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Review

Head and neck sarcomas in adulthood: current trends and evolving management concepts

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Abstract

Sarcomas are rare, malignant bone and soft-tissue tumours of mesenchymal origin, and their overall incidence accounts for 1% and 0.2%, respectively, of all malignancies. The aim of this article is to provide a reference on the evolving management concepts and trends of treatment of adult sarcomas of the head and neck in a major head and neck sarcoma centre. Early diagnosis remains a challenge due to non-specific symptomatology. Imaging such as ultrasound (US), magnetic resonance (MRI), computed tomography (CT), and positron emission tomography (PET) CT assist with diagnosis and staging, and biopsy is essential for diagnosis, tumour differentiation, and grading. Staging is dependent on histological grade, size of tumour, and metastasis. Sarcomas spread via the haematogenous route. Adequate clearance of locoregional disease and prevention of distant micrometastases are key to improved disease-free survival outcomes so multimodal treatment at a sarcoma reference centre is imperative. In the head and neck, the treatment for most bone sarcomas is neoadjuvant chemotherapy followed by compartmental resection. The interim tumour response to neoadjuvant chemotherapy is evaluated by PET CT and MRI. Heavy-particle therapy (proton beam) in combination with surgery is increasingly being used to treat otherwise unresectable disease, particularly in children. For soft tissue sarcomas of the head and neck, treatment is complex and depends on grade. Surgery is the principle mode of treatment in low-grade tumours that are amenable to resection. High-grade tumours can be treated with neoadjuvant chemotherapy followed by surgery and radiotherapy. In such cases, the response to the chemotherapy might be used as a guide of potential biological aggressiveness, and has an impact on the planning of the operation and the type and extent of radiotherapy. As a general rule, radiotherapy is reserved for high-grade, advanced soft-tissue sarcomas of the head and neck. Those of bone are radioresistant, and radiotherapy is only administered for palliative purposes when no surgical option exists, an exception being Ewing sarcoma. The role of proton beam therapy is promising, but to our knowledge no long-term data currently exist. The survival advantage of innate immune-modulation remains uncertain for disease in the head and neck.

Keywords: Osteosarcoma; Head & neck; Sarcomas; Surgery; Chemotherapy; Radiation; PET CT

Introduction

Sarcomas are rare, heterogeneous, malignant tumours.[1] In adults, about 10% of all sarcomas affect the head and neck,[2] but in children 21% of all malignancies are sarcomas,[3] of which 7%-10% affect the soft tissues.[4] Unlike carcinomas, which are epithelium-derived, sarcomas are of mesenchymal origin, and are broadly classified as bone sarcomas (BS) and soft-tissue sarcomas (STS). BS are more prevalent in the lower extremities (34%), while those in the soft tissue affect the upper and lower extremities equally (25%).[5] In the UK, those of the head and neck account for about 10% of the annual incidence of new cases. The incidence for new STS is 30/10^6 (about 190 tumours) and for BS is 8/10^6 (about 38 tumours)/annum.[6]

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Table 1
Head and neck soft tissue sarcoma in adulthood (2007-2019) at the London Sarcoma Service.

Distribution of soft tissue sarcomas	No. of patients (n = 124)
Histopathological classification (Fig. 1):	
Rhadomyosarcoma	24 (19)
Pleomorphic sarcoma	18 (15)
Malignant peripheral nerve sheath tumour (MPNST)	15 (12)
Leiomyosarcoma	13 (11)
Spindle cell sarcoma	14 (11)
Liposarcoma	13 (11)
Angiosarcoma	8 (7)
Synovial sarcoma	3 (3)
Dermatofibrosarcoma	4 (3)
Alveolar soft part sarcoma (ASPS)	2 (2)
Myxofibrosarcoma	5 (4)
Myofibrosarcoma	5 (4)
Anatomical:	
Other (extragnathic)	109 (88)
Maxilla	11 (9)
Mandible	4 (3)
Sex:	
Female	63 (51)
Male	61 (49)
Age:	
Adult	105 (85)
Adolescent	19 (15)

Bimodal variation and incidence based on age distribution are not typical to head and neck sarcomas.[7] Instead, a gradual increase with age from 0.3/million in the 0-4 years age group to 1.9/million in those aged 80-84 years is observed in cases of BS.[6] Head and neck bone sarcomas (HNBS) have a higher predilection for the mandible (54%) than the maxilla (34%). Extragnathic presentations account for 11%, and most HNBS are high grade (91%) with earlier reports varying between 56% and 79%.[7–9] In contrast, 87% of head and neck soft-tissue sarcomas (HNSTS) are extragnathic with 8% presenting in the maxilla and 5% in the mandible. A large proportion are high grade (76%).[7]

There is considerable histopathological variation in HNSTS. At the London Sarcoma Service, 245 patients with HNS had surgical treatment between 2007 and 2019. The commonest subtypes of STS were rhabdomyosarcoma (19%), pleomorphic sarcoma (15%), malignant peripheral nerve sheath tumour (12%), leiomyosarcoma (11%), and spindle cell sarcoma (11%) (Fig. 1 and Table 1). The commonest types of HNBS were osteosarcoma (75%), chondrosarcoma (18%), and Ewing sarcoma (7%) (Fig. 2 and Table 2).[7] Variations in multimodal treatment reflect the heterogeneity and diversity of HNS, and overall survival can range from 27% - 84%, based on the management strategy employed.[10–13]

In the UK, care for patients with HNS is centralised to 15 sarcoma multidisciplinary teams (MDT) in contrast to 49 head and neck MDTs. The role of amalgamated surgical, histopathological, oncological, and radiological expert

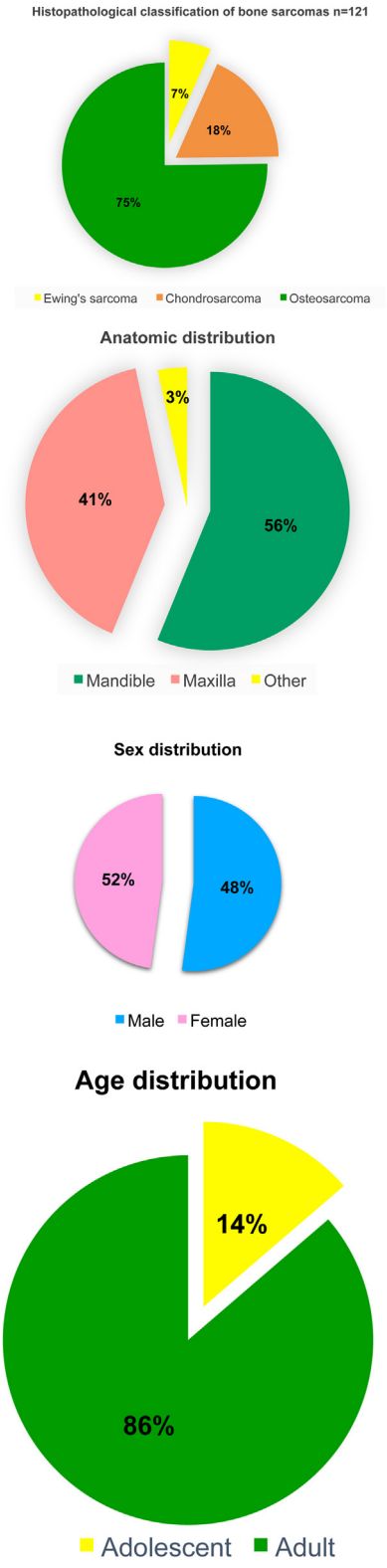

Fig. 1. Histological types of soft tissue sarcomas of the head and neck at the London Sarcoma Service between 2007 and 2019 (Table 1).

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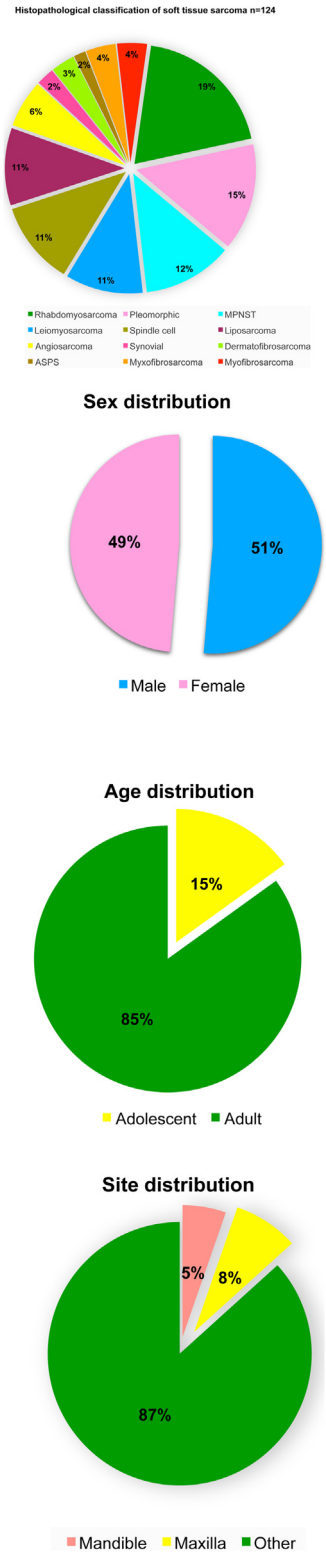

Fig. 2. Histological types of bone sarcomas of the head and neck at the London Sarcoma Service between 2007 and 2019: osteosarcoma (n = 91), chondrosarcoma (n = 22), Ewing sarcoma (n = 8).

Table 2
Head and neck bone sarcomas in adulthood (2007-2019) at the London Sarcoma Service.

Distribution of bone sarcomas	No. (%) of patients (n = 121)
Anatomical:	
Mandible	67 (55)
Maxilla	50 (41)
Other craniofacial skeleton	4 (3)
Sex:	
Female	63 (52)
Male	58 (48)
Age:	
Adult	104 (86)
Adolescent	17 (14)

Table 3
Developmental pathways hijacked by osteosarcoma.

Runx2 (transcription factor for osteoblast differentiation)
Wnt/β-Catenin (osteoblast proliferation)
Fibroblast growth factor (FGF)
Matrix metalloproteinase (MMP) proteins
Insulin-like growth factor (IGF) signalling axis
Bone morphogenetic protein (BMP) signalling
Osterix (Osx) transcription of osteocalcin, osteopontin, and bone sialoprotein
TWIST (regulator of the osteoblast lineage)
Hippo/YAP pathway in osteoblast differentiation
ERBB4 signalling in osteoblast differentiation

knowledge in the improvement of survival outcomes is of paramount importance because of the rarity of the disease. Management should therefore be led by specialised sarcoma MDTs. The website sarcoma.org.uk has a comprehensive up-to-date list of sarcoma centres and clinicians in the UK with their contact details.

Pathogenesis and predisposing factors

Genetic predisposition, acquired gene mutations, previous exposure to radiation or chemotherapy, chemical carcinogens, and viral infections, are all implicated in the pathogenesis of HNS. The hijacking of developmental signalling pathways by BS has a role in the pathogenesis (Table 3).[14]

Clinical presentation and diagnostic principles

Early diagnosis remains a challenge because of insidious clinical presentation. Symptoms such as an enlarging mass with or without the presence of pain, loose teeth, cranial nerve dysfunction, unilateral sinusitis, nodular vascular lesions, ecchymotic diffuse lesions, epistaxis, unilateral nasal mass, hoarseness or a change in voice, or dysphagia or odynophagia, should raise suspicion of a sarcoma and trigger an urgent referral. Bone pain at night should always be considered a red flag.[15–17] Despite the presence of non-specific symptoms, distant metastasis at presentation is seen in 25% of cases of HNBS,[18] and in 10% of HNSTS.[19]

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Diagnostic imaging such as ultrasound (US), magnetic resonance (MRI), computed tomography (CT), and positron emission tomography (PET) CT are employed in the head and neck instead of plain radiographs. US and MRI are used for STS while MRI and CT are used for BS.[15,16] Biopsy is essential for tumour differentiation and grading. Percutaneous core biopsies are recommended for suspected STS and open biopsies for suspected BS or when core biopsies are inconclusive. Fine-needle aspiration is not recommended for primary diagnosis because of poor tissue yield.[16] Excisional biopsies must be avoided at all costs to prevent contamination of the field, which would jeopardise treatment and outcomes.

Staging

Staging is dependent on histological grade, size of tumour, and presence or absence of metastases. The two commonly used staging systems are Enneking and TNM.

Enneking surgical musculoskeletal staging

This system stages sarcoma into three stages (I,II, and III) that are predominantly based on grade and metastasis.[20] It does not include Ewing sarcoma and undifferentiated round cell sarcoma.

AJCC TNM 8th edition[21]

HNBS is based on primary tumour (T), regional lymph node status (N), presence or absence of distant metastases (M), and histological grade (G). Staging (I-IV) is primarily based on histological grade followed by primary tumour. The TNM classifications for BS and STS of the head and neck vary in the definition of primary tumour (T), and the prognostic staging for STS is not defined. Certain STS such as embryonal, alveolar rhabdomyosarcoma, cutaneous angiosarcoma, Kaposi sarcoma, and dermatofibrosarcoma protuberans (DFSP), are excluded.

Grading

Grading (1-3) is based on three important criteria: tumour differentiation (1-3), tumour necrosis (0-2), and mitotic index (1-3). Currently two systems are in use, the French Federation of Cancer Centres Sarcoma Group (FNCLCC) and the National Cancer Institute (NCI). The FNCLCC is the most accurate prognosticator of tumour mortality, development of metastases, and consideration for adjuvant therapy.[22,23]

Rationale of treatment

Prevention of early distant micrometastases and locoregional clearance are key to improved disease-free survival (DFS), and these goals can be realised with multimodal treatment. Neoadjuvant chemotherapy has indeed revolutionised the management of sarcomas of the extremities, as it not only reduces the risk of distant metastases, but also allows surgical procedures to evolve into "limb-sparing" techniques.[24] No randomised studies have confirmed a similar impact in the head and neck for obvious reasons, but the extrapolation of this model has lowered the risk of early lung metastases and led to the development of surgical concepts that aim to improve functional outcomes.

A classic paradigm, locoregional treatment of HNBS, is based on the mode of histological spread. Most cases arise from the mesenchyme and spread primarily within trabecular bone before causing cortical erosion and associated periosteal apposition. In contrast, squamous cell carcinomas (SCC) are epithelial soft-tissue malignancies that opportunistically invade the facial bones by virtue of their proximity. SCC of the head and neck presents with relatively early involvement of the regional lymph nodes, whereas HNBS manifests as large local disease with a low potential of metastasis to the lymph nodes and the early presence of distant metastases. This biological behaviour has led to the development of the "in-out" model of local spread for HNBS and has clear repercussions for surgical management.[7]

The lack of anatomical boundaries within the facial bones in cases of advancing HNBS obviates the need for a "compartmental" excision by use of the affected bone as the epicentre of the resection. This requires "large" bony margins that either surround the boundaries of the compartment, or are delineated by the presence of a natural barrier, and encompass the surrounding soft tissue spatial "compartment". These margins are necessary, as they address the main focus of the potential insidious spread of the sarcoma, and at the same time warrant clearance of the resection in "difficult" areas, such as the mandibular condyle which, in cases that affect the angle or ramus, is invariably affected by malignant cells, even in the absence of clear radiological evidence (Fig. 3).[7]

Treatment strategy for bone sarcomas of the head and neck

Neoadjuvant chemotherapy is administered to prevent the spread of microsatellite tumour deposits, to shrink the tumour, and control symptoms. Systemic therapy includes high-dose methotrexate (M), doxorubicin (Adriamycin^{TM} Pfizer), ifosfamide, and cisplatin (P). The most common induction therapy regimen in the UK is MAP for a period of 10 weeks.[25] In patients over 40 years of age, dual therapy with AP is recommended. Adjuvant chemotherapy is administered postoperatively if interruption occurs in the neoadjuvant setting, and chemotherapy is part of the standard treatment for Ewing sarcoma, undifferentiated pleomorphic sarcoma, and spindle cell sarcoma. In cases of chondrosarcoma, chemotherapy is reserved for the dedifferentiated and mesenchymal subtypes. The exact role of chemotherapy,

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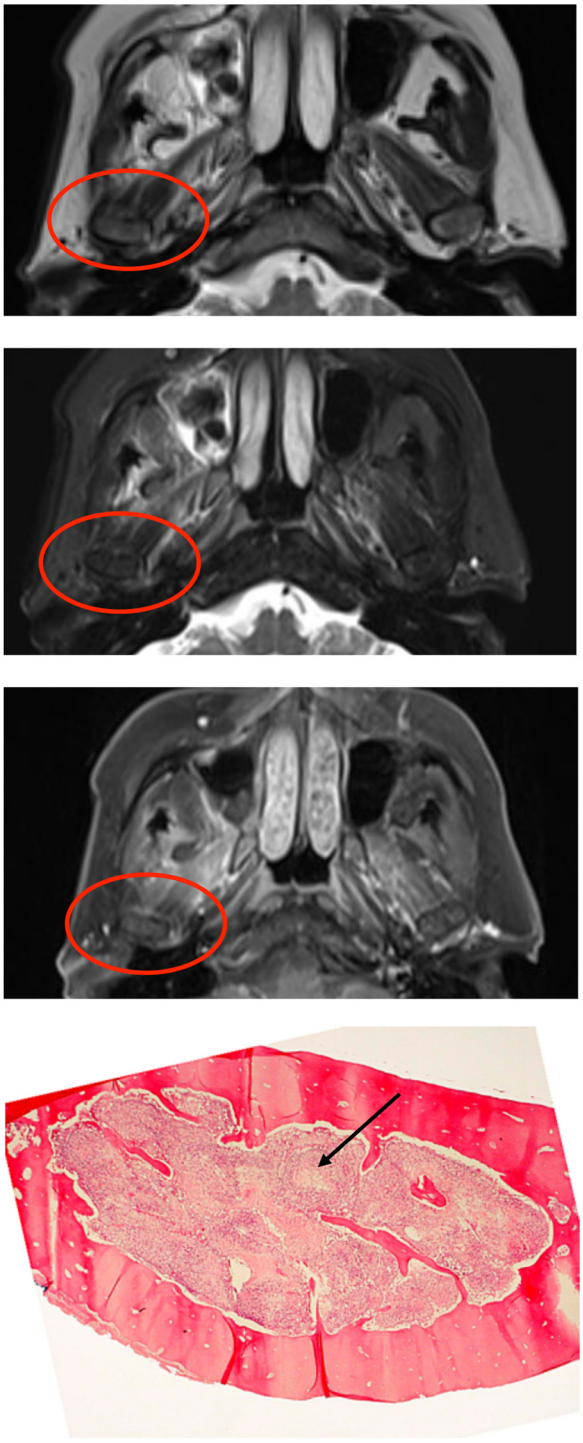

Fig. 3. Discrepancy between magnetic resonance imaging (MRI) and histological findings in high-grade osteosarcoma. T1 and T2 magnetic resonance axial images show radiologically disease-free right condylar head (2 weeks preoperatively). Histopathological specimen of the condylar head shows infiltration of the marrow space by osteosarcoma cells (haematoxylin and eosin, original magnification × 4).

however, is yet to be defined in periosteal and craniofacial osteosarcomas.[16]

Compartmental resection is the surgical technique of choice, and planning should be based on scans done before neoadjuvant chemotherapy. A staged approach to resection and reconstruction may be best when the overall physiology of the patient takes precedence, when it is predetermined by cardiopulmonary exercise testing,[26] or when there is uncertainty about tumour clearance in potentially difficult anatomical areas, such as the base of the skull. Condylar disarticulation and frank hemimandibulectomy must be considered when tumour extends to the mandibular ramus. However, low grade sarcomas such as parosteal and central osteosarcoma are treated with surgery alone, as they have low malignant potential.

In our experience, assessment of the tumour and the planned resection by the segmentation of scans provides a thorough 3-dimensional understanding of the resection that is required. It also helps us to plan the corresponding reconstruction based on the extent of the sub-site defect and, more importantly, provides visual cues that are invaluable intraoperatively. Intraoperative CT after resection is recommended to evaluate the adequacy of the planned resection in "difficult" areas such as the orbital apex or base of the skull (Figs. 4–7).

Radiotherapy is often used in the definitive management of Ewing sarcoma, but is otherwise reserved for palliative treatment and for selected cases with positive margins.

The use of heavy-particle radiation such as proton beam or carbon ion therapy is promising, particularly in patients with unresectable primary BS. Excellent outcomes have been reported in local disease control of chondrosarcoma of the skull base (70%-90%) with proton beam therapy and surgery.[27] Two centres in the UK provide proton beam therapy: Christie's at Manchester and from late 2020, University College Hospital, London (UCHL).

Treatment strategy for head and neck soft-tissue sarcomas

The treatment strategy for HNSTS is complex, and the diverse histological subtypes and variable responses to different treatments pose a challenge. Grading has an important role in decisions about the timing and type of treatment. The use of neoadjuvant chemotherapy may vary depending on histological grade, with a focus on high and intermediate-grade tumours, while the number of cycles and the duration of treatment are modulated by the extent of the disease and the response, with interim assessment with PET CT and MRI.[28] The surgical principles are similar to those used in HNBS, and compartmental resection is recommended to prevent local recurrence. Low-grade disease is treated primarily with surgery, and postoperative radiotherapy is given to patients with high-grade or advanced disease. The role of adjuvant chemotherapy for most of these tumours, however, remains unproven,[29] but it is considered in cases that are high risk and

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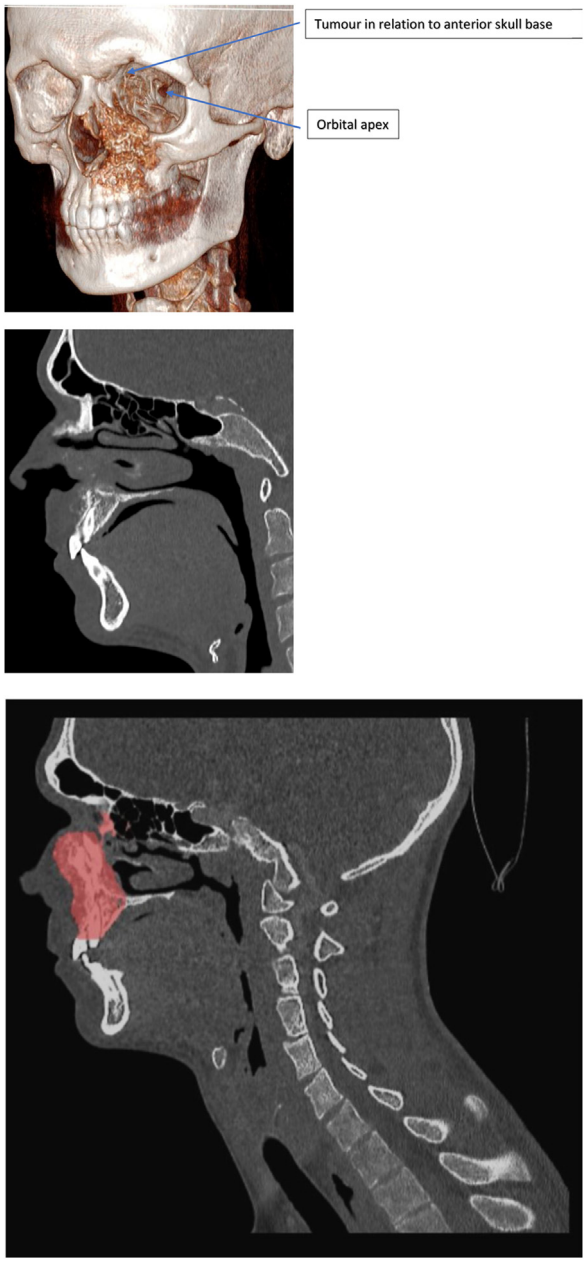

Fig. 4. Computed tomogram showing left-sided osteosarcoma anatomically close to the anterior base of the skull and orbital apex.

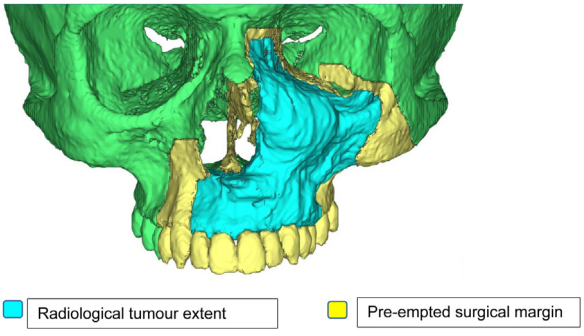

Fig. 5. Segmentation of computed tomogram for the mapping of tumour and resection margins.

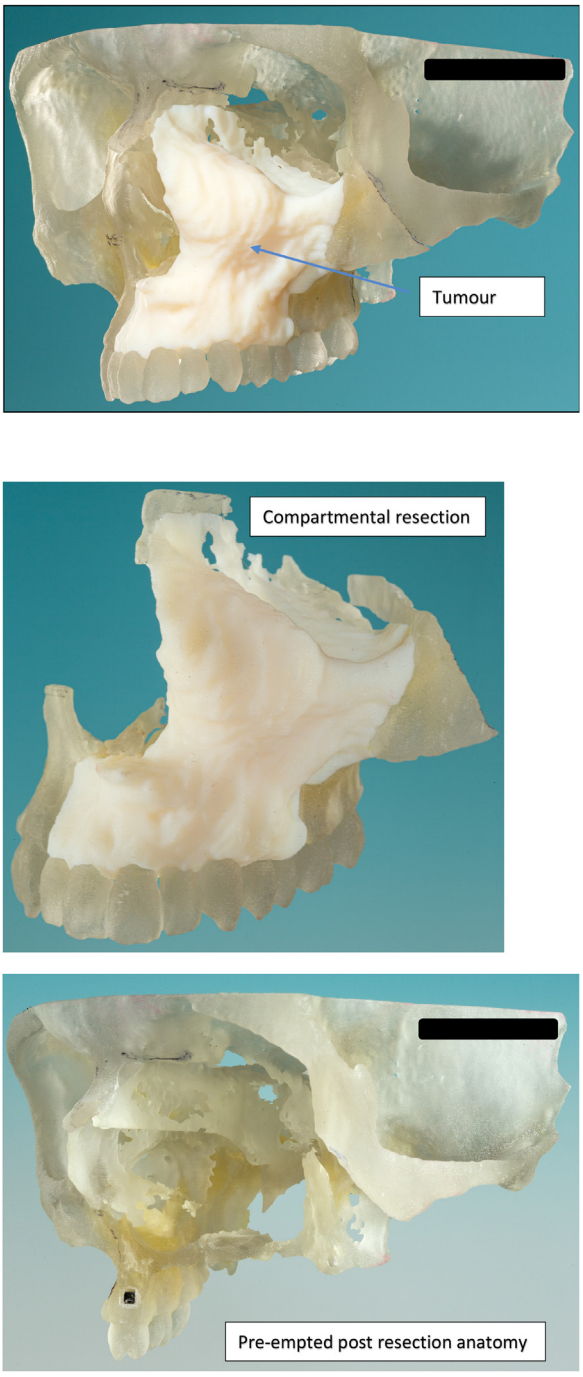

Fig. 6. Three-dimensional detachable model based on virtual surgical planning as an intraoperative guide to aid compartmental resection.

chemosensitive, and when local relapse cannot be surgically salvaged.[16]

Prognosticators of head and neck sarcomas

Surgical principles are driven by our current knowledge of the prognosticators of sarcomas: grade of tumour,[30] anatomical subsite or location, tissue of origin, adequacy of margins,[31]

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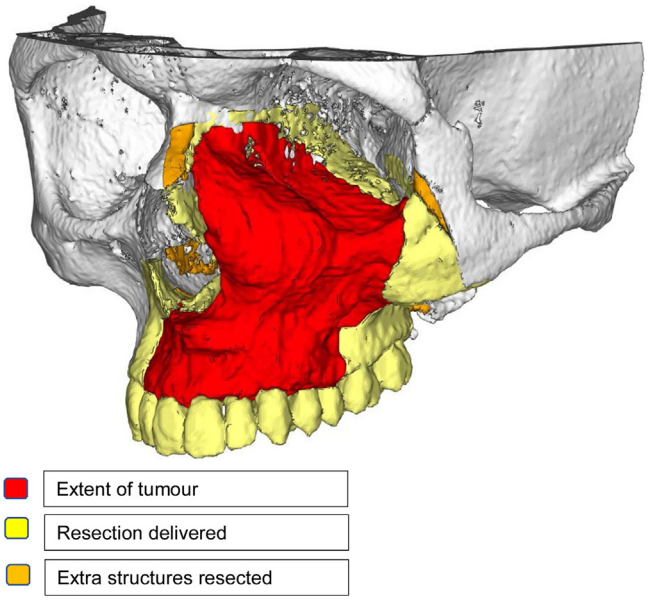

Fig. 7. Virtual surgical planning computed tomogram (CT) superimposed on to resection CT to check for adequacy of surgical margins.

presence of perineural invasion,[32] and response to neoadjuvant chemotherapy.

The response to neoadjuvant chemotherapy is evaluated by interim PET CT and MRI. In cases of HNBS, assessment is more reliable with fluorodeoxyglucose (FDG) PET than with standard imaging, and may correlate better with outcome than histological response.[28] A reduction in overall metabolic activity by more than 30% with a corresponding shrinkage in volume is considered a good response. However, the ultimate benchmark is more than 90% tumour necrosis on post resection histological analysis. Emerging evidence has shown that about 7% of HNBS do not respond to neoadjuvant chemotherapy (UCHL unpublished data). The resultant impact on prognosis is currently unknown.

Surgical success is defined by the presence of adequate tumour-free margins. Although no clear guidance is available for HNS, our data show that bony margins that are histologically clear of tumour by more than 5 mm have a significant impact on DFS ($p = 0.012$). Involved bony margins and uninvolved margins (less than 5 mm), even in the absence of a breach of periosteum, have similar poor outcomes. Soft-tissue margins, unless frankly involved, do not have an impact on survival probability in BS. What constitutes an adequate negative surgical margin in HNSTS, however, remains unclear from our data, and other authors have echoed our observations.[33]

Follow up

Intermediate or high-grade sarcomas commonly relapse within two to three years, in a similar timescale to that of epithelial carcinomas. Secondary cancers that are related to or independent of irradiation may arise in survivors of BS.[34] Acute myeloid leukaemia in particular may be observed as early as two to five years after chemotherapy. Follow up therefore, should include clinical history and examination, US or MRI of the primary site for STS and MRI for BS to rule out local recurrence, and appropriate imaging of the chest.[16]

Surgical follow up should include the consideration of secondary surgical refinement procedures, but currently a lacuna exists for understandable reasons. Newer evidence specific to the head and neck has shown that facial lipofilling can improve fibrotic conditions such as scarring and radiation fibrosis in HNS,[35] and we have found that it serves as an important adjunct to the success of more definitive secondary facial procedures.

The recommended follow up for intermediate or high-grade BS and STS is every two to four months for the first three years after completion of therapy, then every six months for years four and five, and annually thereafter.[36]

Future of head and neck sarcomas

As staging systems emphasise "personalised" cancer care, the development of early diagnostics and the delivery of treatment remains quintessential to improve outcomes. The identification of reliable genomic alterations could potentially contribute to the development of simpler, accurate, non-invasive diagnostic tests, and better targeted molecular agents. The development of inconspicuous surgical access in the head and neck, and of 3-dimensional volumetric reconstruction and secondary refinement techniques in facial surgery must be encouraged. Artificial intelligence may pave the way for in-depth knowledge of HNS as a disease entity, and may help to identify patients who do not respond to neoadjuvant chemotherapy early on. The resultant algorithms could lead to a paradigm shift in the overall management of HNS.

Ethics statement/confirmation of patients' permission

Ethics approval not required as it is a review article. Patients' permission not applicable.

Conflict of interest

We have no conflicts of interest.

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References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;**57**:43–66.
2. Kraus DH. Sarcomas of the head and neck. *Curr Oncol Rep* 2002;**4**:68–75.
3. Burningham Z, Hashibe M, Spector L, et al. The epidemiology of sarcoma. *Clin Sarcoma Res* 2012;**2**:14.
4. Birch JM, Alston RD, Quinn M, et al. Incidence of malignant disease by morphological type, in young persons aged 12-24 years in England, 1979-1997. *Eur J Cancer* 2003;**39**:2622–31.
5. Bone sarcoma incidence statistics. Cancer Research UK 2010-2012. Available from URL: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bone-sarcoma/incidence#heading-Three.
6. *National Cancer Intelligence Network: head and neck sarcoma of the bone and soft tissue – incidence, survival and surgical treatment*. Public Health England; 2014.
7. Vassiliou LV, Lalabekyan B, Jay A, et al. Head and neck sarcomas: a single institute series. *Oral Oncol* 2017;**65**:16–22.
8. Mardinger O, Givol N, Talmi YP, et al. Osteosarcoma of the jaw. The Chaim Sheba Medical Center experience. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;**91**:445–51.
9. Clark JL, Unni KK, Dahlin DC, et al. Osteosarcoma of the jaw. *Cancer* 1983;**51**:2311–6.
10. August M, Magennis P, Dewitt D. Osteogenic sarcoma of the jaws: factors influencing prognosis. *Int J Oral Maxillofac Surg* 1997;**26**:198–204.
11. Fernandes R, Nikitakis NG, Pazoki A, et al. Osteogenic sarcoma of the jaw: a 10-year experience. *J Oral Maxillofac Surg* 2007;**65**:1286–91.
12. Mücke T, Mitchell DA, Tannapfel A, et al. Outcome in adult patients with head and neck sarcomas—a 10-year analysis. *J Surg Oncol* 2010;**102**:170–4.
13. Peng KA, Grogan T, Wang MB. Head and neck sarcomas: analysis of the SEER database. *Otolaryngol Head Neck Surg* 2014;**151**:627–33.
14. Mortus JR, Zhang Y, Hughes DP. Developmental pathways hijacked by osteosarcoma. *Adv Exp Med Biol* 2014;**804**:93–118.
15. Gerrand C, Athanasou N, Brennan B, et al. UK guidelines for the management of bone sarcomas. *Clin Sarcoma Res* 2016;**6**:7.
16. Dangoor A, Seddon B, Gerrand C, et al. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res* 2016;**6**:20.
17. Price P, Sikora K, editors. *Treatment of cancer*. 6th ed. CRC Press; 2015.
18. Kempf-Bielack B, Bielack SS, Jürgens H, et al. Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). *J Clin Oncol* 2005;**23**:559–68.
19. Farhood AI, Hajdu SI, Shiu MH, et al. Soft tissue sarcomas of the head and neck in adults. *Am J Surg* 1990;**160**:365–9.
20. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. 1980. *Clin Orthop Relat Res* 2003;**415**:4–18.
21. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017;**67**:93–9.
22. Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol* 1997;**15**:350–62.
23. Coindre JM. Grading of soft tissue sarcomas: review and update. *Arch Pathol Lab Med* 2006;**130**:1448–53.
24. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol* 2002;**20**:776–90.
25. Whelan JS, Bielack SS, Marina N, et al. EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment. *Ann Oncol* 2015;**26**:407–14.
26. Levett DZ, Jack S, Swart M, et al. Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Br J Anaesth* 2018;**120**:484–500.
27. Ares C, Hug EB, Lomax AJ, et al. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. *Int J Radiat Oncol Biol Phys* 2009;**75**:1111–8.
28. Frezza AM, Beale T, Bomanji J, et al. Is [F-18]-fluorodeoxy-D-glucose positron emission tomography of value in the management of patients with craniofacial bone sarcomas undergoing neo-adjuvant treatment? *BMC Cancer* 2014;**14**:23.
29. Woll PJ, Reichardt P, Le Cesne A, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. *Lancet Oncol* 2012;**13**:1045–54.
30. Van Damme JP, Schmitz S, Machiels JP, et al. Prognostic factors and assessment of staging systems for head and neck soft tissue sarcomas in adults. *Eur J Surg Oncol* 2010;**36**:684–90.
31. Bentz BG, Singh B, Woodruff J, et al. Head and neck soft tissue sarcomas: a multivariate analysis of outcomes. *Ann Surg Oncol* 2004;**11**:619–28.
32. Tajudeen BA, Fuller J, Lai C, et al. Head and neck sarcomas: the UCLA experience. *Am J Otolaryngol* 2014;**35**:476–81.
33. Makary RF, Gopinath A, Markiewicz MR, et al. Margin analysis: sarcoma of the head and neck. *Oral Maxillofac Surg Clin North Am* 2017;**29**:355–66.
34. Bassal M, Mertens AC, Taylor L, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2006;**24**:476–83.
35. Griffin MF, Almadori A, Butler PE. Use of lipotransfer in scleroderma. *Aesthet Surg J* 2017;**37**(Suppl 3):S33–7.
36. Bielack S, Carrle D, Casali PG, et al. Osteosarcoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009;**20 Suppl 4**:137–9.

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