Management of sinonasal and skull base non-mesenchymal chondrosarcoma, a narrative review*

Mark S. Ferguson¹, Valerie J. Lund¹,², David Howard³, Henrik Hellquist⁴, Guy Petruzelli⁵, Carl Snyderman⁶, Primož Strojan⁷, Carlos Suarez⁸, Alessandra Rinaldo⁹, Fernando Lopez¹⁰, Alfo Ferlito¹¹

¹ Professorial Unit, The Royal National Throat, Nose and Ear Hospital, London, UK
² Rhinology Research Unit, University College London, UK
³ Department of ENT and Head and Neck Surgery, Imperial College London, UK
⁴ Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal
⁵ Center for Cranial Base Surgery, Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
⁶ Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia
⁷ Institute of Investigación Sanitaria del Principado de Asturias and CIBERONC, ISCIII, Oviedo, Spain
³ University of Udine School of Medicine, Udine, Italy
¹⁰ Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
¹¹ Coordinator of the International Head and Neck Scientific Group

Abstract

**Background:** Chondrosarcoma (CS) is a rare malignant cartilage forming tumor accounting for 6% of skull base neoplasia. CS mostly commonly occur in isolation but they can develop in non-hereditary skeletal disorders characterized by multiple enchondromas (Ollier disease and Maffucci syndrome), and these conditions are associated with IDH1 and IDH2 mutations. Previous irradiation and previous intravenous thorium dioxide contrast use has been described as a possible cause of these tumours. Other reported associations include malignant conditions such as osteosarcoma, malignant melanoma, fibrosarcoma and leukaemia as well as benign pathologies including fibrous dysplasia and Paget’s disease.

**Methods:** A review of English language literature identified 20 studies to which we added a case series from one institution.

**Results:** Total number of patients included was 734. Main treatment modality was surgery performed in combination with post-operative radiotherapy (64.0%) or surgery alone (30.4%). The majority of patients recorded were either alive and well (68.1%) or alive with disease (16.6%) with 15.3% dead of disease.

**Conclusions:** On present evidence, surgery should form the primary treatment with a goal of complete resection. Inaccessible recurrences or high grade tumors are candidates for proton beam radiotherapy following surgery.

**Key words:** chondrosarcoma, skull base, sinonasal, endoscopic, proton beam

Introduction

Chondrosarcoma (CS) is a rare malignant cartilage forming tumour (1). CS mostly commonly occur in isolation but they can develop in non-hereditary skeletal disorders characterized by multiple enchondromas (Ollier disease and Maffucci syndrome), and these conditions are associated with IDH1 and IDH2 mutations (2-5). Previous irradiation and previous intravenous thorium dioxide contrast use has been described as a possible cause of these tumours. Other reported associations include malignant conditions such as osteosarcoma, malignant melanoma, fibrosarcoma and leukaemia as well as benign pathologies including fibrous dysplasia and Paget’s disease (6, 7).
The differentiation of chordomas from CS can be difficult and relies on clinical, radiological and histological features. The clinical features of chordoma and chordosarcoma are similar; headache and diplopia (abducens nerve palsy) are common in both groups. Multiple cranial nerve palsies are more common in patients with chordosarcoma, reflecting the tendency of chordomas to originate in the clivus whereas chordosarcomas are more likely to originate in the petroclival synchondrosis (junction of clivus and petrous bone) or sinonasal region.

Radiological imaging can help differentiate chordoma and chordosarcoma based on location. Calcifications are more common with chordosarcomas with characteristic ring-forming calcifications with computed tomography (CT). Both tumour types are heterogeneously bright on T2-weighted magnetic resonance imaging (MRI). It is possible that diffusion weighted MRI may make imaging even more reliable in the future.

The morphology of chordoma is highly variable but three features are constantly present but in different proportions. There are strands of tumour cells, formation of alveoli or large lobules of tumour, and thirdly presence of the typical “physaliferous” cells (bubble cells). There are also different variants of chordoma such as chordoid chordoma with its bluish ground substance which can easily be confused with a well-differentiated or low-grade chordosarcoma. Previously, immunohistochemical staining for cytokeratin and epithelial membrane antigen (EMA) were used to differentiate chordosarcoma from chordoma. CS is cytokeratin and EMA negative but chordoid chordoma is cytokeratin and EMA positive (Table 1). Oakley et al., using a microarray approach, reported that podoplanin, (D2-40 antibody), could be a useful positive marker for CS. The accuracy of podoplanin is however less than previously reported, and the staining pattern can be somewhat difficult to interpret. Although further studies have indicated that low grade chordosarcomas are S100 positive in virtually 100% of cases, chordoma is positive in well over 90% of cases. Similarly SOX-9 is positive in both chordosarcomas and chordomas. On the other hand, brachyury (a transcription factor essential for notochordal cell differentiation) appears to be negative in the vast majority of chordosarcoma but positive in most chordomas. Thus, a panel of cytokeratin (pancytokeratin or AE1/AE3), EMA, brachyury and D2-40 is currently the gold standard. Recently detection of a variety of genetic differences have been used to characterise CS more thoroughly, e.g. detection of mutations by direct sequencing of isocitrate dehydrogenases 1 and 2 (IDH1/2).

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Chordoma</th>
<th>Chondrosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>EMA</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>S-100</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>SOX-9</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Brachyury</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Podoplanin (D2-40)</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Table 1. Immunohistochemical comparison chordoma vs chondrosarcoma (EMA, epithelial membrane antigen).

head and neck region accounting for 6% of skull base tumours in total, CS were classified into primary, secondary and mesenchymal by Myers and Thawley in 1979. Mesenchymal CS arise from primitive mesenchymal cells whereas secondary CS arise from pre-existing cartilaginous lesions such as chordoma or exostosis. Mesenchymal CS is considered a distinct clinical entity compared to CS as it has a more aggressive clinical course and as such it is not discussed any further in this review. Primary CS can occur within cartilaginous structures or bones that ossified from cartilage but curiously they can also arise within soft tissue. These lesions are thought to arise from ectopic chondroid precursor cells or from cartilaginous differentiation of primitive mesenchymal cells that have failed to be resorbed during development and this potential origin may help to explain the multifocal nature of the disease. Further attempts have been made to grade CS based on histological appearance.

The World Health Organization (WHO) classification recognizes 3 grades, based upon nuclear size, staining pattern (hyperchromasia), mitotic activity, and degree of cellularity. WHO Grade I is well differentiated and low grade. The cellularity is higher than with enchondroma but with occasional plump nuclei. The classic histological subtype falls into this category and is the most common type seen in the skull base (approximately 90%), and in more elderly patients (60–70 years), WHO Grade II is moderately differentiated with an intermediate grade. There is increased cellularity and distinct nuclei are seen in the majority of cells. WHO Grade III is poorly differentiated and high grade. These are highly malignant lesions histologically characterised by high cellularity, prominent nuclear atypia, and the presence of mitosis. This is seen more in younger patients (20–40 years) and has a higher tendency for recurrence.

In keeping with other sinonasal malignancies, CS often present insidiously with nasal obstruction, epistaxis or facial pain and if there is skull base involvement, various cranial nerves can also be affected. Anatomical sites commonly involved include the ethmoid and the maxillary sinuses, the nasal septum (either superior or inferior to invade anterior skull base or hard palate.
respectively), the petro-clival area and clivus. However, the disease can also be multifocal (2, 7, 23, 29, 30). Low grade CS almost never metastasise but they do have an indolent and progressive course leading eventually to significant morbidity and mortality.

The initial aim of this study was to perform a meta-analysis of the management of CS of the skull base and sinonasal areas. However, it became clear during the literature review that there had been no previous meta-analysis on this topic and only one systematic review was identified (31). This was because there were no large series with standardized treatments and follow up regimes. Thus meaningful statistical analysis has not been possible. Rather we have focussed on an up-to-date narrative review of the management of CS, adding to the cases identified in the literature together with the experience of 2 of the senior authors (VJL & DH).

Materials and methods
Review of the literature
A review of the English language literature using the search string “chondrosarcoma AND (skull base OR sinonasal OR nasal OR nose OR sinus) NOT mesenchymal” was undertaken using the Cochrane review, Embase and Pubmed databases. 555 articles were initially identified, the titles and abstracts were examined with studies excluded if they did not pertain to CS. More than 50 single patient case reports were identified but they were excluded and only studies with greater than 3 patients were included. Finally only studies with survival data that included lesions within the mandible, maxilla, sinonasal region or skull base were included in the final analysis. Studies that also included lesions elsewhere in the head & neck region or included mesenchymal CS were included as long as data on the sinonasal non-mesenchymal cases could be extracted. This left 20 studies that are described in Table 2. One further study has been added to Table 2 that includes the data from two of the senior authors (VJL & DH). The evidence presented in Table 2 is comprised, at best, from pooled analysis of small to medium-sized case series. The data is heterogeneous and the quality of the data, in terms of treatment and outcomes is often poor. There are no randomised controlled trials nor any prospective trials of any nature reported in the literature. Thus meta-analysis was not possible and it is extremely difficult to arrive at any firm conclusions.

Single centre data
All patients treated at The Royal National Throat Nose and Ear Hospital, London, UK for low grade sinonasal CS over a 37 year period, from 1980 to 2017, were included in the study. Data was collected prospectively by the authors (VJL & DH) along with long-term follow up. All cases were examined by an expert pathologist in sinonasal tumours confirming the histological diagnosis. On presentation all patients had a contrast enhanced CT scan of the sinuses and, from 1987 onwards a MRI scan. During the pre-operative period, age, sex, site of presentation, previous treatment and agreed surgical management were recorded. Regular post-operative assessment occurred with complications, recurrence, any subsequent treatment and survival data being noted. Patients were either treated by craniofacial or endoscopic resection of the tumour with curative intent. The disease was resected as necessary according to the extent of the tumour with primary repair of the dura and skull base as needed. Involvement of the orbital periosteum was resected endoscopically but, if the disease extended into the orbit then craniofacial resection (CFR) would be undertaken with orbital clearance. All patients were treated surgically for primary tumour and any recurrence combined with conventional radiotherapy (RT) in a small number of cases.

Results
Table 2 illustrates the 20 published studies to which we have added the prospective data from VJL & DH. These studies have collected data on patients over a 90 year period from 1927 to 2017. The age range is from 20 months old to 88 years old. The total number of patients included is 734 and there were slightly more women than men in the included studies (M:F, 1:1.3). All the studies were retrospective case series and as such constitute level 4 evidence. All the included cases involve the sinonasal, mandible, maxilla or skull base regions. The grades of the CS were noted when reported; there were 314 grade 1, 254 grade 2, and 15 grade 3 lesions. No mesenchymal lesions were included in this work. The mainstay of treatment was surgery performed in combination with post-operative radiotherapy (RT) (64.0%) and the vast majority of these patients (greater than 80%) were treated with adjuvant proton beam therapy (3, 32). Surgery alone accounted for 30.4% of patients. These 2 treatment strategies accounted for almost all the patients (94.4%), however there were a variety of less often used therapies which are illustrated in Table 3. Trying to establish a combined outcome measure or subset survival analysis of these heterogeneous studies has proven impossible, mostly because they have used different outcome reporting measures with various follow up times, and different treatment modalities. Information for example on gross total resection was often lacking. Despite this, the majority of studies (15/18, Lund VJ, 33-36) did include individual patient status and it is certainly possible to conclude that the majority of patients recorded were either alive and well (AEW, 156/229 (68.1%)) or alive with disease (AWD, 38/229 (16.6%)) with only 15.3% (35/229) reported as dead of disease. The range of follow-up for this data was 3 months to 39 years but it is not possible to determine any standardized survival metrics.

Those few studies with long term follow-up (4, 23, 34, 37, 41, 42, 47) show

Ferguson et al.
Table 2. Included studies of management of chondrosarcoma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Years cases recruited</th>
<th>Age; Sex (M:F)</th>
<th>Study type; subsite</th>
<th>No. of cases; Grade</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund &amp; Howard</td>
<td>1980-2017</td>
<td>5-76yrs; 23:20</td>
<td>Retrospective study; sinonasal (43)</td>
<td>43; not stated</td>
<td>CFR + RT (3), CFR (34), ES (6)</td>
<td>CFR, DSS 94% at 5yrs, 56% at 10yrs, 37% at 15yrs; ES AEW (follow range 1-8.3yrs)</td>
</tr>
<tr>
<td>Carlson et al</td>
<td>1995-2015</td>
<td>12.6-74yrs; 22:25</td>
<td>Retrospective study; petroclival (47)</td>
<td>47; Grade 1 (27), Grade 2 (19)</td>
<td>Sx (15), Sx + RT (30), RT (1), biopsy only (1)</td>
<td>AWD (9), AEW (38), follow up 0.9-23yrs</td>
</tr>
<tr>
<td>Kiratli et al</td>
<td>Not stated</td>
<td>43-75yrs; 1:2</td>
<td>Retrospective study; maxillary sinus (1), sphenoid (1), ethmoid (1)</td>
<td>3; Grade 1 (2), Grade 3 (1)</td>
<td>Sx + RT (2), Sx (1)</td>
<td>AEW (3, range 2-4yrs)</td>
</tr>
<tr>
<td>Vaz-Guimaraes et al</td>
<td>2004 -2013</td>
<td>19-87yrs; 14:21</td>
<td>Retrospective study; skull base (35)</td>
<td>35; Grade 1 (18), Grade 2 (13); Management</td>
<td>Sx + RT (17)</td>
<td>AEW (17, range 0.25-10.2yrs), AWD (8, range 1.7-5.8yrs), DOD (6, 0.2-4.8yrs), lost to follow up (4)</td>
</tr>
<tr>
<td>Feuvret et al</td>
<td>1996-2013</td>
<td>12-83yrs; 72:87</td>
<td>Retrospective study; skullbase (145), sphenoid (8), ethmoid (6)</td>
<td>159; Grade 1 (77), Grade 2 (82)</td>
<td>Sx + RT (146), biopsy only then RT (13)</td>
<td>OS 5yr 94.9%, 10yr 87%</td>
</tr>
<tr>
<td>Sbaihat et al</td>
<td>1990-2012</td>
<td>31-60yrs; 5:8</td>
<td>Retrospective study; skull base (13)</td>
<td>13; Grade 1 (8), Grade 2 (4), Grade 3 (1)</td>
<td>Sx (6), Sx + RT (7)</td>
<td>AEW (11, range 7months - 6.1yrs), AWD (2, 3.1yrs &amp; 7.2 yrs)</td>
</tr>
<tr>
<td>Lustig et al</td>
<td>1977-2007</td>
<td>6-67yrs; 4:8</td>
<td>Retrospective study; skull base (9), ethmoid (1), maxillary sinus (2)</td>
<td>12; Grade 1 (4), Grade 2 (6), Grade 3 (2)</td>
<td>CFR + RT (5), CFR (7),</td>
<td>AEW (9/12, range 5-33yrs), AWD (1, 8yrs), DOD (1), lost to follow up (1)</td>
</tr>
<tr>
<td>Obeso et al</td>
<td>1977-2006</td>
<td>30-88yrs; 3:3</td>
<td>Retrospective study; sinonasal (6)</td>
<td>6; Grade I (4), Grade II (2)</td>
<td>CFR (1), Paralateronasal rhinotomy (3); Subtemporal-reauricular (1), ES (1)</td>
<td>AEW (4), AWD (1), DOAD (1) (follow 8-198 months)</td>
</tr>
<tr>
<td>Cho et al</td>
<td>1991-2005</td>
<td>23-54yrs; 9:2</td>
<td>Retrospective study; skull base (11)</td>
<td>11; not stated</td>
<td>CFR + RT (4), CFR (5), CFR + gamma knife (2)</td>
<td>All AEW, OS at 3yrs &amp; 5yrs 100%, DFS at 3yrs &amp; 5yrs 88.9% &amp; 80%</td>
</tr>
<tr>
<td>Wanebo et al</td>
<td>1983-2003</td>
<td>2-73yrs; 9:14</td>
<td>Retrospective study; skull base (23)</td>
<td>23; not stated</td>
<td>Sx (13), Sx + RT (10)</td>
<td>DOD (5), AEW (4), AWD (13), no follow (1); absolute 5yr survival 93%, 10yr survival 71%</td>
</tr>
<tr>
<td>Lee et al</td>
<td>1990-2002</td>
<td>26-56yrs; 3:1</td>
<td>Retrospective study; ethmoid (2), maxillary sinus (1), skull base (1)</td>
<td>4; Grade 1 (1), Grade 2 (2), Grade 3 (1)</td>
<td>CFR + RT (2), CFR (2)</td>
<td>AEW (range 2.5 -14.25yrs)</td>
</tr>
<tr>
<td>Prado et al</td>
<td>1953-2002</td>
<td>11-70yrs; 9:7</td>
<td>Retrospective study; maxilla (7), ethmoid (1), mandible (4), infratemporal region (1), parieto-occipital region (1), nasal cavity (2)</td>
<td>16; not stated</td>
<td>Sx (6), Sx + RT (3), Sx + CRT (1), CRT (1), no treatment (2), RT (2), C (1)</td>
<td>DOD (8, range 3months - 39yrs), no follow up (2), AEW (5, range 3-12yrs), DOAC (1, 6yrs)</td>
</tr>
<tr>
<td>Gadwal et al</td>
<td>1970-1997</td>
<td>3-18yrs; 8:6</td>
<td>Retrospective study; maxillary sinus (4), mandible (3), nasal cavity (2), nasopharynx (1), orbit (1), skull base (1)</td>
<td>14; Grade 1 (9), Grade 2 (1), Grade 3 (4)</td>
<td>Sx (7), Sx+RT (7)</td>
<td>AEW (11), AWD (1), no follow data (3)</td>
</tr>
<tr>
<td>Rosenberg et al</td>
<td>1978-1997</td>
<td>10-79yrs; 87:113</td>
<td>Retrospective study; skull base (188), sphenoid/ethmoid (12)</td>
<td>200; Grade 1 (101), Grade 2 (99)</td>
<td>Sx + RT (200)</td>
<td>Follow up 2.1months - 18.5yrs, 5yr &amp; 10yr local control rate 99% &amp; 98%; OS 5yr &amp; 10yr 99%</td>
</tr>
<tr>
<td>Study</td>
<td>Years cases recruited</td>
<td>Age; Sex (M:F)</td>
<td>Study type; subsite</td>
<td>No. of cases; Grade</td>
<td>Management</td>
<td>Outcome</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------</td>
<td>---------------</td>
<td>-------------------------------------------------------------</td>
<td>---------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Saito et al</td>
<td>1927-1992</td>
<td>1.5-88yrs; 27:29</td>
<td>Retrospective study; maxilla/maxillary sinus (25), nasal septum/ ethmoid/sphenoid (23), mandible (6), nasal tip (2)</td>
<td>56; Grade 1 (43), Grade 2 (13)</td>
<td>Sx (46), CRT (2), RT (1), biopsy only (2), unknown treatment (5)</td>
<td>LR (14), uncontrolled LR (9); Survival 5yrs 80.7%, 10yrs 65.3%, 15yrs 56%</td>
</tr>
<tr>
<td>Burkey et al</td>
<td>1965-1990</td>
<td>1.5-78yrs; 7:1</td>
<td>Retrospective study; ethmoids (2), frontal (1), maxillary (1), nasal cavity (1), nasal septum (2), mandible (1),</td>
<td>8; Grade 1 (4), Grade 2 (1), Grade 3 (3)</td>
<td>CFR + RT (2), CFR + C (1), CFR (4), C (1)</td>
<td>Follow up 4 month - 10yrs, no follow up (1), AEW (1), DOD (4)</td>
</tr>
<tr>
<td>Mark et al</td>
<td>1955-1988</td>
<td>Not stated</td>
<td>Retrospective study; head &amp; neck region</td>
<td>18; not stated</td>
<td>Sx (10), Sx + RT (5), RT (1), Sx + C (2)</td>
<td>Follow up 3months-14yrs, OS 5yrs 68% (11/16), DFS 56% (9/16) at 5yrs</td>
</tr>
<tr>
<td>Ruark et al</td>
<td>1950-1985</td>
<td>10-72yrs; 15:13</td>
<td>Retrospective study; maxilla (11), cervical vertebra (7), mandible (3), skull (2), sphenoid/ethmoids (2), frontal (1), nasal septum (1), orbit (1)</td>
<td>28; not stated</td>
<td>Sx (15), Sx + RT (13)</td>
<td>Follow up 5-35yrs, AEW (12/28) at 5yrs or better; LR most common cause of death</td>
</tr>
<tr>
<td>Finn et al</td>
<td>1949-1982</td>
<td>10-71yrs; 4:11</td>
<td>Retrospective study; maxilla (2), mandible (2), oral cavity (2), skull base (2), nasal septum (1), nasal cavity (2), nasopharynx (2), sphenoid / ethmoid (2)</td>
<td>15; Grade 1 (6), Grade 2 (7), Grade 3 (2)</td>
<td>Sx (12), C (2), biopsy only (1)</td>
<td>AEW (8/15), AWD (3/15), DOD (4/15); follow up 4months - 29yrs</td>
</tr>
<tr>
<td>Coates et al</td>
<td>1952-1977</td>
<td>Not stated; 6:7</td>
<td>Retrospective study</td>
<td>13; not stated</td>
<td>Local excision (7), CFR (6)</td>
<td>Local excision LR (5), CFR AEW (4) DOD (2)</td>
</tr>
<tr>
<td>Fu et al</td>
<td>Not stated</td>
<td>20months-69yrs; 6:4</td>
<td>Retrospective study; involving nasal cavity/paranasal sinuses/nasopharynx</td>
<td>10; Grade 1 (6), Grade 2 (3), Grade 3 (1)</td>
<td>Sx (9), biopsy only (1)</td>
<td>AEW (6), follow up 2yrs, 3yrs, 3yrs, 6yrs, 11yrs, 13yrs; DOD (4), 0.5yr, 1yr, 1.5yrs, 4yrs</td>
</tr>
</tbody>
</table>

Key: Sx + RT = surgery then radiotherapy; CRT = chemoradiotherapy; RT = radiotherapy alone; CFR = craniofacial resection; AEW = alive and well; AWD = alive with disease; LR = local recurrence; DOD = dead of disease; CFR + RT = craniofacial resection then radiotherapy; CFR + C = craniofacial resection then chemotherapy; C = chemotherapy alone; OS = overall survival; DFS = disease free survival; DOAC = dead of another cause; ES = endoscopic surgery.

That the majority of cases develop recurrence either close to the site of origin or elsewhere in the anatomical area which can occur many years later. These have been treated surgically, in some cases multiple times but with increasing inaccessibility particularly in the middle cranial fossa, which may ultimately result in the patient’s death. Thus whilst 5 year survival rate of 94% was found after craniofacial resection in a cohort of 24 patients, at 15 years this has fallen to 37%.<ref>48</ref>

**Discussion**

**Treatment strategies**

Although the literature is entirely comprised of retrospective case series, it is clear that surgery has been the primary treatment in almost all cases. Formal craniofacial resection provided the gold standard approach from the 1980’s onwards; however, more recently ES has been employed where applicable. Extensive disease extending beyond the dura, or laterally into the orbits is less amenable to an ES approach, but in those cases where the principles of oncologic resection can be preserved, ES is an acceptable approach for the resection of sinonasal CS. Unfortunately there are no studies directly comparing different surgical strategies in CS. An unresolved question is whether complete surgical resection or maximum safe resection should be the aim when several authors have reported excellent local control (LC) and overall survival (OS) rates with only partial resection followed by post-operative proton beam therapy.<ref>5, 32, 49</ref>

**Surgery**

The vast majority of included studies used surgery as the primary form of treatment with 63.3% opting to use some
Radiotherapy however, significantly improves local control when it accompanies surgery. The evidence, although not high quality, appears to favour post-operative proton beam treatment over conventional photon-based irradiation. Due to physical characteristics of photon beam therapy, it seems to be less toxic though not more efficient. Concerning local tumour control, a systematic review of the literature published up to 2007 by Lodge et al concluded that there is no difference between proton beam therapy, conventional therapy or ion therapy studies.

Conventional RT, however, has been found by various investigators to be effective as an adjunct therapy. Sahgal et al reported on 18 patients treated with surgery initially (biopsy or partial resection) followed by intensity modulated RT (IMRT) at 70 Gy (2Gy/fraction). They reported a 5-yr OS of 87.8% and LC rates of 88.1%. Interestingly, they reported that the predictors for LC were gross total surgical resection and age. Potluri et al reported that surgical resection is essential but that adjunct high dose photon therapy can keep small volume disease under control. Gwak et al reported that stereotactic radiation technique using the Cyberknife system with hypofractionated doses was an effective treatment in these tumours. Gamma knife radiosurgery has also been reported as a useful adjunct strategy after surgery. Martin et al reported actuarial LC for chondrosarcomas at 5 years was 80 ± 10.1% after post-operative gamma knife radiosurgery. In addition, Kano et al reported on 46 patients treated for CS, 36 of which had prior surgical treatment. The actuarial OS after stereotactic radiosurgery was 89% at 3 years, 86% at 5 years, and 76% at 10 years.

Proton beam radiotherapy has several advantages over conventional photon beam radiotherapy, chief amongst which is the ability to limit damage to normal tissues surrounding the target lesion better. Sparing of normal tissue allows delivery of higher doses that increase chances for effective eradication of vital tumour cells. This is of crucial importance when treating residual disease located in close proximity to vital structures at the skull base. The evidence, although not high quality, appears to favour post-operative proton beam treatment over conventional photon-based irradiation. Due to physical characteristics of photon beam therapy, it seems to be less toxic though not more efficient. Concerning local tumour control, a systematic review of the literature published up to 2007 by Lodge et al concluded that there is no difference between proton beam therapy, conventional therapy or ion therapy studies.

Table 3. Treatment of patients.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery then radiotherapy</td>
<td>470 (64.0%)</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>223 (30.4%)</td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>18 (2.5%)</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Unknown treatment</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Surgery then chemotherapy</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>No treatment</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Surgery then chemoradiotherapy</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>734</strong></td>
</tr>
</tbody>
</table>
ment, post-operative proton treatment offered high rates of LC with low toxicity. The authors described OS rates of 94.9% and 87% at 5 and 10 years, respectively. Similarly Rosenberg et al reported LC rates at 5 and 10 years of 99% and 98%, respectively, and OS of 99% at 5 and 10 years when treating 200 CS with surgery then proton beam therapy; similar results have been reported by others. Encouragingly, Srivastava et al report that proton beam therapy does not have a significant impact on health-related quality of life parameters.

Several authors have reported that carbon ions are also a safe and effective treatment for CS. In addition to spatial superiority in distribution of radiation dose when compared to conventional photon techniques, the carbon ions also have a higher biological impact in irradiated tissues then either protons or photons. Uhl et al reported that carbon ion therapy in 79 patients with CS resulted in 3-yr, 5-yr, and 10-yr LC rates of 95.9%, 88%, and 88% respectively with OS rates of 97.5%, 97.5%, and 91.5%, respectively. However, since 67 of the 79 pts had some form of surgical treatment first (12 had biopsies), this approach would still be considered adjunct therapy. Meanwhile, Nikoghosyan et al initiated a phase III trial comparing carbon ions with proton beam radiotherapy in skull base CS (Clinical-Trials.gov identifier: NCT01182753), so this paradigm may be challenged in the future. While many of the authors report that treatment with proton beam or carbon ions radiotherapy is safe there remains a lack of long term follow up studies in the literature and so there is still the possibility that such treatments may have deleterious effects on surrounding neurovascular structures over time.

Outcomes
Jones et al performed a study using data from the USA Surveillance Epidemiology and End Results database (SEER) between 1973 and 2009. They identified 226 patients with skull base CS and 92.5% of the patients had surgery and the 10-yr OS was 68.2%. Survival was improved in the surgery group compared to no surgery (69.3% vs. 53.9%). Furthermore prognostic indicators of survival with univariate analysis were surgery, female sex, being younger at presentation, and being diagnosed at a later time in the study period. Subgroup analysis revealed that smaller tumour size and younger age predicted an improved survival. Carlson et al have also demonstrated that higher tumour stage, larger categorical size (<4cm versus ≥4cm), lack of adjuvant radiation, and longer duration of follow-up were associated with greater risk of recurrence. Several other authors have also separately reported that gross tumour volume and age were negative prognostic indicators.

Around 90% of all lesions are altogether WHO Grades I and II. The predominance of the low-grade types within the skull base gives this condition its overall good prognosis. Grade III tumours are rare in the skull base and are associated with a worse prognosis.

Bloch et al performed a systematic review to study the relationship between proposed prognostic factors and survival in 560 chondrosarcomas of the skull base. A total of 364 patients had grade I, 80 patients had grade II, and 8 patients had grade III chondrosarcoma. Not surprising, mortality rate increased with grade: grade I (5%), grade II (10%) and grade III group (25%) (p < 0.012). In addition, Evans et al reported 5-year survival rates of grade I, II, and III chondrosarcomas to be 90%, 81%, and 43%, respectively. In the present review, the series with the highest number of cases (200 and 159) only had patients with grade I and II chondrosarcomas, reaching 10-year survival rates of 99% and 87%, respectively.

There is no consensus on how to treat recurrent disease. Some authors choose to treat with proton beam treatment whereas others have opted for surgery. The majority of included studies used a combination of approaches and certainly further work is needed to clarify the situation. It is likely that surgery if feasible would offer the best chance of cure and the form that this surgery took would be dictated by the extent and location of the disease, whilst proton beam treatment is useful for disease that is inaccessible or in high risk anatomical areas such as the optic chiasm. Indeed CS is one of only a few sinonasal tumours that can affect both optic nerves and/or chiasm leading to blindness. Judgement of operability is subjective, however, and depends greatly on the experience of the surgical team.

Although there is a lack of high level evidence available for the treatment of this condition, we have suggested a treatment protocol based partly on the authors’ experience and partly on the European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base which is illustrated in Figure 1. This algorithm advocates lifelong follow-up as recurrence in CS can occur in distinct separate, previously uninvolved, anatomical areas of the skull base many years after initial treatment.

Future treatments
Huang et al have suggested a mechanism for chemoresistance of CS which they report is due in part to overexpression of miR-23b. This has been shown in vitro to increase cisplatin resistance in CS. Thus restoration of src kinase activity might be a therapeutic target in the future. Studies of the molecular pathogenesis of CS have led to interesting preliminary discoveries on the alterations in several signalling pathways. The Src, Hedgehog, PI3k-Akt-mTOR, and angiogenic signalling have been hypothesised to contribute to CS tumorigenesis.
Summary
There is limited level 4 evidence available in the literature for the treatment of non-mesenchymal CS which indicates that surgery (open or ES) should form the primary treatment. Low and intermediate grade tumours may be managed with observation or surgery for recurrence. Inaccessible recurrences or high-grade tumours are candidates for proton beam radiotherapy following surgery.

Acknowledgements
We have no competing interests nor did we receive any financial help.

Authorship contribution
Mark S. Ferguson and Prof Valerie Lund were the principle investigators and they take responsibility for the integrity of the content of the manuscript. Profs Lund & Howard contributed their patient series to this manuscript. The manuscript was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com). All other co-authors reviewed and edited the manuscript.

Conflict of interest
There are no conflict of interests.


Management of sinonasal chondrosarcoma


