Sinonasal Malignancies: Long Term Follow Up After Surgical Management—An Analysis of Outcomes

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Abstract Sinonasal malignancies are rare and survival analysis in affected patients is arduous and perplexing due to various factors. In this review article, attempt has been made to overcome some of those factors while analysing survival outcomes. **Aims and objectives:** The aim of this study was to share the experience of a tertiary care centre in the surgical management of sinonasal malignancies over 12 years. **Materials and Methods:** This study is a retrospective chart review, and in this study, hospital records of 58 patients with biopsy proven sinonasal malignancies were studied. Only the patients undergoing primary or salvage surgery at our institution from May-2000 to April-2012 with a minimum follow up of 2 years were included. Statistical analyses such as means, proportions, Kaplan–Meier analysis and Cox’s regression model were done. **Results:** Majority of the patients were males ($n = 43$) belonging to fourth and fifth decades. Squamous cell carcinoma was the most common ($n = 17$) histopathological type, followed by adenoid cystic carcinoma ($n = 14$). Majority presented with stage IV disease ($n = 42$). 17 patients were operated for recurrent disease. Over all 5 year survival was 72 % and disease free survival was 44 %. Separate analysis for epithelial and matched non-epithelial group showed poorer prognosis with epithelial group ($p = 0.0120$). Multivariate analysis showed

histopathological type (epithelial) and presence of pathological risk factors (positive margins and/or perineural invasion) affecting survival. **Conclusions:** Advanced stage presentation is the norm for sinonasal malignancies. This study noted a 5 year overall survival of 72 % and disease free survival of 44 %. Epithelial histopathology carries poorer prognosis than other counterparts and incomplete removal is shown to add to poor prognosis independently.

Keywords Sinonasal malignancies ·
Squamous cell carcinoma · Survival analysis ·
Long term outcomes

Introduction

Sinonasal tumours are rare tumours, constituting 3 % of all head and neck tumours [1]. Nonspecific symptoms like nasal obstruction and blood tinged nasal discharge often lead to delayed diagnosis. Surgery, with adjuvant radiotherapy is considered as main modality of treatment [1]. Advanced stage at presentation not only carries poor prognosis, but surgical treatment for advanced malignancies itself adds significantly to morbidity. Variety of histopathological subtypes, each one having distinctly different natural course and differential response to treatment, makes outcome analysis of such tumours difficult. Rarity of such tumours adds to difficulty in aggregating data and analysing it. The aim of this retrospective analysis is to identify the poor prognostic factors in sinonasal tumours and their long term outcome. In this study, we are sharing a single tertiary institute’s experience, in surgical management of sinonasal malignancies over 12 years. Comprehensive analysis of outcomes has been performed, along with review of literature.

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Subjects and Methods

A thorough analysis of hospital medical records was done retrospectively. The data of all patients with biopsy proven sinonasal malignancy who were treated with curative intent, under department of otolaryngology head-neck surgery unit II between year 2000 and 2012 was analysed. All treatment decisions were made at a tumour board with comprehensive multimodality treatment clinic comprising head and neck surgery, radiotherapy and medical oncology.

A total of 89 case files were retrieved. Only 58 patients had follow up period of more than 2 years, thus remaining were excluded. Those patients who had non salvageable recurrence within 2 years were also included in the study, irrespective of total duration of follow up. Demographics data was recorded in terms of age, sex, risk factors, histopathological subtype, stage at presentation and site of origin.

Kaplan–Meier survival analysis was carried out collectively for overall data and separately for grouped data. Cox's regression model was used to identify factors affecting overall survival of the patients.

Results

Among the 58 cases evaluated, age range was between 13 and 78 years with a mean of 42.56 years. Male to female ratio was 3:1. The histopathological types were categorized according to tissue of origin and tabulated in Table 1. Squamous cell carcinoma was noted to be the most common type among all categories ($n = 17$, 29.3 %).

In our series we have categorized the tumours according to site of origin as maxillary sinus tumours, ethmoidal tumours and nasal cavity tumours. Due to close proximity of the subsites and propensity of asymptomatic spread to

surrounding sites [2] and involvement of multiple sites at presentation, it was difficult to ascribe a tumour to particular site. Based on radiological characteristics (attachment to bone, sclerosis of surrounding bone etc.) and surgeons opinion on intraoperative finding, anatomical classification into subsite of origin was done as shown in Table 2. Maxillary Sinus ($n = 32$) was the most common site of origin of such tumours. Though no patient had isolated frontal or sphenoid sinus disease in our series, these sinuses were found to be secondarily involved in 20 % cases.

Known risk factors like occupational exposure and smoking were found in 17 patients. In this series of patients there were 16 smokers; seven among epithelial group and nine among nonepithelial group. Also two patients working in tyre industry were identified to be exposed to occupational risk factors known to predispose to sinonasal malignancies. There was no statistically significant difference in risk factors distribution among patients with tumour of epithelial origin and non epithelial group.

Epithelial tumours were staged as per TNM staging proposed by AJCC [3]. Similarly other tumours also were staged using the appropriate classification system based on histopathological types [4]. 72.4 % ($n = 42$) of the patients had stage IV disease at the time of presentation and remaining 16 patients had either stage III/II disease. Out of the 58 patients, 70.6 % ($n = 41$) had surgery as primary treatment while 29.3 % ($n = 17$) patients had salvage surgery for recurrence after prior treatment with either surgery, chemotherapy and/or radiotherapy. Among the primary surgery group, 11 patients had surgery as a single modality of treatment while 28 patients received adjuvant radiotherapy in post-operative period. In two patients, chemotherapy was also added.

Various surgical techniques were employed, based on patient factors, disease extent and histopathological subtypes. Total maxillectomy was the most common

Table 1 Histopathological distribution of the sinonasal tumors in our series

Tissue of origin	Histopathological type	Number of cases	%
Epithelial (23)	Squamous cell carcinoma	17	29.31
	Transitional cell carcinoma	6	10.34
Glandular (21)	Adenocarcinoma	6	10.34
	Adenoid cystic carcinoma	14	24.14
	Mucoepidermoid carcinoma	1	1.72
Neuroectodermal (5)	Olfactory neuroblastoma	3	5.17
	Malignant melanoma	2	3.45
Mesenchymal (9)	Rhabdomyosarcoma	1	1.72
	Osteosarcoma	1	1.72
	Chondrosarcoma	4	6.90
	Angiosarcoma	1	1.72
	Inflammatory myofibroblastic tumour	2	3.45

Table 2 Distribution of tumor according to site of origin

Site of origin ^a	Number of cases	Percentage
Maxillary sinus	32	55.17
Ethmoids	19	32.76
Nasal cavity	7	12.07

^a Site of origin was decided based on radiological characteristics and intraoperative findings

procedure performed ($n = 25$), followed by lateral rhinotomy ($n = 9$), partial maxillectomy ($n = 7$), craniofacial resection ($n = 7$), extended maxillectomy ($n = 6$) and unassisted endoscopic excision was possible only in four patients.

Survival analysis were performed by Kaplan–Meier curves. For the overall data 5 year overall survival (OS) and disease free survival (DFS) rates of 72 and 44 % respectively were observed as shown in Fig. 1a, b. On further analysis of the data separately for histopathological types, epithelial malignancies had 5 year OS of 50 % and DFS of 25 %, whereas other malignancies (non-epithelial) had OS and DFS of 87 and 58 % respectively. As shown in Fig. 1c, d, epithelial malignancy group had poor prognosis as compared to non epithelial tumour group and this difference in prognosis was statistically significant in terms of OS, but statistically insignificant in terms of DFS. The epithelial and non-epithelial groups were fairly matched in terms of stage, presentation (primary/recurrent) and age as shown in Table 3.

Prognosis of sinonasal malignancies was also analysed separately for different stages at presentation. It was evident that patients with stage 4 disease had poorer prognosis as compared to stage 2 or 3 disease as shown in Fig. 1e. Also in the group of patients with recognized pathological/surgical risk factors, prognosis was poorer compared to those, who did not have any of such factors (Fig. 1f). Those factors were positive margins ($n = 9$), perineural invasion ($n = 3$) either in isolation or in combination ($n = 2$).

By Coxs regression analysis, certain factors were tested for affecting survival and as shown in Table 4, only epithelial origin and presence of surgical risk factor had statistically significant bearing on overall survival. A trend was also noted with smoking being a poor prognostic factor.

Discussion

Sinonasal malignancies comprise of tumours with multiple histopathological types, each having varied natural course. As already been mentioned in literature late presentation of such tumours not only implies poor prognosis [5, 6], but also makes analysis of such an entity of tumours difficult.

Occurrence of such tumours being very rare, compounds the problem of survival analysis. In the present series, despite grouping together of various types of malignant tumours affecting sinonasal region for analysis, the total number of cases treated over a period of 12 years has been small. This is not only due to the above mentioned peculiarities in natural course of the disease, but also due to the inclusion of only surgically treated patients and those with minimum follow up period of 2 years.

In this series of patients, men were affected three times more common than women, as reported in other studies available in literature [7, 8]. Common involvement of maxillary sinus has also been reported earlier in literature [9]. Majority of patients were of advanced stage at presentation, which is explained on anatomic basis of roomy cavity [2] of sinonasal tract, closely inter-communicating subsites and proximity to stage defining vital structures in the vicinity. The advanced stage of presentation as reported here may also be a reflection of our referral pattern, and has also been noted from other series' reported by tertiary care centers [9, 10]. Mention needs to be made here about the overlapping symptomatology of malignant diseases with that of commoner benign diseases like nasal polyposis and with that of intermediate tumours like inverted papilloma and hemangiopericytoma, because of which many patients seek medical treatment or casual surgical treatment like polypectomy without detailed evaluation or biopsy.

Squamous cell carcinoma was most commonly operated sinonasal malignant tumour closely followed by adenoid cystic carcinoma. Similar distribution has been observed in various reported reviews [7, 11, 20]. Predefined social risk factors like smoking and occupational exposure were encountered often in our series, but due to even distribution in compared groups, and by the fact that small number of patients were affected by these factors, no meaningful intergroup or intragroup comparison and inference could be drawn. Although patients working in tyre industry were not able to give details of the chemical(s) they were exposed to, in general tyre industry workers are exposed to various chemicals, many of them are carcinogenic like β -naphthylamine and 4-aminobiphenyl. However, later in the attempt to determine the factors affecting survival it was found that diseased patients with history of tobacco smoking had poor prognosis when compared to patients who weren't smoking, the difference in survival though was not statistically significant, but showed a trend.

Among the various surgical approaches it was noted that curative endoscopic resection could be achieved in four patients only, because of advanced stage cohort presenting to us and considering oncological principles [12] while planning for surgery. Ever since the advent of nasal endoscopic surgeries [13] and its exploration in the field of oncological surgeries, much has been debated and currently

Fig. 1 **a** Overall survival. **b** Disease free survival. **c** Overall survival by tissue of origin. **d** Disease free survival by tissue of origin. **e** Overall survival by stage of the disease. **f** Overall survival by pathological risk factors

consensus is to use it in early staged diseases and in advanced stage for debulking [14]. Issues of piecemeal resection-tumour spillage and adequacy of margin, during endoscopic surgeries have been discussed by Bogaerts et al. [15] and endoscopic resection has been concluded to be safe in terms of disease clearance and overall survival

with reduced morbidity, in selected cases like carcinomas of ethmoids without intradural extension, similar results have been replicated by Arnold et al. [16].

In our series, majority of stage IV patients were treated by radical surgery with postoperative radiotherapy. In all referred cases after non curative treatment and in recurrent

Table 3 Comparison of the groups as per age and stage at presentation

Epithelial	Variable	Non-epithelial	<i>p</i> value [#]
<i>Age distribution</i>			
0	<10	0	0.0885
0	10–20	3	
3	21–30	7	
5	31–40	8	
8	41–50	8	
3	51–60	7	
4	>60	2	
<i>At presentation</i>			
18	Primary	23	0.090
6	Recurrent	11	
<i>Stage</i>			
7	Stage III/<	9	0.821
16	Stage IV	26	

[#] *p* value was determined to check for any statistically significant difference in distribution of the patients between epithelial and non-epithelial group in terms of the variables mentioned

Table 4 Cox's multivariate analysis for individual risk factors

Parameters	Variables (v/s)	Haz. ratio	Std. err.	<i>z</i>	<i>p</i>
Tissue of origin	Epithelial/non-epithelial	0.207	0.131	−2.47	0.013
At presentation	Primary/recurrent	0.428	0.280	−1.3	0.195
Stage of disease	Stage III or less/ stage IV	2.561	2.197	1.1	0.273
Smoking	Yes/no	3.848	2.787	1.86	0.063
Pathological factors	Present/absent	10.388	7.373	3.3	0.001

cases following earlier treatment (excluding those who have been irradiated earlier), salvage surgery was followed by postoperative radiotherapy. Most of the studies in literature [17, 18] have shown that post operative adjuvant radiotherapy helps in achieving better overall survival and disease free survival than surgery alone. Some authors, however, believe that timing of radiotherapy given, either pre operatively or post operatively does not make any difference on survival [19]. Resto et al. [12] showed excellent local control rates with high dose radiation therapy using proton beam, irrespective of extent of surgery but disease free survival rate was predicted to be better with complete surgical resection. In general, the role of chemotherapy in sinonasal malignancies is limited. Chemotherapy is recommended for palliation only in cases of advanced, unresectable sinonasal malignancies, though initial reports by Madison et al. [20] showed promising results with neoadjuvant chemotherapy.

Survival analysis calculated by Kaplan–Meier curves showed, overall survival and disease free survival of 72 and 44 % respectively at 5 years, which are comparable with the reports from other authors [7, 21]. Five year survival rates showed poor prognosis with epithelial group in terms of overall survival, compared to age and stage matched non epithelial group. This can be due to aggressive behavior of squamous cell carcinomas and early involvement of surrounding vital structures making disease clearance difficult [22, 23], resulting in frequent local recurrence. In our series, a total of 28 patients had loco-regional recurrence, among whom 10 were not salvageable (five patients with distant metastasis and five patients with advanced locoregional recurrence) and were offered palliative or supportive treatment.

We separately listed the disease related variables which are thought to be having bearing on outcomes and were distributed variably among the cohorts. They were included under 'pathological risk factors'. Presence of pathological risk factor is shown to significantly affect overall survival, most common factor in our series being positive margin. According to Spiro et al. [24] extent of surgery did not affect the prognosis, whereas Resto et al. [12] reports negative surgical margins carrying better prognosis. Though in literature opinion on this aspect is contradictory, we recommend meticulous and complete removal of disease. In Literature, various other factors like stage of the disease [25] and previous treatment have been shown to affect the survival. In our series though patients with stage III or lesser stage had better survival compared to stage IV patients, stage of the disease was not significantly affecting the survival, which may be accounted to unequal distribution of patients in each stage, complicated by less comparability between the groups. Similarly due to the questionable comparability between various groups with respect to other parameters, such parameters could not be tested for statistical significance.

Conclusion

Sinonasal malignancies when treated with surgery with without radiotherapy carry 5 year overall survival of 72 % and disease free survival of 44 %. Epithelial histopathology carries statistically significant poor prognosis. Proper assessment and complete removal with vigilant follow up can help in reducing morbidity and mortality from such tumours. We recommend multidisciplinary approach in management of such tumours on basis of patient and disease characteristics to achieve best results.

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Conflict of interest The authors declare that they have no conflict of interest.

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