323 Published online by Cambridge University Press

also been explored for their ability to predict the risk of developing distant metastasis after treatment of head and neck SCC. [25,26]

Based on similar lines, if a reliable model could be extended to predict distant metastasis at the time of presentation of head and neck SCC, oncologists could get assistance in choosing the appropriate investigation in each case. For instance, a plain radiograph of the chest could suffice in model-predicted, low-risk cases for distant metastasis, with restriction of ^{18}F-FDG-PET/CT only to high-risk cases or to those cases with suspicious nodules on a plain radiograph. Such models also could aid multidisciplinary tumour boards in the prognostication of the patients as well as in choosing appropriate therapeutic approaches.

Our study reiterates that distant metastasis is the most critical prognostic factor in head and neck SCC. The results of this study show that survival in head and neck SCC patients with distant metastasis is independent of the site and size of the primary tumour and the status of regional metastasis. However, a recent study, based on an extensive population-based database, with 1240 patients of head and neck SCC who had distant metastasis at presentation, has reported some of the above-mentioned factors as independent prognosticators of overall survival.[27] This disparity could be explained by the small sample size and retrospective nature of our study, with missing data on the follow-up in several of our patients, suggesting the need for further large and prospective studies in this regard. Also, although recently approved checkpoint inhibitors and cisplatin-based regimens are known to prolong the survival in metastatic head and neck SCC, we could not analyse the survival in our cohort by factoring the therapeutic regimen offered to our patients, because there was dearth in the relevant data regarding their utility, which mitigated further statistical analysis.[28] Nevertheless, the poor utilisation of immunotherapeutic regimens in low- and medium-income countries has been documented by a recent study from another tertiary care centre.[29] On the other hand, there has been increasing acceptance of curative intent therapy for oligometastatic disease of head and neck SCC, in appropriately selected clinical contexts, which also could not have been evaluated in our cohort.[30,31]

- The head and neck squamous cell carcinoma are known to have distant metastasis at the time of presentation, particularly when presented in advanced stages
- The rate of distant metastasis at the time of presentation of head and neck squamous cell carcinoma in our study was approximately 10 per cent
- Apart from the advanced local stage, the tumours with poor differentiation, higher nodal stage, presence of extranodal extension and hypopharyngeal primary carry higher risk of distant metastasis
- Appropriate investigations to rule out the distant metastasis should be undertaken in the head and neck cancer patients with these risk factors
- Although ^{18}F-fluoro-deoxy glucose positron emission tomography can aid in diagnosis of distant metastasis whenever present, conventional radiological investigations such as computed tomography, ultrasound and plain radiograph can suffice in selected cases with low risk for distant metastasis
- The most common site of distant metastasis in head and neck cancer is lung; however, the survival rates among the patients with distant metastasis did not vary as per the site of metastasis

Lastly, there are a few limitations in the existing guidelines that are used for differentiating the connected tumours from second primary tumours.[32–34] These diagnostic dilemma are particularly critical for separating a metachronous second primary tumour from a local recurrence.[32] However, these guidelines are also applicable for differentiating a distant metastasis from a concurrent second primary at a distant site, such as lung or liver, and thus, one cannot rule out a slight overestimation of the distant metastasis rates in this study.[33,34]

Conclusion

The rate of distant metastasis at the time of presentation of head and neck SCC in our study was approximately 10 per cent. According to our results, patients with poorly differentiated tumours, locally advanced primary lesions, and higher nodal stages, particularly with extranodal extension and hypopharyngeal primary, are at increased risk for distant metastasis at the time of presentation and, therefore, should be submitted to robust pre-therapeutic metastatic work-up. In cases with several highly predictive factors, a tool with higher sensitivity, such as ^{18}F-FDG-PET/CT, may be warranted to rule out distant metastasis.

Acknowledgements. None.

Funding. There was no funding for the study.

Competing interests. None declared.

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