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REVIEW ARTICLE

Current update on the diagnosis and management of head and neck soft tissue sarcomas

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Head and neck soft tissue sarcomas are a group of rare heterogeneous tumours arising from embryonic mesoderm. They comprise <1% of all head and neck malignancies and 5–15% of all sarcomas with most head and neck sarcomas arising from soft tissues. Although rare, they are associated with both high recurrence and mortality rates. We review the current management of head and neck soft tissue sarcomas.

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Introduction

Head and neck soft tissue sarcomas (STS) are rare malignant neoplasms of mesenchymal origin with an annual incidence of 5 per 100 000 (1, 2). They comprise 5–15% of all sarcomas and 1% of head and neck malignancies (1). More than 50 histological subtypes have been described (3) with the majority (80%) arising from soft tissues (4). The most frequent histological subtypes seen are malignant fibrous histiocytoma (MFH), fibrosarcoma, angiosarcoma, malignant peripheral nerve sheath tumour and non-classified/non-differentiated sarcoma (5). Immunopositivity for vimentin, α1-antichymotrypsin and Ki-67 help to differentiate MFH from other STS (4). These tumours usually present as a painless mass and are often asymptomatic (6). Less frequent manifestations include otalgia, epistaxis and neurological symptoms including motor and sensory disturbances (7). Head and neck STS occur more frequently in men (male to female ratio 2:1), and the mean age of presentation is around 50–55 years (8). However, there is variation of mean presentation age as other studies (7, 9) have reported 47 and 62 years and a trimodal distribution has been described, <10 years (rhabdomyosarcoma, fibrosarcoma, neuroblastoma), 11 and 40 (epithelioid sarcoma, malignant peripheral nerve sheath tumour) and over 40 years (the majority of STS) (10). The tumour site is an important factor in head and neck STS which influences surgical management, surgical margins and both aesthetics, function and quality of life. The management of STS requires multidisciplinary support (Fig. 1).

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Radiology

Diagnostic imaging for STS includes CT, also useful for staging the chest, and MRI, which is usually used for soft tissue imaging and good at assessing bone invasion. There are no specific radiological diagnostic criteria for STS, but worrying features include a progressively enlarging mass (Fig. 2), tumour size >5 cm with sub-aponeurotic irregular contours, necrotic areas (although these are also found in metastatic squamous cell carcinoma) and irregular septa within the tumour (5). Increased heterogeneity may be seen on both T1- and T2-weighted images (7). Suspected STS patients also should have chest CT for staging purposes as between 10 and 40% of patients develop metastases during follow-up, predominantly in the lung (11), particularly in high-grade STS primary tumours (12). Positron emission tomography (PET) can also be useful both in diagnosis and for assessing tumour recurrence (13).

Pathology

Certain reactive processes can mimic sarcoma (14), and it is not always possible to diagnose or classify STS based on cytology or core biopsy Therefore, STS diagnosis is often based on open biopsy or following tumour resection (14). Core biopsies, even under ultrasound guidance, can result in inappropriate sampling, with for example a high-grade STS being misdiagnosed as low-grade. If necrosis is present, it should display coagulative change. The role of frozen section is useful in ensuring that there is viable tissue for resection margin evaluation thought it is often difficult to make a formal diagnosis. Immunohistochemistry is used to

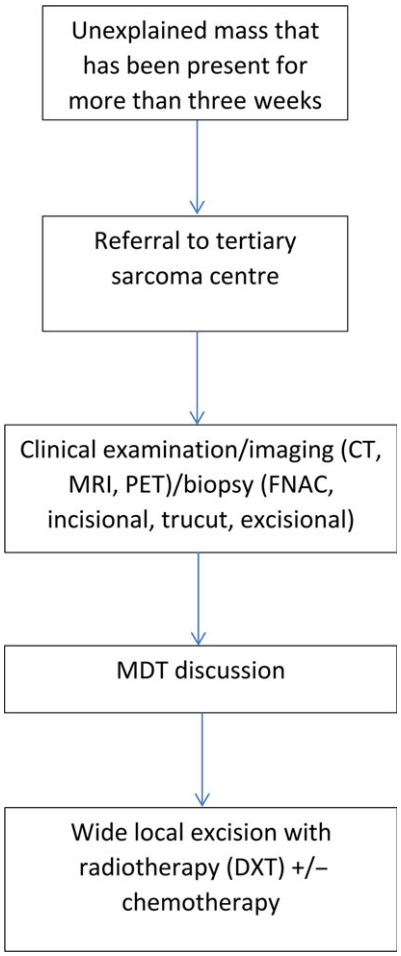

Figure 1 Flow chart of management of head and neck soft tissue sarcoma (based on 7).

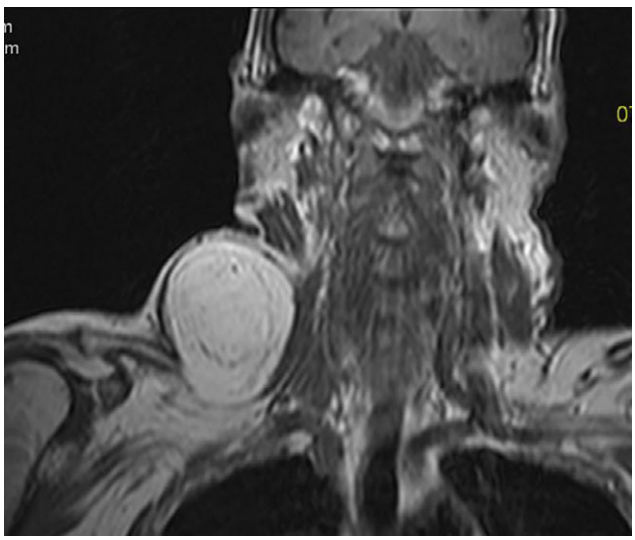

Figure 2 T1-weighed coronal MRI showing a large right-sided 7-cm liposarcoma. This was a long-standing benign lipoma that suddenly increased in size causing pain, with malignant transformation.

assess both diagnosis and prognosis of STS and is useful to exclude a non-mesenchymal tumour (14). Figure 3 shows the histopathological features of some soft tissue head and neck sarcomas. In Fig. 2D, the presence of necrosis in a leiomyosarcoma is shown. In all of these cases, immunohistochemical analysis was necessary to confirm the diagnosis and recently described genetic and chromosomal abnormalities have been described as useful diagnostic tools. Sarcomas can be differentiated into two groups: sarcomas that have specific genetic alteration containing simple karyotypes including reciprocal translocations resulting in fusion genes and sarcomas that have non-specific karyotypes containing chromosomal losses or gains (15).

Due to the rarity of STS, these tumours can be both misdiagnosed and misclassified. In a review of head and neck STS, there was a change of diagnosis in between 33 and 48% of cases (16–18). In one study (18) of a histopathological review of 41 patients treated for head and neck STS, no STS was found in 7% of cases and there was a change of tumour histotype in 39%, particularly in fibrosarcoma and malignant fibrous histiocytoma. The authors postulated this was likely due to the results of immunohistochemistry and changes in tumour nomenclature. Davis et al (19). also showed that in 30 patients treated for liposarcoma, one-third of cases had a misdiagnosis. It can therefore be argued that a pathological review is needed prior to starting treatment (20).

Staging

There is no generally agreed system for grading STS. One of the most widely used staging systems is the American Joint Committee on Cancer (AJCC) with three prognostic factors summarising primary size, regional lymph node invasion, metastases and sarcoma grade (Table 1). The Memorial Sloan-Kettering Cancer Centre (MSKCC) classification also applies similar criteria and has been described as being more accessible as it includes more unfavourable characteristics and emphasises the importance of each clinical variable slightly differently (Table 1).

Van Damme et al (20). assessed both the AJCC and MSKCC system for their prognostic value, finding that the AJCC was more relevant than the MSKCC staging system and a better predictor of both disease-specific and overall survival. A later study (17) identified that both AJCC and MSKCC are good predictors of outcome in head and neck STS.

The French Federation of Cancer Centres Sarcoma group (FNCLCC) and the National Cancer Institute (NCI) staging systems are also used and have three grades based on mitotic activity, necrosis and differentiation which correlates with prognosis (Table 1) (21). The NCI system requires that cellularity and pleomorphism are also quantified for some sarcoma histotypes. The TNM staging system also advocates the use of FNCLCC system, although some tumour histotypes such as angiosarcoma and rhabdomyosarcoma cannot be graded and if histotypes cannot be established or diagnosis is in doubt, grading may not be possible (22, 23).

Prognosis and survival from head and neck STS

Overall survival is poorer in head and neck STS than for other locations. Some authors such as Galy Bernadoy &

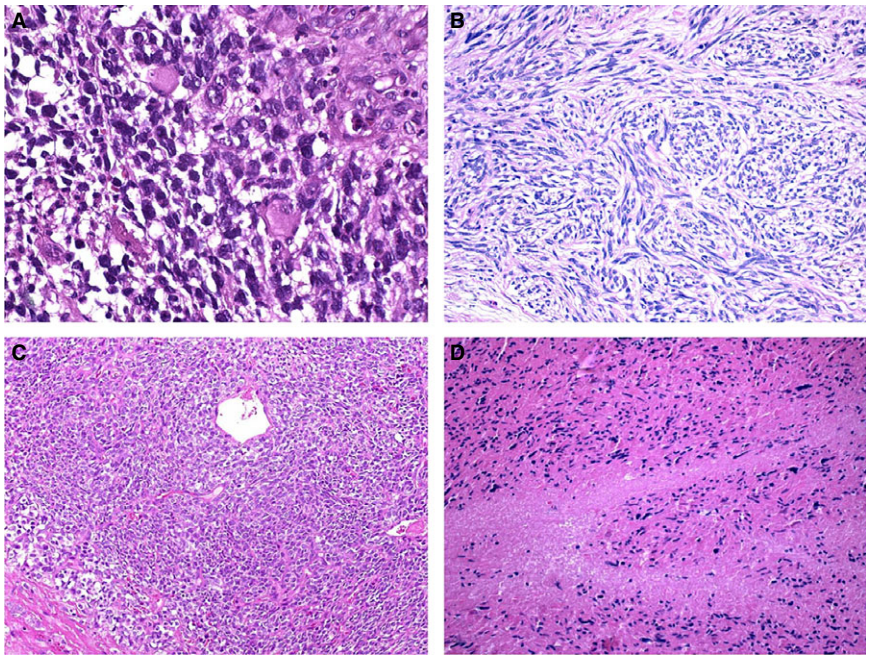

Figure 3 Histopathological features of rhabdomyosarcoma (A), malignant peripheral nerve sheath tumour (B), monophasic synovial sarcoma (C) and leiomyosarcoma (D).

Garrel (5) suggest this may be due to the distribution of histotypes with more aggressive tumours such as angiosarcoma and fibrosarcoma arising in the head and neck. However, overall generalisations of prognosis can also be difficult due to the heterogeneity of the histotypes (24). It is also relatively more difficult to achieve clear margins in the head and neck due to the proximity of vital structures and the relatively confined anatomical area. A recent study (25) found an estimated 5-years disease-specific survival for the study group was 72% and the estimated overall survival was 61%, which is comparable to other studies showing 5-years disease-specific survival of 72–83% (26–28). Overall 5-years survival from studies between 1993 and 2016 varies from 44 to 80% (5, 28). Margin status is also an important factor that can affect prognosis. One study (26) showed that 72% of patients with negative margins had local control compared to 34% with either borderline or positive margins. These results are comparable to more recent studies that have found margin status affects recurrence-free survival and overall survival (29). A tumour size of >5 cm has statistically significant prognostic value and can influence overall survival, disease-free survival and disease-specific survival (16, 20, 29), but others have found that 10 cm or greater has more prognostic significance (30). Additionally, more aggressive tumour histotypes increase local, regional and distant recurrence (29–32). It has also been suggested that male gender has also been associated with a poorer prognosis (30).

Neck metastases

Regional lymph node metastases are a poor prognostic indicator for patients with STS and are more likely in embryonic rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, synovial cell sarcoma and angiosarcoma (33). Mucke et al (11). identified nodal metastases as an independent prognostic factor on multivariate analysis but the overall rate was 7%, but the study focussed on osteo- and chondrosarcomas which are distinct from STS. Other studies have found similar results (29).

Metastatic neck nodes are associated with disease-specific mortality (<0.001), and in 86% of 183 patients studied, the primary tumours were <5 cm (22, 34). Therefore, in contrast to metastatic squamous cell carcinoma most authors therefore do not advocate elective neck dissection unless there is either clinical or radiological evidence of nodal involvement (5).

Surgery

Surgery is the best treatment option to give any chance of cure, with a wide excision and clear margins being required to achieve disease-free survival. With aggressive tumours, close margins can result in similar recurrence rates to resections with positive margins.

There is currently no consensus as to the size of resection margin, but many surgeons would agree that at least 2 cm is required (5). Sarcomas expand tissue adjacent to the tumour, and a local inflammatory response often leads to the formation of a pseudo-capsule containing both normal tissue and inflammatory and malignant cells (19). Sarcomas also tend to follow fascial planes (20). Owing to the proximity of vital structures including the carotid tree, upper aerodigestive tract and important cranial nerves, it can be difficult to obtain a 2 cm margin safely in head and neck surgery compared to STS arising in other parts of the body, with one study finding positive margins in 31.2% of patients (29).

Table 1 Common staging systems used for head and neck soft tissue sarcoma

Staging system	
AJCC/ UICC (16)	T1: <5 cm in greatest dimension T2: 5 cm or more in greatest dimension N0 vs. N1 – any nodal disease M0 vs. M1 – any distant metastases G1: well differentiated G2: moderately differentiated G3: poorly differentiated G4: undifferentiated I – G1-2, T1a or b or T2a, N0, M0 II – G1-2, T2b, N0, M0 or G3-4, T1a-b/T2a, M0, III- G3-4, T2b, N0, M0 or N1 (any G, any T) IV- any M1
MSK (16)	Unfavourable signs: more than 5 cm in greatest dimension, deep invasion, high grade Stage 0: no unfavourable signs Stage I: one unfavourable sign Stage II: two unfavourable signs Stage III: three unfavourable signs Stage IV: any metastases
FNCLC (17)	*Definition of parameters* Tumour differentiation: score 1 (sarcomas resembling normal mesenchymal tissue and difficult to discriminate from benign tissue), score 2 (sarcomas for which the histotype is certain, score 3 (sarcomas of doubtful type, embryonal and undifferentiated sarcomas, synovial sarcomas) Mitotic count: score 1 (mitotic count 0–9 mitoses per 10 HPF), score 2 (mitotic count 10–19 per 10 HPF), score 3 (more than 19 mitoses per 10 HPF) Tumour necrosis – score 0 (no necrosis), score 1 (<50% of tumour necrosis), score 3 (50% or more tumour necrosis) Histological grade: grade 1 (total score 2–3), grade 2 (score 4–5), grade 3 (total score 6–8) *Histological type (differentiation score)* Well differentiated sarcomas (liposarcoma, leiomyosarcoma): 1 Conventional leiomyosarcoma, conventional malignant peripheral nerve sheath tumour, myxofibrosarcoma: 2 Poorly differentiated/pleomorphic leiomyosarcoma, de-differentiated liposarcoma, epithelioid sarcoma, undifferentiated spindle cell or pleomorphic sarcoma: 3

A recent study (25) of 49 patients treated with wide local excision and variable reconstruction, if required, found that free tissue transfer using the anterolateral thigh (ALT) flap or latissimus dorsi (LD) flaps was the most commonly used. Clear histopathological margins were achieved in 88% of cases, highlighting that wide excision can be achieved if reconstructed appropriately after resection. Another recent study (7) also found that 82% of patients treated with wide local excision of the tumour and reconstruction had clear margins. Select patients with low-grade histotypes at a favourable disease site can have resection with regular monitoring and assessment with repeat resection if required. In cases where clear margins are not achieved, further resection can sometimes be performed, a technique widely accepted in the literature (35, 36) and associated with improved outcomes which also reduces the need for adjuvant radiotherapy (37). There is a significant difference in local-control rate using surgery as compared to radiotherapy (90% vs. 52%) (38).

Radiotherapy (DXT)

Although surgery remains the best treatment modality for head and neck STS, surgery might not obtain clear margins, so most authors advocate external beam radiotherapy (DXT) for patients with close (<1 cm) or involved margins or in high-grade tumours (39, 40).

Patients who have higher than 60 Gy seem to have a significantly higher local disease control than those who are given <60 Gy (40), a finding consistent with other studies (41).

Andra et al. performed a retrospective analysis of 26 patients that either received post-operative or definitive DXT with local-control rates of 86% at three and 5 years. There was one patient that failed at distant sites. As expected with head and neck DXT, side effects included mucositis, dysphagia and dry mouth (42).

Combined surgery and DXT may improve survival with one study finding 5-years survival rate of 67% with surgery and DXT compared to 60% with surgery alone (43). A recent study (44) analysed outcomes and treatment failures in patients finding a lower rate of disease-free survival in patients over 60 years of age. Of note was that surgery and adjuvant DXT resulted in better local tumour control and overall survival outcome. The study highlighted that there is no prospective study that has compared pre-operative with post-operative DXT. Both can results in considerable morbidity with pre-operative DXT causing severe wound breakdown whereas post-operative DXT has a higher risk of fibrosis and oedema (45). DXT should ideally be avoided before surgery to the oro-pharyngeal/laryngeal mucosa due to the increased risk of fistula formation (46).

Chemotherapy

The role of chemotherapy is unclear in head and neck STS. Some recommend neo-adjuvant chemotherapy for patients with inoperable and locally advanced disease or in an attempt to reduce tumour size prior to resection (47). The most widely used chemotherapy combination is doxorubicin, dacarbazine and ifosfamide (48). However, while chemotherapy might improve improved local tumour control, it does not appear to have any benefit in overall survival, apart from in a few isolated studies (49, 50). However, these studies have potential issues due to low patient numbers, patient heterogeneity and short follow-up periods (51). Other studies have concluded that chemotherapy improves survival in patients with grade 3 sarcoma (52) and angiosarcoma (53).

Conclusion

Head and neck STS are a rare, aggressive and heterogeneous group of tumours that have different presentations. The main treatment for curative intent is surgical resection with an aim to obtaining negative surgical margins. Radiotherapy when combined with surgery may improve overall prognosis whereas some STS such as angiosarcoma achieve better outcomes when chemotherapy is used. As these tumours are rare and difficult to manage, they need to be treated in centres where there can be cross-specialty

collaboration, with further multicentre randomised control trials being required to guide and improve treatment.

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