

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

Mark S. Ferguson¹, Valerie J. Lund^{1,2}, David Howard³, Henrik Hellquist⁴, Guy Petruzzelli⁵, Carl Snyderman⁶, Primož Strojjan⁷, Carlos Suarez⁸, Alessandra Rinaldo⁹, Fernando Lopez¹⁰, Alfio Ferlito¹¹

Rhinology Online, Vol 1: 94 - 103, 2018

<http://doi.org/10.4193/RHINOL/18.025>

***Received for publication:**

May 27, 2018

Accepted: August 22, 2018

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 Curtis & Elizabeth Anderson Cancer Institute, Memorial University Medical Center Savannah GA, USA

⁶ Center for Cranial Base Surgery, Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

⁷ Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia

⁸ Instituto de Investigación Sanitaria del Principado de Asturias and CIBERONC, ISCIII, Oviedo, Spain Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, Oviedo, Spain

⁹ University of Udine School of Medicine, Udine, Italy

¹⁰ Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, Instituto de Investigación Sanitaria del Principado de Asturias and CIBERONC, ISCIII, 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 often presents insidiously, it almost never metastasizes but it has an indolent progressive course leading to significant morbidity and mortality due to invasion of the clivus and central skull base. This study performed a review of the management of CS.

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 muta-

tions⁽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^(8,9). The clinical features of chordoma and chondrosarcoma are similar; headache and diplopia (abducens nerve palsy) are common in both groups^(10,11). Multiple cranial nerve palsies are more common in patients with chondrosarcoma, reflecting the tendency of chordomas to originate in the clivus whereas chondrosarcomas 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 chondrosarcoma based on location. Calcifications are more common with chondrosarcomas with characteristic ring-forming calcifications with computed tomography (CT)⁽¹²⁾. 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⁽¹³⁻¹⁵⁾.

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 chondroid chordoma with its bluish ground substance which can easily be confused with a well-differentiated or low-grade chondrosarcoma. Previously, immunohistochemical staining for cytokeratin and epithelial membrane antigen (EMA) were used to differentiate chondrosarcoma from chordoma. CS is cytokeratin and EMA negative but chondroid chordoma is cytokeratin and EMA positive⁽¹⁶⁾ (Table 1). Oakley et al.⁽¹⁷⁾, 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 chondrosarcomas are S100 positive in virtually 100% of cases, chordoma is positive in well over 90% of cases. Similarly SOX-9 is positive in both chondrosarcomas and chordomas. On the other hand, brachyury (a transcription factor essential for notochordal cell differentiation) appears to be negative in the vast majority of chondrosarcoma but positive in most chordomas^(17,18). 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)^(19,20).

CS account for 10-20% of all malignant bone tumours most commonly arising in the long bones and pelvis^(2,21,22). In about 3% to 10% of cases it has been reported that CS has arisen in the

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

Antigen	Chordoma	Chondrosarcoma
Cytokeratin	Positive	Negative
EMA	Positive	Negative
S-100	Positive	Positive
SOX-9	Positive	Positive
Brachyury	Positive	Negative
Podoplanin (D2-40)	Negative	Positive

head and neck region^(2,12,23) accounting for 6% of skull base tumours in total⁽²⁴⁾. CS were classified into primary, secondary and mesenchymal by Myers and Thawley in 1979⁽²⁵⁾. Mesenchymal CS arise from primitive mesenchymal cells whereas secondary CS arise from pre-existing cartilaginous lesions such as chondroma or exostosis. Mesenchymal CS is considered a distinct clinical entity compared to CS as it has a more aggressive clinical course⁽²⁶⁾ 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^(12,22) 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⁽⁵⁾.

The World Health Organization (WHO) classification recognizes 3 grades, based upon nuclear size, staining pattern (hyperchromasia), mitotic activity, and degree of cellularity⁽²⁷⁾. 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 nucleoli 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⁽²⁸⁾.

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 diag-

nosis. 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^(5, 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,^(4, 29, 33-46)) 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

Table 2. Included studies of management of chondrosarcoma.

Study	Years cases recruited	Age; Sex (M:F)	Study type; subsite	No. of cases; Grade	Management	Outcome
Lund & Howard	1980-2017	5-76yrs; 23:20	Retrospective study; sinonasal (43)	43; not stated	CFR + RT (3), CFR (34), ES (6)	CRF, DSS 94% at 5yrs, 56% at 10yrs, 37% at 15yrs; ES AEW (follow range 1-8.3yrs)
Carlson et al ⁽³⁴⁾	1995-2015	12.6-74yrs; 22:25	Retrospective study; petroclival (47)	47; Grade 1 (27), Grade 2 (19)	Sx (15), Sx + RT (30), RT (1), biopsy only (1)	AWD (9), AEW (38), follow up 0.9-23.5yrs
Kiratli et al ⁽³⁹⁾	Not stated	43-75yrs; 1:2	Retrospective study; maxillary sinus (1), sphenoid (1), ethmoid (1)	3; Grade 1 (2), Grade 3 (1)	Sx + RT (2), Sx (1)	AEW (3, range 2-4yrs)
Vaz-Guimaraes et al ⁽⁴⁶⁾	2004 -2013	19-87yrs; 14:21	Retrospective study; skull base (35)	35; Grade 1 (18), Grade 2 (13);	Sx (18), Sx + RT (17)	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)
Feuvret et al ⁽³²⁾	1996-2013	12-83yrs; 72:87	Retrospective study; skullbase (145), sphenoid (8), ethmoid (6)	159; Grade 1 (77), Grade 2 (82)	Sx + RT (146), biopsy only then RT (13)	OS 5yr 94.9%, 10yr 87%
Sbaihat et al ⁽⁴³⁾	1990-2012	31-60yrs; 5:8	Retrospective study; skull base (13)	13; Grade 1 (8), Grade 2 (4), Grade 3 (1)	Sx (6), Sx + RT (7)	AEW (11, range 7months - 6.1yrs), AWD (2, 3.1yrs & 7.2 yrs)
Lustig et al ⁽⁴⁾	1977-2007	6-67yrs; 4:8	Retrospective study; skull base (9), ethmoid (1), maxillary sinus (2)	12; Grade 1 (4), Grade 2 (6), Grade 3 (2)	CFR + RT (5), CFR (7),	AEW (9/12, range 5-33yrs), AWD (1, 8yrs), DOD (1), lost to follow up (1)
Obeso et al ⁽⁴⁵⁾	1977-2006	30-88yrs; 3:3	Retrospective study; sinonasal (6)	6; Grade I (4) Grade II (2)	CFR (1), Paralaterronasal rhinotomy (3); Subtemporal-reauricular (1), ES (1)	AEW (4), AWD (1), DOD (1) (follow 8-198 months)
Cho et al ⁽³⁵⁾	1991-2005	23-54yrs; 9:2	Retrospective study; skull base (11)	11; not stated	CFR + RT (4), CFR (5), CFR + gamma knife (2)	All AEW, OS at 3yrs & 5yrs 100%, DFS at 3yrs & 5yrs 88.9% & 80%
Wanebo et al ⁽⁴⁴⁾	1983-2003	2-73yrs; 9:14	Retrospective study; skull base (23)	23; not stated	Sx (13), Sx + RT (10)	DOD (5), AEW (4), AWD (13), no follow (1); absolute 5yr survival 93%, 10yr survival 71%
Lee et al ⁽⁴⁰⁾	1990-2002	26-56yrs; 3:1	Retrospective study; ethmoid (2), maxillary sinus (1), skull base (1)	4; Grade 1 (1), Grade 2 (2), Grade 3 (1)	CFR + RT (2), CFR (2)	AEW (range 2.5 - 14.25yrs)
Prado et al ⁽⁴¹⁾	1953-2002	11-70yrs; 9:7	Retrospective study; maxilla (7), ethmoid (1), mandible (4), infratemporal region (1), parieto-occipital region (1), nasal cavity (2)	16; not stated	Sx (6), Sx + RT (3), Sx + CRT (1), CRT (1), no treatment (2), RT (2), C (1)	DOD (8, range 3months - 39yrs), no follow up (2), AEW (5, range 3-12yrs), DOAC (1, 6yrs)
Gadwal et al ⁽²⁹⁾	1970-1997	3-18yrs; 8:6	Retrospective study; maxillary sinus (4), mandible (3), nasal cavity (2), nasopharynx (1), orbit (1), skull base (1)	14; Grade 1 (9), Grade 2 (1), Grade 3 (4)	Sx (7), Sx+RT (7)	AEW (11), AWD (1), no follow data (3)
Rosenberg et al ⁽⁵⁾	1978-1997	10-79yrs; 87:113	Retrospective study; skull base (188), sphenoid/ethmoid (12)	200; Grade 1 (101), Grade 2 (99)	Sx + RT (200)	Follow up 2.1 months - 18.5yrs, 5yr & 10yr local control rate 99% & 98%; OS 5yr & 10yr 99%

Study	Years cases recruited	Age; Sex (M:F)	Study type; subsite	No. of cases; Grade	Management	Outcome
Saito et al ⁽²³⁾	1927-1992	1.5-88yrs; 27:29	Retrospective study; maxilla/maxillary sinus (25), nasal septum/ethmoid/sphenoid (23), mandible (6), nasal tip (2)	56; Grade 1 (43), Grade 2 (13)	Sx (46), CRT (2), RT (1), biopsy only (2), unknown treatment (5)	LR (14), uncontrolled LR (9); Survival 5yrs 80.7%, 10yrs 65.3%, 15yrs 56%
Burkey et al ⁽³³⁾	1965-1990	1.5-78yrs; 7:1	Retrospective study; ethmoids (2), frontal (1), maxillary (1), nasal cavity (1), nasal septum (2), mandible (1),	8; Grade 1 (4), Grade 2 (1), Grade 3 (3)	CFR + RT (2), CFR + C (1), CFR (4), C (1)	Follow up 4 month - 10yrs, no follow up (1), AEW (3), DOD (4)
Mark et al ⁽⁴⁷⁾	1955-1988	Not stated	Retrospective study; head & neck region	18; not stated	Sx (10), Sx + RT (5), RT (1), Sx + C (2)	Follow up 3months-14yrs, OS 5yrs 68% (11/16), DFS 56% (9/16) at 5yrs
Ruark et al ⁽⁴²⁾	1950-1985	10-72yrs; 15:13	Retrospective study; maxilla (11), cervical vertebra (7), mandible (3), skull (2), sphenoid/ethmoids (2), frontal (1), nasal septum (1), orbit (1)	28; not stated	Sx (15), Sx + RT (13)	Follow up 5-35yrs, AEW (12/28) at 5yrs or better; LR most common cause of death
Finn et al ⁽³⁷⁾	1949-1982	10-71yrs; 4:11	Retrospective study; maxilla (2), mandible (2), oral cavity (2), skull base (2), nasal septum (1), nasal cavity (2), nasopharynx (2), sphenoid / ethmoid (2)	15; Grade 1 (6), Grade 2 (7), Grade 3 (2)	Sx (12), C (2), biopsy only (1)	AEW (8/15), AWD (3/15), DOD (4/15); follow up 4months - 29yrs
Coates et al ⁽³⁶⁾	1952-1977	Not stated; 6:7	Retrospective study	13; not stated	Local excision (7), CFR (6)	Local excision LR (5), CFR AEW (4) DOD (2)
Fu et al ⁽³⁸⁾	Not stated	20months-69yrs; 6:4	Retrospective study; involving nasal cavity/paranasal sinuses/nasopharynx	10; Grade 1 (6), Grade 2 (3), Grade 3 (1)	Sx (9), biopsy only (1)	AEW (6), follow up 2yrs, 3yrs, 3yrs, 6yrs, 11yrs, 13yrs; DOD (4), 0.5yr, 1yr, 1.5yrs, 4yrs

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% ⁽⁴⁸⁾.

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; how-

ever, 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 ^(5, 32, 49).

Surgery

The vast majority of included studies used surgery as the primary form of treatment with 63.3% opting to use some

Table 3. Treatment of patients.

Treatment Type	Number of patients
Surgery then radiotherapy	470 (64.0%)
Surgery alone	223 (30.4%)
Radiotherapy alone	18 (2.5%)
Biopsy only	5 (0.7%)
Unknown treatment	5 (0.7%)
Chemotherapy alone	4 (0.5%)
Chemoradiotherapy	3 (0.4%)
Surgery then chemotherapy	3 (0.4%)
No treatment	2 (0.3%)
Surgery then chemoradiotherapy	1 (0.1%)
Total	734

form of post-operative RT. No studies directly compared open surgery to ES indeed a wide range of surgical approaches were employed from lateral rhinotomy to midfacial degloving and traditional craniofacial resections as well as both endoscopic and combined open & endoscopic strategies. The more recent studies have employed ES as this approach became more feasible. There is growing evidence that in selected cases ES is a good approach for the clearance of CS^(50,51) and that it has been found to be both safe and effective⁽⁵²⁾. There have been several studies reporting in a small number of patients that ES is an acceptable approach for clearance of CS⁽⁵³⁻⁵⁷⁾. Moussazadeh et al⁽⁵⁸⁾ reported on 8 patients treated with ES. They achieved greater than 95% resection of the tumours in 5 out of 8 of their patients with only one cerebrospinal fluid leak as a complication and partial improvement in existing cranial neuropathies. However, there was no long-term data on survival in this study. Folbe et al⁽⁵⁹⁾ argue that ES has become the standard of care for many clival lesions although other techniques maybe necessary if the lesions are very extensive or extend laterally. Messerer et al⁽⁶⁰⁾ reported that the ES approach allows excellent access to midline clival lesions and can be combined with an open approach to achieve excellent tumour clearance.

Chemotherapy and radiotherapy

Chemotherapy does not play any role in the treatment of CS at present. Conventional cytotoxic chemotherapy regimens have been employed in both the adjuvant and neoadjuvant settings. These include sarcoma derived therapies such as high dose methotrexate and combination doxorubicin and cisplatin chemotherapy. However as our understanding of the biology of these tumours increases there may be evolving roles for target therapies (see Future Treatments below).

Radiotherapy however, significantly improves local control

when it accompanies surgery⁽⁶¹⁾. 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⁽⁶²⁾.

Conventional RT, however, has been found by various investigators to be effective as an adjunct therapy. Sahgal et al⁽⁶³⁾ 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⁽⁴⁹⁾ reported that surgical resection is essential but that adjunct high dose photon therapy can keep small volume disease under control. Gwak et al⁽⁶⁴⁾ 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⁽⁶⁵⁾. Martin et al⁽⁶⁶⁾ reported actuarial LC for chondrosarcomas at 5 years was 80 ± 10.1% after post-operative gamma knife radiosurgery. In addition, Kano et al⁽⁶⁷⁾ 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⁽⁶⁸⁾. Demizu et al⁽⁶⁹⁾ treated 72 patients with sarcomas of the skull base (the majority) or spine of which 20 were CS; the 5-year OS, progression-free survival, and LC rates were 75.3%, 49.6%, and 71.1%, respectively. They concluded that proton beam treatment was a safe and effective treatment. Weber et al⁽⁷⁰⁾ reported the largest single institution series of patients treated with only proton beam radiotherapy (77 patients). They reported the actuarial 8 year LC and OS were 89.7% and 93.5%, respectively, with high-grade radiation-induced toxicity observed in 6 patients. Similar to other studies they reported that protons were both safe and effective. Feuvret et al⁽³²⁾ reported on 159 patients treated initially with surgery and then either protons alone or combination of protons and photons. They concluded that although maximal safe surgery forms the mainstay of treat-

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⁽⁵⁾ 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⁽⁷¹⁾. Encouragingly, Srivastava et al⁽⁷²⁾ 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^(73,74). 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 than either protons or photons. Uhl et al⁽⁷⁴⁾ 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⁽⁷⁵⁾ initiated a phase III trial comparing carbon ions with proton beam radiotherapy in skull base CS (ClinicalTrials.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⁽⁷⁶⁾ 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⁽³⁴⁾ 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^(70,71).

Around 90% of all lesions are altogether WHO Grades I and II⁽⁷⁷⁾. 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⁽⁷⁸⁾.

Bloch et al⁽⁷⁹⁾ 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⁽⁸⁰⁾ 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^(5,32).

There is no consensus on how to treat recurrent disease. Some authors choose to treat with proton beam treatment^(5,32) whereas others have opted for surgery^(48,55). 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⁽⁶¹⁾ 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^(48,55).

Future treatments

Huang et al⁽⁸²⁾ 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. Polychro-

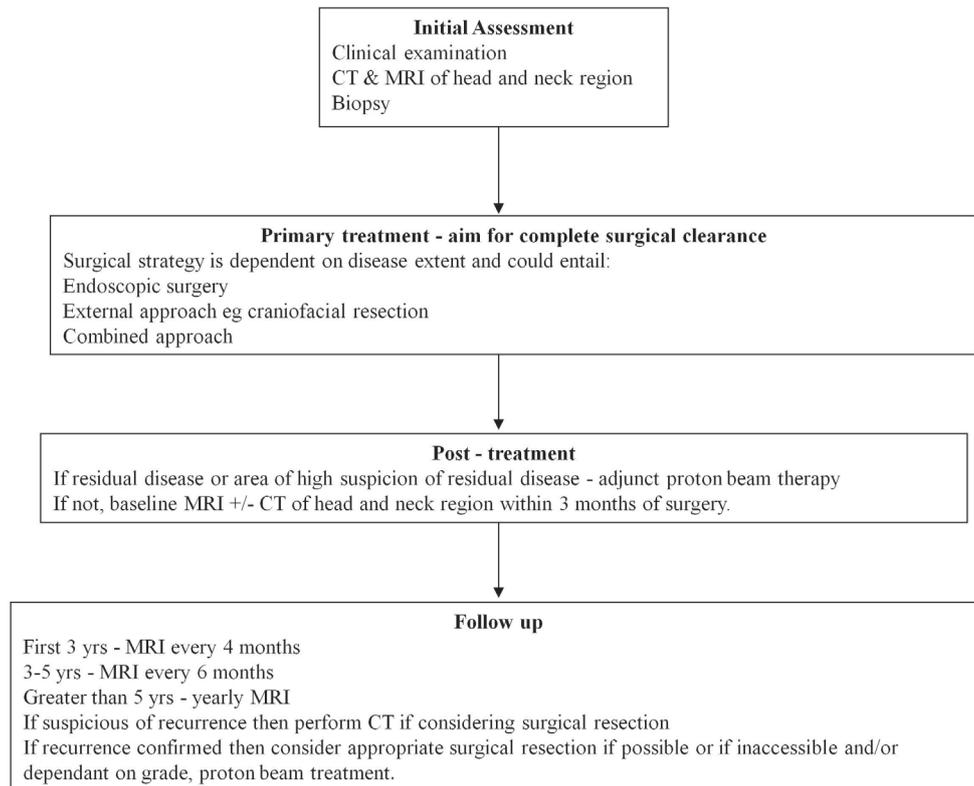


Figure 1. Proposed management algorithm for non-mesenchymal chondrosarcoma of the sinonasal and skull base region (modified from Lund et al. ⁽⁶¹⁾).

nidou et al ⁽⁶³⁾ have written an excellent review of other future therapeutic targets for the treatment of CS, chief amongst them IDH inhibitors.

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.

1. Pheemister DB. Chondrosarcoma of bone. *Surg, Gynec & Obst.* 1930;50:216-233.
2. Downey TJ, Clark SK, Moore DW. Chondrosarcoma of the nasal septum. *Otolaryngol Head Neck Surg.* 2001 Jul;125(1):98-100.
3. Hyde GE, Yarrington CT, Jr., Chu FW. Head and neck manifestations of Maffucci's syndrome: chondrosarcoma of the nasal septum. *Am J Otolaryngol.* 1995 Jul-Aug;16(4):272-5.
4. Lustig LR, Sciubba J, Holliday MJ. Chondrosarcomas of the skull base and temporal bone. *J Laryngol Otol.* 2007 Aug;121(8):725-35.
5. Rosenberg AE, Nielsen GP, Keel SB, Renard LG, Fitzek MM, Munzenrider JE, et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. *Am J Surg Pathol.* 1999 Nov;23(11):1370-8.
6. Barton RP. Metachranous chondrosarcoma and malignant melanoma of the nose. *J Laryngol Otol.* 1985 May;99(5):497-500.
7. Chen CC, Hsu L, Hecht JL, Janecka I. Bimaxillary chondrosarcoma: clinical, radiologic, and histologic correlation. *AJNR Am J Neuroradiol.* 2002 Apr;23(4):667-70.
8. Heffelfinger MJ, Dahlin DC, MacCarty CS, Beabout JW. Chordomas and cartilaginous

- tumors at the skull base. *Cancer*. 1973 Aug;32(2):410-20.
9. Pamir MN, Ozduman K. Analysis of radiological features relative to histopathology in 42 skull-base chordomas and chondrosarcomas. *Eur J Radiol*. 2006 Jun;58(3):461-70.
 10. Korten AG, ter Berg HJ, Spincemaille GH, van der Laan RT, Van de Wel AM. Intracranial chondrosarcoma: review of the literature and report of 15 cases. *J Neurol Neurosurg Psychiatry*. 1998 Jul;65(1):88-92.
 11. Volpe NJ, Liebsch NJ, Munzenrider JE, Lessell S. Neuro-ophthalmologic findings in chordoma and chondrosarcoma of the skull base. *Am J Ophthalmol*. 1993 Jan;115(1):97-104.
 12. Rassekh CH, Nuss DW, Kapadia SB, Curtin HD, Weissman JL, Janecka IP. Chondrosarcoma of the nasal septum: skull base imaging and clinicopathologic correlation. *Otolaryngol Head Neck Surg*. 1996 Jul;115(1):29-37.
 13. Freeze BS, Glastonbury CM. Differentiation of skull base chordomas from chondrosarcomas by diffusion-weighted MRI. *AJNR Am J Neuroradiol*. 2013 Oct;34(10):E113.
 14. Muller U, Kubik-Huch RA, Ares C, Hug EB, Low R, Valavanis A, et al. Is there a role for conventional MRI and MR diffusion-weighted imaging for distinction of skull base chordoma and chondrosarcoma? *Acta Radiol*. 2016 Feb;57(2):225-32.
 15. Yeom KW, Lober RM, Mobley BC, Harsh G, Vogel H, Allagio R, et al. Diffusion-weighted MRI: distinction of skull base chordoma from chondrosarcoma. *AJNR Am J Neuroradiol*. 2013 May;34(5):1056-61, S1.
 16. Ishida T, Dorfman HD. Chondroid chordoma versus low-grade chondrosarcoma of the base of the skull: can immunohistochemistry resolve the controversy? *J Neurooncol*. 1994;18(3):199-206.
 17. Oakley GJ, Fuhrer K, Seethala RR. Brachyury, SOX-9, and podoplanin, new markers in the skull base chordoma vs chondrosarcoma differential: a tissue microarray-based comparative analysis. *Mod Pathol*. 2008 Dec;21(12):1461-9.
 18. Sangoi AR, Dulai MS, Beck AH, Brat DJ, Vogel H. Distinguishing chordoid meningiomas from their histologic mimics: an immunohistochemical evaluation. *Am J Surg Pathol*. 2009 May;33(5):669-81.
 19. Kanamori H, Kitamura Y, Kimura T, Yoshida K, Sasaki H. Genetic characterization of skull base chondrosarcomas. *J Neurosurg*. 2015 Oct;123(4):1036-41.
 20. Kitamura Y, Sasaki H, Yoshida K. Genetic aberrations and molecular biology of skull base chordoma and chondrosarcoma. *Brain Tumor Pathol*. 2017 Apr;34(2):78-90.
 21. Coppit GL, Eusterman VD, Bartels J, Downey TJ. Endoscopic resection of chondrosarcomas of the nasal septum: a report of 2 cases. *Otolaryngol Head Neck Surg*. 2002 Dec;127(6):569-71.
 22. Koch BB, Karnell LH, Hoffman HT, Apostolakis LW, Robinson RA, Zhen W, et al. National cancer database report on chondrosarcoma of the head and neck. *Head Neck*. 2000 Jul;22(4):408-25.
 23. Saito K, Unni KK, Wollan PC, Lund BA. Chondrosarcoma of the jaw and facial bones. *Cancer*. 1995 Nov 01;76(9):1550-8.
 24. Berkmen YM, Blatt ES. Cranial and intracranial cartilaginous tumours. *Clin Radiol*. 1968 Jul;19(3):327-33.
 25. Myers EM, Thawley SE. Maxillary chondrosarcoma. *Arch Otolaryngol*. 1979 Mar;105(3):116-8.
 26. Xu J, Li D, Xie L, Tang S, Guo W. Mesenchymal chondrosarcoma of bone and soft tissue: a systematic review of 107 patients in the past 20 years. *PLoS One*. 2015;10(4):e0122216.
 27. Fletcher CD, Unni KK, Mertens F, editors. *Cartilage tumours 2002*.
 28. Awad M, Gogos AJ, Kaye AH. Skull base chondrosarcoma. *J Clin Neurosci*. 2016 Feb;24:1-5.
 29. Gadwal SR, Fanburg-Smith JC, Gannon FH, Thompson LD. Primary chondrosarcoma of the head and neck in pediatric patients: a clinicopathologic study of 14 cases with a review of the literature. *Cancer*. 2000 May 01;88(9):2181-8.
 30. Koka V, Vericel R, Lartigau E, Lusinchi A, Schwaab G. Sarcomas of nasal cavity and paranasal sinuses: chondrosarcoma, osteosarcoma and fibrosarcoma. *J Laryngol Otol*. 1994 Nov;108(11):947-53.
 31. Khan MN, Husain Q, Kanumuri VV, Boghani Z, Patel CR, Liu JK, et al. Management of sinonasal chondrosarcoma: a systematic review of 161 patients. *Int Forum Allergy Rhinol*. 2013 Aug;3(8):670-7.
 32. Feuvret L, Bracci S, Calugaru V, Bolle S, Mammar H, De Marzi L, et al. Efficacy and Safety of Adjuvant Proton Therapy Combined With Surgery for Chondrosarcoma of the Skull Base: A Retrospective, Population-Based Study. *Int J Radiat Oncol Biol Phys*. 2016 May 01;95(1):312-21.
 33. Burkey BB, Hoffman HT, Baker SR, Thornton AF, McClatchey KD. Chondrosarcoma of the head and neck. *Laryngoscope*. 1990 Dec;100(12):1301-5.
 34. Carlson ML, O'Connell BP, Breen JT, Wick CC, Driscoll CL, Haynes DS, et al. Petroclival Chondrosarcoma: A Multicenter Review of 55 Cases and New Staging System. *Otol Neurotol*. 2016 Aug;37(7):940-50.
 35. Cho YH, Kim JH, Khang SK, Lee JK, Kim CJ. Chordomas and chondrosarcomas of the skull base: comparative analysis of clinical results in 30 patients. *Neurosurg Rev*. 2008 Jan;31(1):35-43; discussion
 36. Coates HL, Pearson BW, Devine KD, Unni KK. Chondrosarcoma of the nasal cavity, paranasal sinuses, and nasopharynx. *Trans Sect Otolaryngol Am Acad Ophthalmol Otolaryngol*. 1977 Sep-Oct;84(5):ORL919-26.
 37. Finn DG, Goepfert H, Batsakis JG. Chondrosarcoma of the head and neck. *Laryngoscope*. 1984 Dec;94(12 Pt 1):1539-44.
 38. Fu YS, Perzin KH. Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. 3. Cartilaginous tumors (chondroma, chondrosarcoma). *Cancer*. 1974 Aug;34(2):453-63.
 39. Kiratli H, Dikmetas O, Tarlan B, Onerci M. Orbital chondrosarcoma arising from paranasal sinuses. *Int Ophthalmol*. 2013 Aug;33(4):403-7.
 40. Lee SY, Lim YC, Song MH, Seok JY, Lee WS, Choi EC. Chondrosarcoma of the head and neck. *Yonsei Med J*. 2005 Apr 30;46(2):228-32.
 41. Prado FO, Nishimoto IN, Perez DE, Kowalski LP, Lopes MA. Head and neck chondrosarcoma: analysis of 16 cases. *Br J Oral Maxillofac Surg*. 2009 Oct;47(7):555-7.
 42. Ruark DS, Schlehaider UK, Shah JP. Chondrosarcomas of the head and neck. *World J Surg*. 1992 Sep-Oct;16(5):1010-5; discussion 5-6.
 43. Sbaihat A, Bacciu A, Pasanisi E, Sanna M. Skull base chondrosarcomas: surgical treatment and results. *Ann Otol Rhinol Laryngol*. 2013 Dec;122(12):763-70.
 44. Wanebo JE, Bristol RE, Porter RR, Coons SW, Spetzler RF. Management of cranial base chondrosarcomas. *Neurosurgery*. 2006 Feb;58(2):249-55; discussion -55.
 45. Obeso S, Llorente JL, Diaz-Molina JP, Sanchez-Fernandez R, Rodrigo JP, Suarez C. [Surgical treatment of head and neck chondrosarcomas]. *Acta Otorrinolaringol Esp*. 2010 Jul-Aug;61(4):262-71.
 46. Vaz-Guimaraes F, Fernandez-Miranda JC, Koutourousiou M, Hamilton RL, Wang EW, Snyderman CH, et al. Endoscopic Endonasal Surgery for Cranial Base Chondrosarcomas. *Oper Neurosurg (Hagerstown)*. 2017 Aug 1;13(4):421-34.
 47. Mark RJ, Tran LM, Sercarz J, Fu YS, Calcaterra TC, Parker RG. Chondrosarcoma of the head and neck. The UCLA experience, 1955-1988. *Am J Clin Oncol*. 1993 Jun;16(3):232-7.
 48. Howard DJ, Lund VJ, Wei WL. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses: a 25-year experience. *Head Neck*. 2006 Oct;28(10):867-73.
 49. Potluri S, Jefferies SJ, Jena R, Harris F, Burton KE, Prevost AT, et al. Residual postoperative tumour volume predicts outcome after high-dose radiotherapy for chordoma and chondrosarcoma of the skull base and spine. *Clin Oncol (R Coll Radiol)*. 2011 Apr;23(3):199-208.
 50. Beer-Furlan A, Balsalobre L, Vellutini EA, Stamm AC. Endoscopic Endonasal Approach in Skull Base Chondrosarcoma Associated with Maffucci Syndrome: Case Series and Literature Review. *World Neurosurg*. 2016 Jan;85:365 e7-15.
 51. Ditzel Filho LF, Prevedello DM, Dolci RL, Jamshidi AO, Kerr EE, Campbell R, et al. The Endoscopic Endonasal Approach for Removal of Petroclival Chondrosarcomas. *Neurosurg Clin N Am*. 2015 Jul;26(3):453-62.

52. Mesquita Filho PM, Ditzel Filho LF, Prevedello DM, Martinez CA, Fiore ME, Dolci RL, et al. Endoscopic endonasal surgical management of chondrosarcomas with cerebellopontine angle extension. *Neurosurg Focus*. 2014;37(4):E13.
53. Frank G, Sciarretta V, Calbucci F, Farneti G, Mazzatenta D, Pasquini E. The endoscopic transnasal transsphenoidal approach for the treatment of cranial base chordomas and chondrosarcomas. *Neurosurgery*. 2006 Jul;59(1 Suppl 1):ONS50-7; discussion ONS-7.
54. Kuge A, Sato S, Sakurada K, Takemura S, Kikuchi Z, Saito Y, et al. Technical notes on endoscopic transnasal transsphenoidal approach for clival chondrosarcoma. *Sarcoma*. 2011;2011:953047.
55. Lund VJ, Wei WJ. Endoscopic surgery for malignant sinonasal tumours: an eighteen year experience. *Rhinology*. 2015 Sep;53(3):204-11.
56. Nicolai P, Battaglia P, Bignami M, Bolzoni Villaret A, Delu G, Khrais T, et al. Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: a 10-year experience. *Am J Rhinol*. 2008 May-Jun;22(3):308-16.
57. Zhang Q, Kong F, Yan B, Ni Z, Liu H. Endoscopic endonasal surgery for clival chordoma and chondrosarcoma. *ORL J Otorhinolaryngol Relat Spec*. 2008;70(2):124-9.
58. Moussazadeh N, Kulwin C, Anand VK, Ting JY, Gamss C, Iorgulescu JB, et al. Endoscopic endonasal resection of skull base chondrosarcomas: technique and early results. *J Neurosurg*. 2015 Apr;122(4):735-42.
59. Folbe AJ, Svider PF, Liu JK, Eloy JA. Endoscopic Resection of Clival Malignancies. *Otolaryngol Clin North Am*. 2017 Apr;50(2):315-29.
60. Messerer M, Cossu G, Pasche P, Ikonomidis C, Simon C, Pralong E, et al. Extended endoscopic endonasal approach to clival and paraclival tumors: Indications and limits. *Neurochirurgie*. 2016 Jun;62(3):136-45.
61. Bloch OG, Jian BJ, Yang I, Han SJ, Aranda D, Ahn BJ, et al. Cranial chondrosarcoma and recurrence. *Skull Base*. 2010 May;20(3):149-56.
62. Lodge M, Pijls-Johannesma M, Stirk L, Munro AJ, De Ruyscher D, Jefferson T. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. *Radiother Oncol*. 2007 May;83(2):110-22.
63. Sahgal A, Chan MW, Atenafu EG, Masson-Cote L, Bahl G, Yu E, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. *Neuro Oncol*. 2015 Jun;17(6):889-94.
64. Gwak HS, Yoo HJ, Youn SM, Chang U, Lee DH, Yoo SY, et al. Hypofractionated stereotactic radiation therapy for skull base and upper cervical chordoma and chondrosarcoma: preliminary results. *Stereotact Funct Neurosurg*. 2005;83(5-6):233-43.
65. Hasegawa T, Ishii D, Kida Y, Yoshimoto M, Koike J, Iizuka H. Gamma Knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg*. 2007 Oct;107(4):752-7.
66. Martin JJ, Niranjana A, Kondziolka D, Flickinger JC, Lozanne KA, Lunsford LD. Radiosurgery for chordomas and chondrosarcomas of the skull base. *J Neurosurg*. 2007 Oct;107(4):758-64.
67. Kano H, Sheehan J, Sneed PK, McBride HL, Young B, Duma C, et al. Skull base chondrosarcoma radiosurgery: report of the North American Gamma Knife Consortium. *J Neurosurg*. 2015 Nov;123(5):1268-75.
68. Noel G, Gondi V. Proton therapy for tumors of the base of the skull. *Chin Clin Oncol*. 2016 Aug;5(4):51.
69. Demizu Y, Mizumoto M, Onoe T, Nakamura N, Kikuchi Y, Shibata T, et al. Proton beam therapy for bone sarcomas of the skull base and spine: A retrospective nationwide multicenter study in Japan. *Cancer Sci*. 2017 May;108(5):972-7.
70. Weber DC, Badiyan S, Malyapa R, Albertini F, Bolsi A, Lomax AJ, et al. Long-term outcomes and prognostic factors of skull-base chondrosarcoma patients treated with pencil-beam scanning proton therapy at the Paul Scherrer Institute. *Neuro Oncol*. 2016 Feb;18(2):236-43.
71. Noel G, Habrand JL, Jauffret E, de Crevoisier R, Dederke S, Mammari H, et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. *Strahlenther Onkol*. 2003 Apr;179(4):241-8.
72. Srivastava A, Vischioni B, Fiore MR, Vitolo V, Fossati P, Iannalfi A, et al. Quality of life in patients with chordomas/chondrosarcomas during treatment with proton beam therapy. *J Radiat Res*. 2013 Jul;54 Suppl 1:i43-8.
73. Schulz-Ertner D, Nikoghosyan A, Thilmann C, Haberer T, Jakel O, Karger C, et al. Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas of the skull base. Results in 67 patients. *Strahlenther Onkol*. 2003 Sep;179(9):598-605.
74. Uhl M, Mattke M, Welzel T, Oelmann J, Habl G, Jensen AD, et al. High control rate in patients with chondrosarcoma of the skull base after carbon ion therapy: first report of long-term results. *Cancer*. 2014 May 15;120(10):1579-85.
75. Nikoghosyan AV, Rauch G, Munter MW, Jensen AD, Combs SE, Kieser M, et al. Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study. *BMC Cancer*. 2010 Nov 05;10:606.
76. Jones PS, Aghi MK, Muzikansky A, Shih HA, Barker FG, 2nd, Curry WT, Jr. Outcomes and patterns of care in adult skull base chondrosarcomas from the SEER database. *J Clin Neurosci*. 2014 Sep;21(9):1497-502.
77. Weber AL, Brown EW, Hug EB, Liebsch NJ. Cartilaginous tumors and chordomas of the cranial base. *Otolaryngol Clin North Am*. 1995 Jun;28(3):453-71.
78. Gay E, Sekhar LN, Rubinstein E, Wright DC, Sen C, Janecka IP, et al. Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients. *Neurosurgery*. 1995 May;36(5):887-96; discussion 96-7.
79. Bloch OG, Jian BJ, Yang I, Han SJ, Aranda D, Ahn BJ, et al. A systematic review of intracranial chondrosarcoma and survival. *J Clin Neurosci*. 2009 Dec;16(12):1547-51.
80. Evans HL, Ayala AG, Romsdahl MM. Prognostic factors in chondrosarcoma of bone: a clinicopathologic analysis with emphasis on histologic grading. *Cancer*. 1977 Aug;40(2):818-31.
81. Lund VJ, Stammberger H, Nicolai P, Castelnuovo P, Beal T, Beham A, et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. *Rhinol Suppl*. 2010 Jun 01;22:1-143.
82. Huang K, Chen J, Yang MS, Tang YJ, Pan F. Inhibition of Src by microRNA-23b increases the cisplatin sensitivity of chondrosarcoma cells. *Cancer Biomark*. 2017;18(3):231-9.
83. Polychronidou G, Karavasilis V, Pollack SM, Huang PH, Lee A, Jones RL. Novel therapeutic approaches in chondrosarcoma. *Future Oncol*. 2017 Mar;13(7):637-48.

Professor Valerie J. Lund
Professorial Unit
The Royal National Throat, Nose and Ear Hospital
330 Gray's Inn Rd
Kings Cross
London WC1X 8DA
United Kingdom

Tel: +44 (0)20 3456 7890
E-mail: v.lund@ucl.ac.uk