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# A multicentre UK study of outcomes for locally advanced sinonasal squamous cell carcinoma treated with adjuvant or definitive intensity modulated radiotherapy

Finbar Slevin[a, *], Shermaine Pan[b, *], Hitesh Mistry[c], Mary Denholm[d], Dana Shor[d], Zhu Oong[e], James Price[b], Rashmi Jadon[d], Jason C Fleming[f], Gill Barnett[d, §], Lynne Dixon[g, §], Robin Prestwich[a, §], David Thomson[b, c, §, #]

* Joint first authors
§ Joint senior authors
[a]Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Beckett Street, Leeds LS9 7TF, UK
[b]The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, UK
[c]University of Manchester, Oxford Road, Manchester M13 9PL, UK
[d]Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK
[e]Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Sharoe Green Lane, Fulwood, Preston, Lancashire PR2 9HT, UK
[f]Liverpool University Hospitals NHS Foundation Trust, Liverpool L9 7AL, UK
[g]Weston Park Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Whitham Road, Sheffield S10 2SJ, UK

[#]Corresponding author: David Thomson
Address: The Christie NHS Foundation Trust, Wilmslow Road, Manchester M20 4BX, UK
Email address: David.Thomson2@christie.nhs.uk

Finbar Slevin email address: finbarslevin@nhs.net
Shermaine Pan email address: s.pan@nhs.uk
Hitesh Mistry email address: hitesh.mistry@manchester.ac.uk
Mary Denholm email address: mary.denholm@addenbrookes.nhs.uk
Dana Shor email address: dana.shor@addenbrookes.nhs.uk
Zhu Oong email address: zhu.oong@lthtr.nhs.uk

**James Price email address: james.price@nhs.net**
**Jason Fleming email address: Jason.fleming@liverpool.ac.uk**
**Gill Barnett email address: gill.barnett@addenbrookes.nhs.uk**
**Lynne Dixon email address: lynne.dixon3@nhs.net**
**Robin Prestwich email address: robin.prestwich@nhs.net**

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## Abstract

### Introduction

Sinonasal malignancies are rare; the most common histological subtype is squamous cell carcinoma (SCC). No randomised trial data exist to guide treatment decisions with options including surgery, radiotherapy and chemotherapy. The role and sequence of a primary non-surgical approach in this disease remains uncertain. The aim of this study was to present treatment outcomes for a multicentre population of patients with locally advanced, stage IVa/b sinonasal SCC treated with radical-intent intensity modulated radiotherapy (IMRT), either definitively or post-operatively.

### Materials and Methods

Consecutively treated patients with locally advanced, stage IVa/b sinonasal SCC at four United Kingdom oncology centres between January 2012 and December 2017 were retrospectively identified. Descriptive statistics and survival analyses were performed. Univariable Cox regression analysis was performed to evaluate the relationship between patient, disease and treatment factors and survival outcomes.

### Results

56 patients with sinonasal SCC were included (70% maxillary sinus, 21% nasal cavity, 9% ethmoid/frontal sinus). Forty-one patients (73%) were treated by surgery/adjuvant (chemo)radiotherapy and 15 (27%) by definitive (chemo)radiotherapy. The median duration of follow up was 3.8 years (inter-quartile

range [IQR], 2.0-4.7 years). Estimates for 5-year overall survival (OS) and progression-free survival (PFS) were 30.2% and 24.2% respectively. Local, regional and distant treatment failures were seen in 33%, 33% and 16% of patients respectively. Univariable analysis revealed inferior progression-free survival for patients treated with neck dissection (HR 2.6, 95% CI 1.2-6.1, p=0.022) but no other significant association between the studied factors and survival outcomes.

### Conclusion

We demonstrate poor survival outcomes and high rates of locoregional treatment failure for patients with locally advanced stage IVa/b sinonasal SCC. There is a need to investigate improved treatments for this group of patients.

## Keywords
Sinonasal squamous cell carcinoma; intensity modulated radiotherapy; locally advanced; outcomes

## Introduction

Sinonasal malignancies are a heterogeneous group of diseases arising from the nasal cavity or paranasal sinuses and are rare, affecting < 1 in 100,000 people per year [1, 2]. The most common histological subtype of sinonasal malignancy is squamous cell carcinoma (SCC), which comprises 3-5% of all head and neck cancers [3, 4]. Sinonasal SCC most commonly arises from the maxillary sinus or nasal cavity, and early asymptomatic growth results in almost two-thirds of patients presenting with stage IV disease [1, 5, 6]. The close proximity of critical structures (e.g. the optic apparatus, cranial nerves and brain) and other organs at risk (OAR) presents a major therapeutic challenge.

Despite technological developments in diagnostic imaging and the use of multimodality treatment including endoscopic surgical techniques and highly conformal intensity-modulated radiotherapy (IMRT), the prognosis for sinonasal SCC remains poor with high rates of local failure [3, 7-10]. The rarity and heterogeneous nature of sinonasal malignancies means there is an absence of high-level evidence to guide the optimum combination and sequencing of treatments [3, 4, 10]. There are variations in standard treatment approach for locally advanced disease including maximal surgical resection with adjuvant (chemo)radiotherapy depending on pathological findings, or definitive radiotherapy with or without induction and/or concurrent chemotherapy [11-14].

It has previously been recommended that sinonasal SCC should be evaluated independently in more homogeneous patient cohorts as it is the most common subtype with a more aggressive behaviour and poor prognosis [14]. Here we present disease control and survival outcomes from four UK centres in the largest reported IMRT series of locally advanced stage IVa/b sinonasal SCC.

## Materials and Methods

### Patient Population

This was a retrospective analysis of consecutive patients treated between January 2012 and December 2017 identified from institutional databases at four tertiary cancer centres in the UK: XX, XX, XX and XX. Institutional approval was obtained in each centre. Case notes were reviewed to obtain demographic, clinico-pathological and survival data.

Eligible patients had histologically-confirmed SCC, AJCC 7$^{th}$ edition clinical/radiological and/or pathological stage IVa/b disease and were treated with radical intent [15]. Patients with distant metastatic disease and those treated with palliative intent or surgery alone were excluded. Diagnostic computed tomography (CT) neck/thorax and/or magnetic resonance imaging (MRI) was performed for all patients. Positron emission tomography-computed tomography (PET-CT) was gradually introduced during the study time period. All patients were routinely discussed in head and neck cancer multidisciplinary team meetings prior to treatment.

### Treatment approach

There was variation in treatment approaches both between centres and over time within centres as treatment techniques developed, however in general terms surgery with adjuvant (chemo)radiotherapy was preferred for those with resectable disease.

### Surgery

All patients were discussed in a multidisciplinary team meeting to evaluate the feasibility and appropriateness of surgical resection. The surgical approach depended on the disease subsite, extent of disease, likelihood of achieving clear or close resection margins and the expected functional and cosmetic outcomes (e.g. the need for orbital exenteration).

### Radiotherapy

Patients were treated according to protocols in use at the time at each institution. Typically, for IMRT patients were treated supine and immobilised by a five-point thermoplastic shell. A mouthbite was used to minimise the radiation dose to the inferior oral cavity. Planning CT images were acquired with 2-3 mm slices with intravenous contrast. Planning CT images were transferred to the treatment planning system (Pinnacle [Koninklijke Philips N.V., Amsterdam, Netherlands], Eclipse [Varian Medical Systems, Palo Alto, CA, USA], MasterPlan/Oncentra®, XiO® or Monaco® [Elekta AB, Stockholm, Sweden]).

The definitive radiotherapy dose fractionation schedules used during the study time period varied by institution and are based on those recommended by the Royal College of Radiologists, including 65 Gy in 30 fractions over 6 weeks and 70 Gy in 35 fractions over 7 weeks, once daily [16]. Selected less-fit patients received 55 Gy in 20 fractions over 4 weeks. Patients undergoing adjuvant radiotherapy dose fractionation schedules received 60-66 Gy in 30-33 fractions, depending on pathological risk factors.

For target volume delineation, there was a transition over the study period from a compartmental approach (where the entire involved sinus(es) received a high dose) to a volumetric approach (where the high dose volume was defined by a margin from the gross tumour volume (GTV) and the remainder of the sinus(es) received a lower dose).

For adjuvant radiotherapy where patients had undergone macroscopically complete surgical resection of the tumour, typically one dose level was used (where the clinical target volume (CTV) encompassed the resection cavity and included all invaded/partly invaded sinuses).

Practice varied regarding elective treatment of the clinically node negative neck; node positive disease was treated by neck dissection and adjuvant (chemo)radiotherapy or definitive (chemo)radiotherapy as applicable.

A planning target volume (PTV) was generated by the addition of a 3-5 mm margin to the CTV. The OAR typically delineated included the spinal cord/canal, brainstem, optic nerves, optic chiasm, globes and parotid glands. Patients were inversely planned and treated using IMRT, either 5-7 angle step-and-shoot IMRT or volumetric modulated arc therapy (VMAT).

## Chemotherapy

The addition of induction and/or concurrent chemotherapy was based on an individual clinician's decision. Where used, concurrent chemotherapy with cisplatin was typically given either 3 weekly (100 mg/m$^2$) or weekly (40 mg/m$^2$) for patients aged 70 years or less with a WHO performance status score of 0-1 and adequate renal function (estimated glomerular filtration rate >60 ml/min). The substitution of carboplatin for cisplatin was at clinician discretion. Induction chemotherapy was offered to selected patients prior to surgery or definitive radiotherapy (for example, in cases of locally extensive high grade disease) and typically involved either PF (cisplatin [100 mg/m$^2$ on day 1] and 5-fluorouracil [1000 mg/m$^2$on day 1 for 5 days] or TPF (docetaxel [75 mg/m$^2$ on day 1], cisplatin [75 mg/m$^2$ on day 1] and 5-fluorouracil [750 mg/m$^2$ on day 1 for 4 days], both given every 21 days for up to 3 cycles.

## Follow up

Individual follow up schedules were used at each institution with patients followed up for a minimum of 5 years. For patients treated with definitive radiotherapy, response assessment imaging with CT/MRI was typically performed at 3 months with gradual introduction of PET-CT response assessment. Treatment failure was defined

as the first occurrence of local, regional or distant relapse and was established using a combination of clinical, radiological and histological confirmation of recurrence.

### Analysis of patients with local treatment failure

For patients with local treatment failure, the treatment plan was reviewed to determine whether PTV coverage was compromised/target volume margins had been reduced close to an OAR (e.g. optic apparatus or brain). As a measurement of PTV coverage, the percentage volume of the PTV which received 95% of the prescribed dose was also reported. To determine whether the local recurrence would have been in field (i.e. contained within the 95% prescription isodose) or marginal/out of field, a visual estimate of the most likely point of origin of the recurrence was made on re-staging imaging taking into account the size of the recurrence and its relationship to anatomical structures. The corresponding point was then visually located on the planning CT to determine whether it was contained within the 95% isodose.

### Statistical analysis

Overall survival (OS) and progression-free survival (PFS) outcomes were calculated from the date of histological diagnosis. Patients who had not experienced an event (treatment failure or death) were considered right-censored. Survival analyses were calculated using the Kaplan-Meier method. A time-to-event analysis between OS and PFS and certain patient (age, gender, performance status, smoking), disease (sub-site, grade, stage) and treatment (surgical/non-surgical approach, neck dissection, nodal irradiation, induction/concurrent chemotherapy) characteristics was performed using the Cox proportional hazards model and hazard ratios with 95% confidence intervals and p values reported. All analyses were performed in IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

## Results

### Patient, Disease and Treatment Characteristics

56 patients with locally advanced, stage IVa/b sinonasal SCC were eligible for inclusion. Patient and disease characteristics are summarised in **Table 1**. Nineteen, 18, 12 and 7 patients were treated in each of XX, XX, XX and XX respectively. 70% of cases were maxillary sinus tumours. Clinical/pathological T4 and node-positive disease was observed in 94% and 36% of patients respectively. Treatment details are summarised in **Table 2**. Twelve patients (21%) received induction chemotherapy. Forty-one patients (73%) underwent primary surgery; all patients received adjuvant radiotherapy and 11 of these (20 %) received concurrent chemotherapy. Seventeen patients (31%) received definitive radiotherapy and 6 of these (11%) received concurrent chemotherapy. Of note, two patients received definitive radiotherapy/chemoradiotherapy following surgery for macroscopic residual disease and were included in the surgical cohort for analyses.

### Outcomes

At a median duration of follow up of 3.8 years (inter-quartile range [IQR] 2.0-4.7 years), the median OS for all 56 patients was 42 months (95% confidence interval [CI]

33.1-50.9). Estimated OS at 1, 3 and 5 years was 81.8%, 63.2% and 30.2% respectively. The median PFS was 39 months (95% CI 30.7-47.3). Estimated PFS at 1, 3 and 5 years was 76.8%, 53.1% and 24.2% respectively. Kaplan-Meier plots for OS and PFS are shown in **Figure 1A** and **1B** respectively.

Significantly inferior PFS was observed for patients treated with neck dissection (hazard ratio [HR] 2.6, 95% CI 1.2-6.1, p=0.022) but no other patient, disease or treatment factors evaluated by univariable analysis were significantly associated with OS or PFS.

Treatment failure was observed in 32/56 patients (57%); patterns of failure are described in **Table 3**. The predominant modes of treatment failure were local and regional, observed in 18 patients each (33%). Of the regional failures, eight patients were node positive and 11 had received neck treatment; neck dissection in three patients, nodal irradiation in three and both neck dissection and nodal irradiation in five. Distant failure was seen in 16% of patients.
Further treatments received by patients after treatment failure are shown in **Table 4**. Seven patients received radical salvage treatment as follows: salvage surgery alone (n= 2, 4%), salvage surgery with post-operative re-irradiation (n= 5, 9%), definitive re-irradiation (n= 1, 2%). Of these, three patients remained alive and disease-free at longest follow up.

A summary of clinicopathological and treatment plan characteristics for patients with local failure is shown in **Table 5**. PTV coverage by 95% of the prescribed dose was <95% in two cases. PTV coverage was compromised by reduced coverage close to OARs and/or reduced target volume margins in eight and two cases respectively. One case had dural involvement at diagnosis but PTV coverage was not compromised in this region. Local failures were estimated to have been contained within the 95% isodose in 12 cases (i.e. in field recurrence) and out of field in five cases (in one case, no imaging was performed at diagnosis of local failure).

## Discussion

Prior series reporting clinical outcomes for patients with sinonasal malignancies often include a variety of histological subtypes, both early and locally advanced disease and older radiotherapy techniques (see **Table 6**) [5, 17-31]. In contrast, this is the largest series of patients with stage IVa/b SCC treated with IMRT. Due to the rarity of this disease and the small nature of individual series, we opted to study a particular histological subtype/disease stage in a multicentre setting, accepting the inevitable variability in treatment protocols/approaches. Although more patients were treated by primary surgery than primary radiation (73% versus 27%), the two groups appeared to be well-balanced with regards to other patient and disease factors.

Though direct comparison with the studies in Table 5 is difficult, our estimated respective 5-year OS and PFS of 30.2% and 24.2% are broadly comparable. Rates of

5-year OS in the published IMRT literature range from 43% to 59% but these include early stage disease and non-squamous histologies [14, 17, 19-23, 26, 31].

In our study, the predominant treatment failures were local and regional relapses (33% of patients each), which is in keeping with the findings of previous studies where 5-year estimates of local control range from 33-84% [5, 24, 25, 27, 29, 30]. The causes of local failure in this study were not clearly identified. It is possible that some of the failures were related to compromise of PTV coverage, seen in eight instances. In some patients, the delivered dose was also compromised (for example, three patients were treated with adjuvant chemoradiotherapy 60 Gy in 30 fractions rather than 66 Gy in 33 fractions). However, in only five cases was the central point of recurrence not clearly contained within the 95% isodose (accepting the limitations of this methodology which does not account for the possibility of marginal failures, see below). Nevertheless, as local disease control directly relates to overall survival and the site of locally persistent or recurrent disease is often around the supero-lateral orbital margin, there is significant interest in the role of proton beam therapy (PBT) in the management of sinonasal cancer [32]. It is hypothesised that PBT compared with IMRT may improve target volume coverage while sparing critical structures (e.g. the optic apparatus), and may also improve treatment outcomes by dose escalation or increased biological effectiveness [14, 33-36]. A systematic review and meta-analysis of 41 observational studies of PBT and other charged particles reported increased OS (relative risk [RR] 1.5, 95% CI 1.1-2.0, p = 0.0038) and disease-free survival (RR 1.9, 95% CI 1.4 – 2.8, p = 0.0003) at 5 years compared to IMRT [37]. However, the authors highlighted the poor data quality and risk of bias and even reported increased late neurological toxicity. The role of PBT for sinonasal malignancies is being formally evaluated in an ongoing US phase II trial (NCT01586767) and a UK phase III trial (PROTIS: PROTons vs IMRT for Sinonasal Cancer) is in the design phase.

In additional to local failure, other factors may be responsible for the poor survival observed with sinonasal SCC. Previous large studies from the National Cancer Database and Surveillance, Epidemiology and End Results (SEER) Program suggest that inferior survival is associated with factors including positive surgical margins, advanced stage disease, single modality therapy (especially radiotherapy alone), a history of current smoking, poor performance status/presence of comorbidity (which may preclude multimodality therapy) and treatment within low volume centres [3, 4, 9, 10, 12, 38]. In our study, all patients had stage IVa/b disease, 29% were current smokers and only a minority received induction and/or concurrent chemotherapy (21% and 31% respectively). We did not observe a significant difference in survival between patients treated with primary surgery and definitive (chemo)radiotherapy, possibly because of the differences in patient numbers in each subgroup. In addition, differences in treatment approach and selection bias means that the interpretation of a comparison between patients treated with a surgical versus non-surgical approach is challenging. This heterogeneity in practice also means that the reliability of our finding of statistically poorer PFS for patients treated by neck dissection is uncertain.

There was considerable variation in the combination and sequencing of treatment modalities. This could be attributed to heterogeneity in patient and disease factors and both inter and intra-institutional differences in practice during the study period. The rarity and heterogeneity of sinonasal malignancies and the absence of clinical trial data makes the development of consensus guidance challenging. For T4a disease, the US National Comprehensive Cancer Network (NCCN) guidelines recommend surgical resection with adjuvant radiotherapy, with consideration of concurrent systemic therapy [39]. For patients with inoperable T4b disease, the guidelines suggest that various combinations of induction chemotherapy, (chemo)radiotherapy and surgery may be appropriate. No specific UK National Institute of Health and Care Excellence (NICE) or European Society of Medical Oncology (ESMO) guidelines exist for sinonasal malignancies; UK national multidisciplinary guidelines were published in 2016 with a particular focus on surgical considerations but no specific recommendations were made concerning the optimum combination and sequencing of treatments especially in stage IV disease [13]. A Royal College of Radiologists (RCR) national multidisciplinary audit is currently ongoing to inform development of the PROTIS trial and it is hoped that the design of the control arm of the trial (IMRT) may help establish a national standard for practice, especially for patients with locally advanced disease.

Limitations of this study include its retrospective design and its small size despite including data from four centres (which reflects the rarity of the disease). We did not report toxicity data, since the focus of this study was treatment outcomes and there are inherent biases in the retrospective assessment of toxicity. There was not a standardised treatment approach between centres and, given the complexities in surgical approach to sinonasal cancers, challenges exist in the interpretation of surgical factors such as margin status. The number of patients included in the study may explain why no other patient, disease or treatment factors appeared to be significantly associated with survival on univariable regression analysis. For this reason, a multivariable analysis was not undertaken. Our method of recurrence pattern analysis was descriptive and therefore inherently limited since it relied on a visual estimation of the likely centre of the recurrence. In addition, this methodology assumed that the tumour grew isometrically out from this point, which is flawed given the complex arrangement of anatomical boundaries in the sinonasal region. We were also unable to accurately account for marginal treatment failures. However, the complexities of undertaking a formal analysis using a standardised methodology across four centres were considerable and were considered beyond the scope of this project. In addition, the authors are not aware of such an analysis reported in the literature specifically concerning sinonasal malignancies. We consider that the findings of poor survival and high rates of local failure should be seen as hypothesis generating for future studies and especially as a justification to undertake clinical trials to investigate methods for improving outcomes.

## Conclusion

This retrospective multicentre UK study has identified poor survival outcomes and high rates of locoregional failure in a cohort of patients with locally advanced stage IVa/b sinonasal SCC treated with IMRT. There was also considerable variation in the combination and sequencing of treatment modalities. Our findings justify clinical trials of interventions to try and improve outcomes and establish a standard of care for this group of patients.

**Figure caption**
Kaplan-Meier plots for overall survival (A) and progression free survival (B) for the whole cohort

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## Table 1: Patient and disease characteristics

| *Factor* | *Primary surgery (n = 41)* | *Primary RT (n = 15)* | *Total (n = 56)* |
|---|---|---|---|
| Median age (range) | 60 years (39-85) | 62 years (41-80) | 60 years (39-85) |
| | | | |
| Gender | | | |
| Male | 29 (71%) | 9 (60%) | 38 (68%) |
| Female | 12 (29%) | 6 (40%) | 18 (32%) |
| | | | |
| Performance status | | | |
| 0 | 17 (41%) | 7 (47%) | 24 (43%) |
| 1 | 22 (54%) | 5 (33%) | 27 (48%) |
| 2 | 2 (5%) | 3 (20%) | 5 (9%) |
| | | | |
| Smoking | | | |
| Current smoker | 12 (29%) | 4 (27%) | 16 (29%) |
| Other | 29 (71%) | 11 (73%) | 40 (71%) |
| | | | |
| Disease subsite | | | |
| Maxillary sinus | 33 (80%) | 6 (40%) | 39 (70%) |
| Nasal cavity | 5 (12%) | 7 (47%) | 12 (21%) |
| Ethmoid sinus | 1 (2%) | 2 (13%) | 3 (5%) |
| Frontal sinus | 2 (5%) | | 2 (4%) |
| | | | |
| Tumour grade | | | |
| Well differentiated | 7 (17%) | 2 (13%) | 9 (16%) |
| Moderately differentiated | | | |
| Poorly differentiated | 13 (32%) | 8 (53%) | 21 (38%) |
| Not known | 18 (44%) | 4 (27%) | 22 (39%) |
| | 3 (7%) | 1 (7%) | 4 (7%) |
| T stage | | | |
| T2 | 1 (2%) | 0 (0%) | 1 (2%) |
| T3 | 1 (2%) | 1 (7%) | 2 (4%) |
| T4 (a/b) | 39 (96%) | 14 (93%) | 53 (94%) |
| | | | |
| N stage | | | |
| N0 | 26 (63%) | 10 (67%) | 36 (64%) |
| N positive (N1-3) | 15 (37%) | 5 (33%) | 20 (36%) |

RT; radiotherapy

## Table 2: Treatment characteristics

| *Factor* | *Number (%)* |
|---|---|
| Treatment pathway | |
| Surgical* | 41 (73%) |
| Non-surgical | 15 (27%) |
| | |
| Radiotherapy treatment | |
| Adjuvant radiotherapy | 28 (50%) |
| Adjuvant chemoradiotherapy | 11 (20%) |
| Definitive radiotherapy | 11 (20%) |
| Definitive chemoradiotherapy | 6 (11%) |
| | |
| Neck dissection | |
| Yes | 20 (36%) |
| No | 36 (64%) |
| | |
| Induction chemotherapy | |
| Yes | 12 (21%) |
| No | 44 (79%) |
| | |
| Induction chemotherapy regimen | |
| Cisplatin, docetaxel, 5-fluorouracil | 6 (11%) |
| Cisplatin, 5-fluorouracil | 6 (11%) |
| | |
| Treatment after induction chemotherapy | |
| Radiotherapy | 7 (13%) |
| Concurrent chemoradiotherapy | 2 (4%) |
| Surgery | 3 (5%) |
| | |
| Concurrent chemoradiotherapy | |
| Definitive chemoradiotherapy | 6 (11%) |
| Adjuvant chemoradiotherapy | 11 (20%) |
| | |
| Concurrent chemotherapy regimen | |
| 3 weekly cisplatin | 15 (27%) |
| Weekly cisplatin | 2 (4%) |
| | |
| Radiotherapy dose fractionation: adjuvant | |
| 66 Gy in 33 fractions | 8 (14%) |
| 63 Gy in 30 fractions | 4 (7%) |
| 60 Gy in 30 fractions | 24 (43%) |

| | |
|---|---|
| 50 Gy in 20 fractions | 3 (5%) |
| | |
| Radiotherapy dose fractionation: definitive | |
| 70 Gy in 35 fractions* | 7 (13%) |
| 65 Gy in 30 fractions | 2 (4%) |
| 55 Gy in 20 fractions | 2 (4%) |
| 66 Gy in 33 fractions** | 1 (2%) |
| 60 Gy in 30 fractions** | 4 (7%) |
| 54 Gy in 30 fractions** | 1 (2%) |
| | |
| Definitive radiotherapy CTV delineation | |
| Whole of involved sinus(es) | 6 (11%) |
| GTV plus margin | 10 (18%) |
| | |
| Nodal irradiation | |
| Yes | 26 (46%) |
| No | 30 (54%) |
| | |
| Radiotherapy technique | |
| IMRT | 15 (27%) |
| VMAT | 41 (73%) |

CTV, clinical target volume; GTV, gross tumour volume; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated radiotherapy

*Includes two patients treated with surgery followed by definitive radiotherapy/chemoradiotherapy for macroscopic residual disease

**Dose fractionation schedules not typically considered ‘definitive’ but used in order to meet OAR constraints in these cases

## Table 3: Patterns of recurrence

| *Type of recurrence (32 patients)* | *Number (% of 56)* |
|---|---|
| Local only | 10 (18%) |
| Local and regional | 6 (11%) |
| Local and distant | 1 (2%) |
| Local, regional and distant | 1 (2%) |
| Regional only | 7 (13%) |
| Regional and distant | 4 (7%) |
| Distant only | 3 (5%) |
| *Sites of metastases* | |
| Nodal | 2 (4%) |
| Lung | 6 (11%) |
| Liver | 2 (4%) |
| Bone | 3 (5%) |
| Brain | 1 (2%) |

## Table 4: Further treatment received following recurrence*

| *Type of treatment* | *Number (% of 56)* |
|---|---|
| Salvage surgery | 2 (4%) |
| Salvage surgery/post-operative radiotherapy | 5 (9%) |
| Definitive radiotherapy | 1 (2%) |
| Palliative chemotherapy | 12 (21%) |
| Palliative radiotherapy | 8 (14%) |
| Best supportive care | 8 (14%) |

*Note, the total number of treatments exceeds the number of recurrences since some patients received multiple further treatments

## Table 5: A summary of clinicopathological and radiotherapy planning information for patients with local treatment failure

| *Subsite* | *Stage* | *Treatment 1* | *Treatment 2* | *PTV coverage by 95% of the prescribed dose (%)* | *PTV compromise* | *Estimated primary recurrence centre contained within 95% isodose* | *Further treatment* | *Outcome* |
|---|---|---|---|---|---|---|---|---|
| Maxillary sinus | pT4a pN0 | Surgery | Adjuvant CRT 66 Gy in 33 fractions | 96.99 | No | No | Surgical excision and adjuvant RT | Died with disease |
| Maxillary sinus | T4b N0 | Induction chemotherapy | Definitive RT 70 Gy in 35 fractions | 98.57 | No | Yes | Definitive RT to relapsed neck disease only for local control | Died with disease |
| Maxillary sinus | T4b N0 | Induction chemotherapy | Definitive CRT 70 Gy in 35 fractions | 93.79 | PTV margin reduced/coverage compromised close to optic chiasm/left optic nerve | Yes | Best supportive care | Died with disease |
| Maxillary sinus | pT4a pN2c | Surgery | Definitive RT 70 Gy in 35 | 99.39 | No | Yes | Best supportive care | Died with disease |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | fractions (for locoregional disease progression) | | | | | |
| Maxillary sinus | pT4a pN0 | Surgery | Adjuvant RT 60 Gy in 30 fractions | 98.18 | No | Yes | Best supportive care | Died with disease |
| Maxillary sinus | pT4a pN0 | Surgery | Adjuvant RT 60 Gy in 30 fractions | 97.7 | PTV coverage compromised close to eye | No | Palliative chemotherapy | Died with disease |
| Maxillary sinus | pT4a pN3 | Surgery | Adjuvant CRT 60 Gy in 30 fractions | 96.9 | No | No | Best supportive care | Died with disease |
| Maxillary sinus | pT4a pN0 | Surgery | Adjuvant RT 60 Gy in 30 fractions | 95.6 | PTV coverage compromised close to optic chiasm/eye | No | Palliative chemotherapy | Died with disease |
| Nasal cavity | T4a N0 | Definitive RT 70 Gy in 35 fractions | | 93.6 | PTV coverage compromised close to eyes | Yes | Palliative chemotherapy | Died with disease |
| Maxillary sinus | T4b N2b | Induction chemotherapy | Definitive RT 66 Gy in 33 fractions | 98 | PTV margin reduced/coverage compromised close to optical structures | Yes | Palliative chemotherapy | Died with disease |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Maxillary sinus | pT4a pN0 | Surgery | Adjuvant CRT 66 Gy in 33 fractions | 98.8 | PTV coverage compromised close to eye/optic nerve | No imaging performed | Best supportive care | Died with disease |
| Nasal cavity | T4b N0 | Induction chemotherapy | Definitive RT 60 Gy in 30 fractions | 95.7 | PTV coverage compromised close to brainstem and optic chiasm/optic nerves | Yes | Surgery, palliative chemotherapy | Died with disease |
| Maxillary sinus | pT4a pN2a | Surgery | Adjuvant CRT 66 Gy in 33 fractions | 97.7 | PTV coverage compromised close to orbit | Yes | Palliative chemotherapy | Alive with disease |
| Maxillary sinus | pT4a pN0 | Surgery | Adjuvant RT 60 Gy in 30 fractions | 98.6 | No | Yes | (Best supportive care) | Died with disease |
| Maxillary sinus | pT4 pN2 | Surgery | Adjuvant CRT 60 Gy in 30 fractions | 98.1 | No | Yes | Best supportive care | Died with disease |
| Nasal cavity | pT4 N0 | Induction chemotherapy, followed by surgery | Adjuvant RT 60 Gy in 30 fractions | 98.6 | No | Yes | Palliative chemotherapy, palliative RT to bone metastases | Died with disease |
| Maxillary sinus | pT4a pN1 | Surgery | Adjuvant CRT 60 Gy in 30 fractions | 98.3 | No | Yes | Best supportive care | Died with disease |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Maxillary sinus | pT4a pN0 | Surgery | Adjuvant RT 60 Gy in 30 fractions | 98 | No | No | Surgery and adjuvant RT with in field recurrence during adjuvant RT<br><br>Palliative chemotherapy, palliative immunotherapy and further surgery | Alive without disease |

CRT, chemoradiotherapy; PTV, planning target volume; RT, radiotherapy

## Table 6: Series that evaluated outcomes for patients with sinonasal malignancies treated by adjuvant/definitive intensity modulated radiotherapy and/or focussed on patients with sinonasal squamous cell carcinoma

| Author | Year | Histology | Number of patients (%SCC) | Treatment | RT technique | % stage IV or T4 | Median follow up | Local/regional control | Overall survival |
|---|---|---|---|---|---|---|---|---|---|
| Ferella [22] | 2020 | Mix | 34 (47) | Definitive RT | IMRT | 100% T4b | 73 months | 5 year 33% | 5 year 43% |
| Frederic-Moreau [23] | 2019 | Mix | 34 (38) | Surgery plus adjuvant RT 100% | IMRT | 50% T4 | 44 months | 3 year 81.6% | 3 year 85% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pare [29] | 2017 | SCC | 68 | Surgery plus adjuvant RT 94%<br><br>Definitive RT 6% | Conventional/3dCRT 54%<br><br>IMRT 31%<br><br>Electrons 15% | 75% T4 | 68 months | 2 year 37% | 5 year 58% |
| Askoxylakis [17] | 2016 | Mix | 122 (21) | Surgery plus adjuvant RT 81%<br><br>Definitive RT 19% | IMRT | 71% T4 | 36 months | 5 year 51% | 5 year 54% |
| Park [30] | 2016 | SCC | 73 | Surgery plus adjuvant RT 29%<br><br>Definitive RT 71% | Conventional RT 48%<br><br>3dCRT 30%<br><br>IMRT 22% | 52% stage IV | 23 months | 5 year 84% adjuvant cohort<br><br>5 year 51% definitive cohort | 5 year 84% adjuvant cohort<br><br>5 year 84% definitive cohort |
| Duru Birgi [5] | 2015 | SCC | 43 | Surgery plus adjuvant RT 58%<br><br>Definitive RT 42% | 3dCRT 84%<br><br>IMRT 9%<br><br>Electrons 7% | 67% stage IV | 32 months | 2 year 81% | 2 year 80% |
| Kim [25] | 2015 | SCC | 30 | Surgery plus adjuvant RT 50%<br><br>Definitive concurrent chemoradiotherapy 50% | Technique not specified | 50% T4 | 53 months adjuvant cohort<br><br>31 months | 5 year 58% adjuvant cohort<br><br>5 year 55% definitive cohort | 5 year 55% adjuvant cohort<br><br>5 year 53% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | definitive cohort | | definitive cohort |
| Michel [27] | 2014 | SCC | 33 | Surgery alone 21%<br><br>Surgery plus adjuvant RT 33%<br><br>Concurrent chemoradiotherapy 39% | Technique not specified | 49% T4a/b | 66 months | | 5 year 40% |
| Guan [24] | 2014 | SCC | 59 | Surgery plus adjuvant RT 39%<br><br>Definitive RT 61% | 73% IMRT<br><br>27% 3dCRT | 64% T4a/b | 28 months | 3 year 63% | 3 year 69% |
| Duprez [20] | 2012 | Mix | 130 (18) | Surgery plus adjuvant RT 78%<br><br>Definitive RT 22% | IMRT | 46% T4a/b | 52 months | 5 year 59% | 5 year 52% |
| Wiegner [31] | 2012 | Mix | 52 (54) | Surgery plus adjuvant RT 90%<br><br>Definitive RT 10% | IMRT | 76% T4a/b | 27 months | 2 year 64% (43% for SCC) | 2 years: 66% (53% for SCC) |
| Madani [26] | 2009 | Mix | 84 (20) | Surgery plus adjuvant RT 89%<br><br>Definitive RT 11% | IMRT | 39% T4a/b | 40 months | 5 year 71% | 5 year 59% |
| Nishimura [28] | 2009 | SCC (maxillary sinus | 40 | Definitive RT/chemoradiotherapy (100%) | Conventional RT | 70% T4a/b | 66 months | | 5 year 59% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Daly [19] | 2007 | Mix | 36 (33%) | Surgery plus adjuvant RT 89%<br><br>Definitive RT 11% | IMRT | 69% T4 | 51 months | 5 year 58% | 5 year 45% |
| Combs [18] | 2006 | Mix | 46 (13%) | RT (adjuvant/definitive not specified) | IMRT | 65% T4 | 16 months | 2 year 81% | 1 year 95% |
| Duthoy [21] | 2005 | Mix | 39 (21%) | Surgery plus adjuvant RT 100% | IMRT | 44% T4 | 31 months | 4 year 68% | 4 years 59% |

3dCRT, 3 dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; RT, radiotherapy; SCC, squamous cell carcinoma