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Squamous cell carcinoma of the nasal cavity: A descriptive analysis of cases from the Head and Neck 5000 study

Abstract

Objectives

This paper aims to provide contemporary epidemiological data on squamous cell carcinoma (SCC) of the nasal cavity, which represents a rare type of head and neck cancer.

Design, Setting & Participants

A descriptive analysis of people with nasal cavity SCC treated with curative intent from the Head and Neck 5000 study; a multicentre clinical cohort study of people from the UK with head and neck cancer. People with tumours of the nasopharynx, paranasal sinuses and other sub-sites of the head and neck were excluded.

Main outcome measures

Demographic data and treatment details are presented for all participants. The main outcomes were overall survival and survival according to categories of characteristics (e.g. smoker vs non-smoker); these were explored using Kaplan-Meier plots.

Results

Thirty people with nasal cavity SCC were included in the study, of which most were male (67%) and current or ex-smokers (70%). The majority (70%) presented with early stage (T1/2, N0) tumours. Cervical lymph node metastases at presentation were rare, occurring in only one person. Nine people died during the follow up period (30%). Worse survival outcomes were seen in people with moderate or severe co-morbidities.

Conclusions

This paper provides epidemiological data on nasal cavity SCC in the UK. Patterns of disease and survival outcomes are described, identifying high-risk groups. Further studies should explore whether primary treatment modality alters survival.

Key words: Nasal cavity, nasal septum, nasal mucosa, squamous cell carcinoma, nose neoplasms, epidemiology, radiation, nasal surgical procedures

Introduction

Malignant tumours of the nasal cavity are rare in the UK, with an incidence of less than 1 per 100,000 per annum in England [1]. When considered together with tumours of the paranasal sinuses, they represent 3% of all head and neck malignancies [2]. In all populations, nasal cavity cancer has a male preponderance, but the incidence varies by geographical location, with the highest rates seen in African and Asian populations [3, 4].

Unlike other sub-sites within the head and neck, there is wide histological variation in nasal cavity tumours. The majority of tumours are squamous cell carcinoma (SCC), but a range of other tumour types are also reported, including melanoma, adenocarcinoma, salivary gland-type carcinoma, olfactory neuroblastoma and sinonasal undifferentiated carcinoma (SNUC) [4].

Smoking is an established risk factor for the development of nasal cavity SCC, and more recently, infection with oncogenic types of human papillomavirus (HPV) has also been shown to play a role [4, 5]. Although an association between occupational exposure to hardwood dust and adenocarcinoma of the paranasal sinuses has been identified, its relationship to tumours of the nasal cavity is yet to be defined [6].

Epidemiological data for SCC of the nasal cavity are limited due to the low incidence of nasal cavity cancer and the varied histopathology of tumours. In the majority of studies, nasal cavity cancers are presented alongside those of the paranasal sinuses, despite differences in tumour biology, epidemiology, and treatment response [2].

Head & Neck 5000 is a multicentre prospective cohort study of people with a new diagnosis of head and neck cancer [7, 8]. This paper uses data from this study to describe tumour characteristics, treatment and survival in people with SCC of the nasal cavity.

Methods

The methodology for the Head and Neck 5000 study has been previously described [7]. In brief, between April 2011 and December 2014, a total of 5,511 people with head and neck cancer were recruited from 76 centres. People with lymphoma, skin cancer and secondary tumours were not included in the Head and Neck 5000 study. Lifestyle, quality of life questionnaires and clinical information were collected at baseline (pre-treatment) and at 4 and 12 months after treatment. Biological samples including Formalin Fixed Paraffin Embedded (FFPE) biopsy tissue, blood and saliva were also obtained pre-treatment. Written consent was obtained from all participants.

Case definition

People with a clinical diagnosis recorded by the study centre as nasal cavity cancer (ICD-10 C30, 'nasal cavity') were identified. Pathology reports of individual cases were checked to verify tumour site and subtype. Only cases with consistent clinical and pathological data were included. Tumours of the paranasal sinuses, nasopharynx, skin and other sub-sites within the head and neck were excluded. Treatment intent was identified from pre-treatment data capture forms.

Socio-demographic variables

Age to the nearest year at consent to the study was recorded. Smoking status was collected through self-completed questionnaires at baseline. For analysis, smoking data were aggregated into a binary variable; 'never smoker' or 'current or former smoker'.

Clinical characteristics

Tumour TNM stage (Union for International Cancer Control 7th edition)[9] was obtained from pre-treatment data capture forms. For the purposes of analysis, stage was expressed as a binary variable. Stage I or II (T1 or T2, N0) tumours were defined as 'early stage', and stage III or IV (T3 or T4, N+) tumours were defined as 'late stage'.

Comorbidity was determined using the Adult Comorbidity Evaluation 27 (ACE 27) [10] score obtained from pre-treatment data capture forms. The highest ranked single ailment determined the overall score (excluding newly diagnosed head and neck cancer). Scoring ranged from 0, denoting no comorbidity, to 3 indicating severe decompensation. For analysis the comorbidities were grouped into none/mild, and moderate/severe.

Treatment modality was identified from 4-month data capture forms. For the purposes of analysis, people were grouped according to primary treatment modality (surgery or radiotherapy) +/- adjuvant treatment.

The primary measure of human papillomavirus (HPV) status was serological response to HPV antibodies using a glutathione S-transferase multiplex assay carried out at the German Cancer Research Center (DKFZ) in Heidelberg, Germany [11]. Seropositivity was defined as HPV16 E6 antibodies $\geq$ 1000 Median Fluorescence Intensity units (MFI).

Follow up

Study participants were flagged with the UK Health and Social Care Information Centre, which provided regular notification of the date and cause of death of participants who had died. Survival time was measured from study enrolment until either death or the end of the most recent follow-up period (25th August 2018).

Statistical analysis

Analysis was performed using STATA (Release 15, StataCorp, TX, USA). Characteristics of people with SCC of the nasal cavity were summarised using percentages or medians with interquartile ranges as appropriate. Pairwise associations between the characteristics were assessed using Fisher's exact tests. Overall survival and survival according to each of the categories of the characteristics was explored using Kaplan-Meier plots and log rank tests. Due to the rarity of SCC of the nasal cavity, the sample was not large enough to allow survival models to be fitted to the data [12].

Ethical considerations

The Head & Neck 5000 study was approved by the National Research Ethics Committee (South West Frenchay Ethics Committee, reference 10/H0107/57, 5th November 2010). The analysis of nasal cavity cancer from Head & Neck 5000 was approved by the University of Bristol Faculty of Health Science Research Ethics Committee on 28th April 2016 (reference 35501).

Results

Description of sample

Of the 5,511people who fulfilled the eligibility criteria for the Head and Neck 5000 study, 4,744 had pathology reports available, and 61 were recorded as having nasal cavity cancer. Review of histology showed that six cases did not have a pathology report to confirm the diagnosis, and six had indeterminate pathology or site of origin. These were excluded from the study. The remainder consisted of 30 squamous cell carcinomas, 10 adenocarcinomas, six melanomas, and three olfactory neuroblastomas.

Characteristics for the 30 people with SCC of the nasal cavity are shown in Table 1. The median age at consent to the study was 66 years (interquartile range 56 to 75 years). Two thirds were male, and just over two thirds were smokers (which included 26% current smokers and 44% former smokers). Just over a quarter had moderate or severe comorbidities. Most people (70%) had small (T1 or T2) tumours, and only one person had lymph node metastasis (clinical stage N1). None had distant metastases. Only two people (7% of the 29 with data recorded) were seropositive for HPV16. The primary treatment consisted of primary surgery for half and primary radiotherapy for the other half; full details of the treatment type is given in Table 1. No one received neck dissection. Everyone underwent treatment with curative intent.

Associations between characteristics

Pairwise associations between age, gender, smoking status, comorbidities, tumour TNM stage and treatment are shown in Table 2. There was statistical evidence for an association between being a non-smoker and having surgery ($p=0.03$), and to a lesser degree between not having comorbidities and late stage tumours ($p=0.07$). Possible associations between not smoking and late stage tumours ($p=0.2$), and younger people being female ($p=0.2$) were also identified. There were no associations between any of the other pairs of characteristics ($p \geq 0.4$).

Associations with survival

Nine of the 30 people (30%) died, the median duration of follow up was 34 months (range 7 to 67 months [IQR 18 to 54 months]) for those that died, and 54 months (range 45 to 74 months [IQR 50 to 66 months]) for those that were still alive at the end of the study. Kaplan-Meier analysis of overall survival is shown in Figure 1. Estimates for overall survival and survival according to age, gender, smoking status, comorbidities, tumour TNM stage and treatment are shown in Supplementary Table 1.

There was statistical evidence that survival was worse for people with comorbidities ($p=0.01$) (Figure 2). Survival was worse for males, those who did not have surgery and those with early stage tumours, but there was no statistical evidence for these differences ($p=0.4$ for all) (Figure 2). There were no differences between the age groups or smoking categories ($p=0.9$ for both). Comparisons between categories of characteristics were made at 45 months as this is minimum duration of follow up available for everyone alive at the end of the study).

Discussion

This study provides a descriptive analysis of people with nasal cavity SCC: a rare type of head and neck cancer. The study showed that nasal cavity SCC is predominantly a disease of male smokers, although tumours were also seen in females and in non-smokers. The majority of primary cancers were staged as T1 or T2, indicating that the tumours at presentation remained limited to the nasal cavity. Regional lymph node metastases at presentation were rare; only one patient had metastatic disease in a single cervical lymph node. Worse survival outcomes were seen in people with moderate or severe co-morbidities.

Tumour stage in nasal cavity SCC

The findings from this study are consistent with findings from previous studies suggesting that lymph node metastases are uncommon at diagnosis in nasal cavity SCC, occurring in between 0-6% of people [4, 13-15]. Becker and colleagues reported 39 cases of nasal cavity SCC over a 16-year period, half of which underwent neck dissection. From a total of 305 dissected lymph nodes, only a single node contained metastatic SCC, leading the authors to conclude that treatment of the N0 neck is only indicated in high risk cases [4].

Although the incidence of lymph node metastases at diagnosis is low, regional recurrence has been reported in up to 18% of people with nasal cavity SCC (95% CI, 13%-23%) [16]. This may be explained by the observation that lymph node metastases from mid-facial SCCs are often delayed [17]. Another explanation may be the presence of occult micrometastases in regional lymph nodes, which may not be identified on routine histopathological examination without serial step sectioning [18]. Finally, the high rate of regional recurrence may occur because elective treatment of the neck (either surgery or radiotherapy) is not performed in the context of no clinical or radiological nodal disease. Whatever the explanation, the high rate of regional recurrence mandates close clinical follow-up in this group.

Survival

In this study, overall survival estimates were 83% (95% CI: 65%-93%) and 69% (95% CI: 46%-84%) at 3 years and 5 years respectively. Due to small numbers at longer follow-up durations in this study, confidence intervals are wide, however, the findings are consistent with other recent analyses. Ho and Coman described a series of seventeen people with cancer of the nasal septum and found that three-year survival was 82% [19]. In a meta-analysis of people with nasal cavity SCC, Scurry and colleagues reported a 5-year overall survival (63%; 95% CI, 62%-64%). These figures are however derived from studies published between 1974 and 2000, and therefore may not reflect current treatment outcomes.

Co-morbidity is an established indicator for poor prognosis in head and neck cancer, and the results from this study support the suggestion that co-morbidities confer an

adverse prognosis in people with nasal cavity cancer [20]. Other associations with survival were weak, but there was a suggestion of reduced survival in people treated with radiotherapy compared to surgery. Although the radiotherapy group contained a higher proportion of smokers than the surgery group, there was no association between smoking and survival. Furthermore no association was observed between co-morbidity and treatment modality or tumour stage and treatment modality.

Previous studies have reported that people undergoing non-surgical treatment for nasal cavity cancer may have worse rates of overall survival and loco-regional control than those undergoing surgery [4, 14, 15, 21]. The effect size observed in those studies varied widely, but was broadly comparable to the results of this study. For example, Fornelli and colleagues described 32 people with nasal cavity SCC, 23 received primary surgery, and nine underwent primary radiotherapy. With a mean follow up duration of 4.4 years (range 9 months to 13 years) overall survival was 43% in the surgery group and 33% in the radiotherapy group [15]. In the study by Mendenhall et al., 5 year overall survival was 73% for people treated with primary surgery, 38% for those treated by primary radiotherapy [21]. Although the effect size in that study was large, it included tumours of varied histology and those from the paranasal sinuses, so may not be directly comparable to our study.

Although these studies suggest improved outcomes following surgical management of nasal cavity cancer, much of the results come from historical series. The last two decades have seen improvements in both surgical techniques (e.g. endoscopic surgical approaches, pre-operative assessment and optimisation) and non-surgical treatment modalities (e.g. intensity-modulated radiotherapy & concomitant platinum-based chemotherapy). The association between treatment modality and survival therefore requires further examination and may be an area for future research.

Paradoxically, higher all cause mortality was seen in people with early stage tumours than those with late stage tumours. This finding is at odds with previous studies, and may be explained by the higher proportion of people in the early stage group with moderate or severe co-morbidities (Table 2) or it could represent a chance finding given the small number of cases in this study.

Research implications

This study describes the features of nasal cavity cancer in a small group of people from the UK, and is comparable in size to other case series of nasal cavity SCC. Although exposure to passive smoke was not measured, almost a quarter of those included in the study were non-smokers, suggesting that the pathogenesis and risk factors for nasal cavity cancer may be incompletely understood. In this study only two people had evidence of oncogenic HPV infection but this was based on seroconversion rather than measures of HPV in the tissue. Seroconversion is known to be a good marker of HPV driven oropharyngeal SCC but its ability to detect HPV driven tumours outside the oropharynx is unclear. Recent results from a US study using a real-time multiplex PCR assay to identify fifteen high-risk HPV subtypes from paraffin-preserved tumour tissue, indicated evidence of HPV infection in 62% [5]. Larger prospective cohort studies of people with nasal cavity cancer are required to better describe the risk factors associated with disease, the clinical characteristics of cases and factors associated with better survival.

As previously mentioned, a possible association between treatment modality and survival requires further study in the context of modern treatment paradigms. Given the

low incidence of nasal cavity SCC pooling of existing studies and meta-analysis may allow a further assessment of this relationship and help decide whether further larger observational studies are warranted.

Strengths and weaknesses of this study
This study reports epidemiological data on a rare and highly specific group of people with nasal cavity cancer. In all cases anatomical sub-site and histological type were confirmed by a pathologist, ensuring a high degree of accuracy. Furthermore, cases are drawn from a large national cohort that recruited participants between 2011 and 2014, meaning that treatment regimens represent current best practice in both radiotherapy and surgery. The results are broadly consistent with those from other studies that reported data collected over the course of several decades [2, 4, 15, 21].

The main weakness of this study is the small sample size. This reflects the low incidence of nasal cavity SCC [1]. Therefore many of our findings need to be interpreted with caution. An additional weakness is that smoking data were missing for seven people and co-morbidity data were missing for one. Co-morbidity information was obtained by local clinical teams, but by contrast, smoking data were derived from self-administered questionnaires, completed by participants and returned to the study team. This may explain the higher proportion of missing smoking data.

Conclusion

This study provides a descriptive analysis of people with SCC of the nasal cavity in the UK. The results indicate the characteristics of affected individuals, the pattern of tumour staging and associations between demographic data and survival. The results have also highlighted areas for further research in this rare subgroup of people with head and neck cancer.

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