

Original Research Article

Patterns of second primary malignancies in carcinoma larynx and hypopharynx following surgical management

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ABSTRACT

Background: The objective was to determine the incidence of second primary in patients with squamous cell carcinoma larynx and hypopharynx following surgical management with or without adjuvant treatment.

Methods: A retrospective quantitative descriptive study was conducted on 289 patients who underwent surgical management of squamous cell carcinoma (SCC) of larynx and hypopharynx with or without adjuvant treatment and later developed second primary. This study comprised of patients undergoing treatment during the time period of January 2016 to January 2019 at the department of head and neck surgery, Kidwai institute of oncology.

Results: Second primary malignancies (SPM) developed in 3.1% of patients within a median follow up period of 28 months. Majority of the second primaries developed in patients with hypopharyngeal malignancy.

Conclusions: SPMs are amongst the leading causes of mortality in patients with SCC larynx and hypopharynx. Hence careful surveillance is essential for the early detection of a second primary.

Keywords: Squamous cell carcinoma, Hypopharynx, Second primary malignancies, Loss of heterozygosity

INTRODUCTION

The management of head and neck malignancies requires close and meticulous follow up even after the completion of curative treatment. Factors contributing to morbidity, mortality and overall survival include loco regional recurrences, distant metastasis, treatment related complications and second primary malignancies.

A SPM is defined as a malignant tumor that presents simultaneously or after the diagnosis of the index tumour at a later time. The incidence of second primary tumors in the upper digestive tract varies from 3% to 5%.¹ Majority of cases are diagnosed within 2 years following the diagnosis of the index case. Malignancies that occur within 6 months of index tumour are called synchronous and those diagnosed after 6 months are called

metachronous tumours.² The highest incidence of second malignancy within the head and neck area occurs in oral cavity (58.4%), larynx (18.2%) and oropharynx (13.3%).³

Among the head and neck SCC sites, about one third of patients with oropharyngeal and more than 20% of hypopharyngeal carcinomas will develop a second primary. In patients with carcinoma larynx the long term SPM risk was reported to be in the range of 9.6 to 29%.⁴ Most common sites for SPM include head and neck region, oesophagus and lungs. Smoking, alcohol and the patient's age are considered to be the risk factors for SPM.

The aim of the present study was to estimate the incidence of SPM in patients with SCC larynx and hypopharynx following curative surgical management.

METHODS

A total of 289 patients presenting to the department of head and neck surgery, Kidwai institute of oncology, Bangalore with SCC of larynx/hypopharynx and who later underwent total laryngectomy with or without pharyngectomy and reconstruction/total laryngo-pharyngo-esophagectomy with gastric pullup during the period of January 2016 to January 2019 were enrolled in this analytical retrospective study using convenience sampling method.

Inclusion criteria

Patients diagnosed with biopsy proven SCC of larynx/hypopharynx who underwent curative surgical procedure with or without adjuvant therapy were included in the study.

Exclusion criteria

Patient not consenting for the procedure, patients who had inoperable laryngeal or hypopharyngeal malignancy, patients who were not compliant with the follow up protocols and patients who underwent salvage surgeries were excluded from the study.

Patients who fulfilled the inclusion criteria underwent the curative surgery with or without adjuvant therapy. Once patients recovered from the surgery, they were discharged and advised to come for follow up. All our discharged patients underwent routine monthly follow up for the first three months. Most of the patients took adjuvant treatment with either radiotherapy or concurrent chemoradiotherapy. After the initial three months, patients were followed up monthly for the first six months, 3 monthly for the next six months and six monthly for the next five years.

On each visit, routine clinical examination along with videolaryngoscopic examinations were done to look for recurrence and secondary lesions. In case of any

dysphagia or aerodigestive tract symptoms, oesophagoscopy was done to rule out a second primary. After three months of completion of adjuvant treatment, PET CT/CECT neck and thorax/chest X-ray was done. For any suspicious lesion biopsy was performed on the subsequent visit. Hence the number of second primaries were quantified and assessed along with the time period of the occurrence.

Statistical tool for analysis

Data collected in the proforma was entered in MS excel and analysed statistically using SPSS software version 24. Univariate analysis was used to analyse the data. Sample size was calculated for this retrospective study using the convenience sampling method.

RESULTS

In our analysis of 289 patients, the following demographic data was obtained. The mean age of the study population was 68.5 years (19-75 years). Most of the patients were male (71%). The subsite wise distribution of SPM was in the ratio of 1:1.86 for larynx and hypopharynx. All the patients were in stage III and IV. 92.2% patients took adjuvant RT or CTRT. The mean follow up period was 28 months.

The incidence of second primary malignancies during our follow up period was 9 out of 289 patients. The subsites that were involved were lung (3), oesophagus (2), base of tongue (1), tonsil (1), vallecula (1) and sigmoid colon (1). The time to diagnosis of SPM varied from 4 months to 18 months.

All the second primary lesions were identified after 6 months of follow up following treatment for the primary lesions, hence these second primaries were considered as metachronous SPM except for one case of synchronous SPM which was diagnosed at 4 months of follow up period.

Table 1: Second primary malignancies and their sites.

Primary sites	Age (in years)	TNM stage	SPM sites	Time of detection of SPM (in months)
Piriform fossa	72	T4aN0M0	Lung	9
Supraglottis	67	T4aN2aM0	Lung	4
Supraglottis	62	T4aN2aM0	Lung	11
Piriform fossa	68	T4aN2aM0	Oesophagus	11
Posterioroid	62	T3N1M0	Oesophagus	12
Piriform fossa	55	T4aN0M0	Base of tongue	8
Supraglottis	61	T3N0M0	Sigmoid colon	9
Piriform fossa	58	T4aN1M0	Tonsil	18
Piriform fossa	62	T3N1M0	Vallecula	12

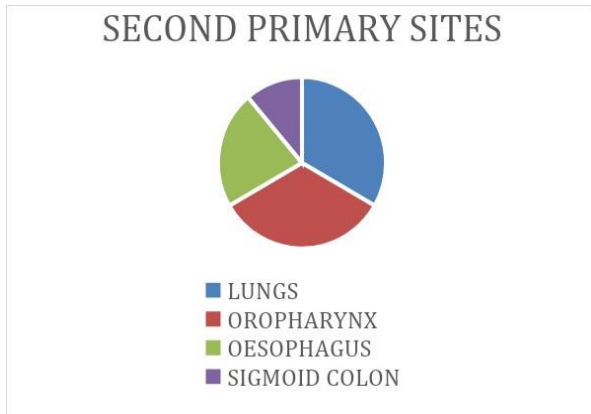


Figure 1: Second primary sites.

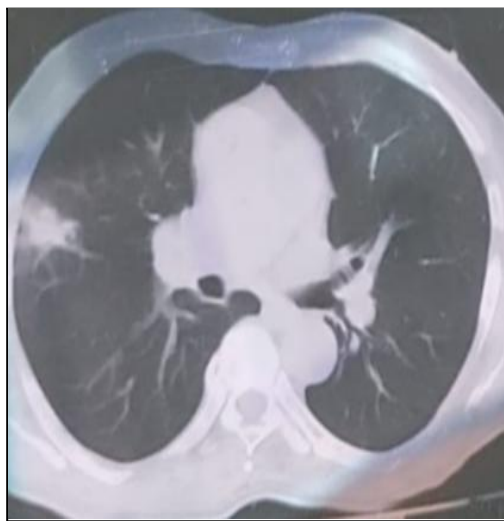


Figure 2: Subpleural nodule in the right lung in a case of carcinoma right pyriform fossa.

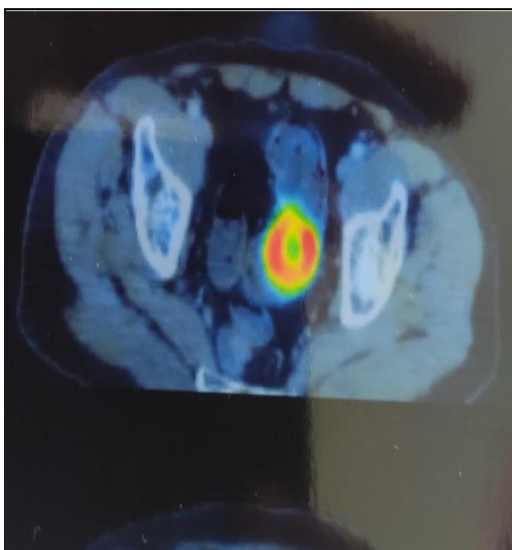


Figure 3: PET CT scan showing second primary in the right tonsil and glossotonsillar sulcus following total laryngectomy for carcinoma pyriform fossa.

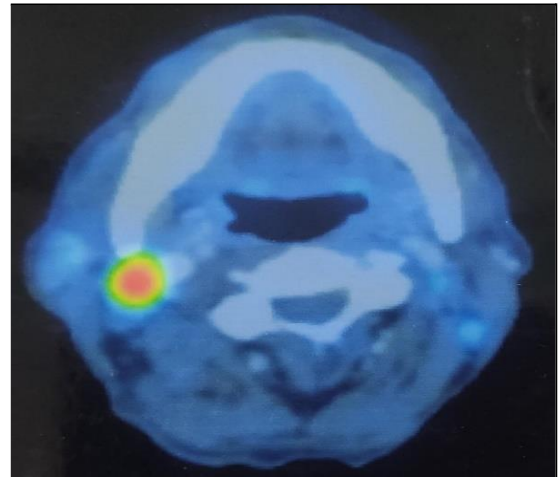


Figure 4: PET CT scan showing second primary in the sigmoid colon following total laryngectomy for carcinoma supraglottis.

DISCUSSION

The development of SPM in the head and neck area may be explained by the concept of field cancerization. In 1953 Slaughter et al proposed the concept of condemned mucosa to explain the high incidence of second malignancies in patients exposed to carcinogens.⁵ He introduced the term field cancerization to explain the occurrence of multicentric squamous cell carcinoma in oral cavity. It was seen that the epithelium surrounding the tumour area (the carcinogen exposed mucosa) had histological changes suggestive of dysplastic foci. The same finding was confirmed by other authors in larynx, pharynx, trachea and bronchi.⁶⁻⁹ Slaughter et al defined field carcinogenesis as the inherent instability of the mucosa of the entire upper aerodigestive tract combined with repeated carcinogenic insults leading to an increased risk of developing multiple independent premalignant and malignant foci.

The molecular level changes identified in head and neck SPM include p53 alterations, p21 and glutathione transferase polymorphisms.¹⁰ The two types of markers widely used are loss of heterozygosity (LOH) causing allelic imbalance and p53 imbalance. Some SPMs are of independent origin and the individual tumors have a totally different genetic makeup (LOH pattern and p53). These are true SPMs. Some tumors may not express the genetic profile of the primary completely. In such scenarios it was difficult to classify whether it was SPM or a recurrence. To differentiate local recurrence and metastasis from SPM, Braakhuis et al proposed a field cancerization model. The cells from the first tumour spread through saliva, lymphatic system, tissue or blood stream. If the fingerprint of early molecular markers like LOH at 3p, 9p, 17p and p53 mutations was similar in both the tumors the second tumour can be considered as metastasis. Following the first tumour excision, if the second tumour arose in more or less the same spot it was

considered as local recurrence. But if it arose at a distant site and there were no field changes between the lesions it was considered as metastasis. The authors also proposed a molecular classification for SPM developing after SCC oral cavity or oropharynx.¹¹ Same or adjacent site: a recurrent tumour, all molecular aberrations were similar; second field tumour; true SPM, molecular profiles were different. Different anatomic site: metastasis, all molecular aberrations were similar; second field tumour; true SPM, molecular profiles were different.

Warren and Gates criteria (1932) for diagnosis of SPM included the following:¹² tumours confirmed on histopathology as malignant; each neoplasm should be geographically distinct (the second primary must be separated by at least 2 cm of normal mucosa); probability of one being metastasis of the other must be excluded.

Explanation for SPM is based on 2 concepts¹³

Polyclonal model

The lesions developing were of independent origin and occurred through mutations at multiple sites of epithelium due to continuous carcinogen exposure. Tumors thus originating will be genetically different but in adjacent fields. In this case the second tumour arose in a genetically altered field that was left untreated. The difference between these SPMs and recurrence is that recurrence develops from tumours that were left behind in the margins after surgery.

Monoclonal model

Lesions shared a common clonal origin and developed due to migration of the cells from the initial lesion. This can happen in two ways: intraepithelial migration: tumor cells or tumor progenitor cells migrated through the submucosa into another site or cells shed into the lumen of an organ from primary tumor site to form tumor in a secondary site; patch field model (lateral spread): large area of mucosa replaced by genetically altered pre neoplastic cells waiting for a 2nd hit to progress to a tumorigenic state.

In our study, the majority cases were malignancy hypopharynx (76.5) with most of them being in pyriform fossa with smoking and alcohol as risk factors.

The SPM risk was about 2% to 4% per year with about 10% to 20% overall lifetime risk.¹ Across various studies the reported incidence of SPM was different. Few large case series reported the incidence of second primary as 10.9%, 14.2% and 9.4%.¹⁴⁻¹⁶ In another large trial by Ping et al with 1512 patients of head and neck carcinoma treated with curative radiotherapy and Kuhl et al following curative treatment the reported incidence of SPM was 9% and 10.3% respectively.^{17,18} Our study has taken only surgical candidates of malignancy hypopharynx and larynx following curative treatment and

the incidence of SPM was 3.1%. All the candidates were of advanced stage (stage III and IV) requiring multimodality treatment. Majority of the cases were male and the mean age was 68.5 years. There were a few studies evaluating these factors as risk factors for SPM. Jones et al found male sex, age less than 60 years and early primary tumours in larynx and oral cavity as risk factors to diagnose SPM.¹⁹ These same factors and age less than 66 years were also reported as risk factors by other authors.²⁰ Kuhl et al predicted the indicators of SPM in their study of head and neck carcinoma. The mean age of patients was 63.5 years and male population was found to have higher rates of SPM. But no significant correlation was established between sex or age with SPM. The sex and age predilection in some studies could be due to the higher habitual exposure to carcinogens.

In our study most of the SPM developed after 6 months. Thus the incidence of metachronous tumours was more with only a single case of synchronous tumour. The most frequent sites of SPM were lung and oropharynx followed by oesophagus. An unusual site reported was sigmoid colon in a patient with carcinoma supraglottis. Most of the recent studies reported UADT (40-59%), lung (31-37.5%) and oesophagus (9-44%) as the most common sites of SPM with more number of synchronous tumors than synchronous tumours.²¹ In a retrospective study of SPM in larynx and hypopharynx, 15% of larynx and 16% of hypopharynx SCC developed SPM. 55% of SPM occurred in respiratory axis for larynx (larynx and lung) and 66% of SPM was in the digestive axis (oral cavity, pharynx, oesophagus) for hypopharynx SCC.²² Chaudhary et al reported common head and neck SPM sites as oral cavity followed by oropharynx and larynx.²³ Patrucco et al and Hujala et al showed larynx as the common site for SPM.^{24,25} Within the larynx, supraglottis showed the highest rate of SPM according to Leon et al.²⁶ Schwartz found oesophagus as the most common site for synchronous primary and lungs for metachronous tumour.²⁷ The most common sites of SPM varies in the literature and it included subsites like lungs, larynx, oropharynx and other UADT areas.

Two most important factors recently studied in SPM were the influence of persistent tobacco and alcohol use on the risk of SPMs in the aerodigestive tract and the differences between HPV-positive patients and negative patients in terms of SPT incidence. Leon et al carried out a matched case-control study in 514 patients with HNC and found that the odds ratio of SPM for patients who continued to smoke was 2.9 and for patients who continued to use alcohol was 5.2. They concluded that there was a strong association between tobacco and alcohol habits with 33% SPMs being associated with these factors.²⁸ The cumulative risk of smoking was assessed in another trial for each group and found the current smokers with 2, 5, 10 and 15 years of smoking history had 1, 6, 18 and 32% rates of SPM incidence respectively.¹⁷ Chu et al demonstrated 2.17 times risk of SPM among smokers

compared to nonsmokers in larynx and hypopharynx SCC.²²

In a study by Morris et al the subsite specific risk for SPM was evaluated. In patients with index oral cavity and oropharyngeal SCC, there was a strong risk for head and neck SPM. We included only larynx and hypopharynx cases with highest incidence in hypopharynx cases. In the era of human papilloma virus associated oropharyngeal carcinoma, there was a regression trend of SPM over time. The risk of SPM was stable or slightly increasing for index tumors of oral cavity, larynx and hypopharynx while the risk of SPM in oropharyngeal SCC has now declined to the lowest level compared to any other head and neck subsites. The rise in HPV related oropharyngeal tumors and decline in smoking related tumors could explain this trend.²⁹ Li et al in another study stated that HPV infected tumors were generally immunosuppressed and hence they were predisposed to SPM.³⁰

Another factor was the effect of chemoradiation. 92% of our patients received adjuvant treatment. Few studies observed decrease in the T cell response and increased risk of SPM in patients who received radiation doses more than 5 Gy.^{31,32} But in head and neck carcinoma, the cumulative dose of radiation was 40 to 60 Gy. Hence this factor in SPM needed to be evaluated further before reaching a conclusion.

All patients in our study group were on routine follow up with triple endoscopy and imaging as detailed earlier. A close follow up with triple endoscopy had been recommended to diagnose SPM in most of the earlier studies. A study with 140 patients with UADT primary screened for 1 to 4 years with triple endoscopy diagnosed around 18 SPMs. They concluded that triple endoscopy in the absence of symptoms will only add the cost with minimal benefit.³³ Haerle et al compared both panendoscopy with PET CT for SPMs and identified the prevalence of SPM detected by each modalities as 4.5% and 6.1% respectively.³⁴ It was found that PET CT was superior. But in early stage cancer, panendoscopy was accurate enough to rule out SPM. The use of lugol chromoendoscopy allowed identifying suspicious mucosal areas for biopsy.³⁵ Narrow band imaging was observed to have good accuracy in detecting early mucosal lesions and cancers. Su et al analysed the accuracy of narrow band imaging in detecting oesophageal SPM in head and neck cancers. They had 147 patients with PET CT identifying 5.44% and narrow band imaging detecting 23.8% oesophageal lesions which showed the superiority of narrow band imaging.³⁶ PET CT was another promising method to diagnose SPM in patients with head and neck carcinoma. In a study by Strobel et al on 589 patients PET CT identified 56 SPMs and half of them were in early stage.³⁷

Limitations

Patients who were non-compliant with follow up protocols were not included in the study and many patients were lost on follow up.

CONCLUSION

The improvement in diagnostic and treatment strategies has increased the number of cancer survivors. As patients developing SPM will have significantly bad prognosis it is important to diagnose SPM at the earliest. The most important measures are prevention and early diagnosis. The modifiable risk factors affecting the incidence of SPM like smoking and alcohol need to be addressed. A regular follow up with careful screening for SPM is the most effective management strategy.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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