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Review Article

Ending 40 years of silence: Rationale for a new staging system for soft tissue sarcoma of the head and neck

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ABSTRACT

The tumor, node, metastases (TNM) anatomic staging system plays a pivotal role in cancer care, research, and cancer control activities. Since the first edition of the American Joint Committee on Cancer TNM staging classification published in 1977, soft tissue sarcomas have been staged in an anatomic site agnostic fashion whereby the primary tumor size (T) was categorized as T1 if <=5 cm and T2 if >5 cm; this remained unchanged through the 7th edition of the TNM. However, soft tissue sarcomas of the head and neck (STSHN) usually present smaller than sarcomas of other sites, but carry a disproportionate risk of local recurrence. Up to 70% of tumors are less than 5 cm at presentation, and therefore classified together as T1. Given the rarity of STSHN, there is a paucity of data to guide progress in their classification. Moreover, the majority of publications only report tumor size as less than or greater than 5 cm, presumably based on conventions of the TNM system that remained unchanged for 40 years, thereby affecting progress of STSHN classification. This formed the impetus for change in the 8th edition in 2 key ways: 1) several soft tissue sarcoma site based changes occurred including STSHN now having its own system, and 2) primary tumor size cut-offs of 2 cm and 4 cm used in STSHN now reflect sizes that head and neck specialists commonly encounter in their practice. This update was pragmatic in modifying the TNM from a system with a T category not serving STSHN and which was originally based on sarcoma data from non-head and neck anatomic sites. The background to this change is outlined which provides a framework in which data can be reported to generate evidence for future staging modifications.

Contents

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1. Introduction

Careful, precise, and accurate description of the anatomical extent of cancer is an important element of cancer care, research, and prognostication [1–3]. The Tumor, Node, Metastases (TNM) classification has served this role for decades and has become part of the lexicon of nearly all practitioners involved in cancer care. The TNM classification has many purposes and serves many different users. It is used in clinical care, providing prognostication and aiding in communication and planning of treatment. The TNM classification also facilitates research in terms of trial design and comparison of outcomes. Furthermore, it provides a rubric for how data should be collected and reported. Cancer registries and cancer control activities rely on such classifications, that need to be robust for widespread use. Accordingly, the TNM classification is used by many, attributable in large part to its stability, ease of use, and wide applicability.

Sarcomas pose unique challenges in terms of categorization and grouping, comprising more than 50 histopathologic subtypes and originating from nearly every anatomical site in the body. Additionally, soft tissue sarcomas (STS) are especially uncommon with an approximate incidence of only 14,000 per annum for Canada and USA combined [4,5]. Head and neck sarcomas are particularly rare accounting for approximately 10% of STS and <1% of head and neck cancers [6–9]. Consequently, the vast majority of data specific to head and neck sarcomas comprise retrospective institutional case series with a distinct paucity of prospective data evaluating outcome. The first edition of the American Joint Committee for Cancer (AJCC) TNM staging was published in 1977 and discriminated primary tumor size using a 5 cm cut-off to distinguish between T1 and T2 tumors; all anatomical sites of STS were staged in this manner, including those of the head and neck (Table 1) [10]. Notably the original data underpinning the first edition TNM for STS included no patients with head and neck sarcomas, which is problematic given the discussion below regarding the relevance of the size cut-off for this disease [11]. The TNM 7th edition published in 2010 remained unchanged, and continued to be applied to head and neck sarcomas, representing stagnation for decades for this disease [12].

Although head and neck soft tissue sarcomas (STSHN) were encompassed in the TNM classification, these tumors are fundamentally and importantly different from other sarcomas in terms of their extent and relationship to normal regional anatomy. STSHN are usually smaller at presentation than those of the extremity, the majority being less than 5 cm [13–16]. The intricate anatomy of the head and neck region places significant constraints on radicality of treatment of STSHN relative to other anatomic sites and local recurrence is more likely compared to other STS. Therefore, the prognostic stratification value based on primary tumor size for STSHN is limited. Additionally, within the published data, the majority of series reporting outcomes based on tumor size also used a 5 cm cut-off to analyze differences, presumably because of the TNM classification conventions that remained unchanged through the 1st-7th AJCC editions.

In an attempt to generate progress and guidance for practitioners caring for patients with STSHN, the TNM 8th edition now includes a categorization unique to these lesions [6]. This edition aims to address the deficiency of previous TNM classifications, i.e. primary tumor size. The new system employs size cut-offs of 2 cm and 4 cm, similar to carcinomas of the head and neck that are more in keeping with primary tumor sizes seen in these anatomical regions. This paper will discuss issues relevant to the TNM classification of STSHN and expand on the rationale for its introduction.

Table 1
First edition of the Tumor, Node, Metastases (TNM) staging system for soft tissue sarcomas published in 1977 [10].

Primary Tumor (T)	
T0	No tumor evident
T1	<=5 cm
T2	>5 cm
T3	Tumor invasion of bone, major vessel, or major nerve
Nodal Involvement (N)	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant Metastasis
M1	Distant metastasis

2. Clinical presentation and natural history

Presenting symptoms are intimately related to the specific location of disease. While many patients present with an asymptomatic mass in the neck, face, or scalp, others experience symptoms related to the sub-site of origin. Dysphagia, hoarseness, airway compromise, nasal obstruction, epistaxis, cranial nerve deficits, and proptosis are potential presenting symptoms depending on the disease location. Additionally, the appearance of the head and neck and facial form are vital for cosmesis and social interaction, making contour distortions or abnormalities more noticeable; in turn significant resulting symptoms or identification of esthetic abnormalities may prompt earlier medical attention than may

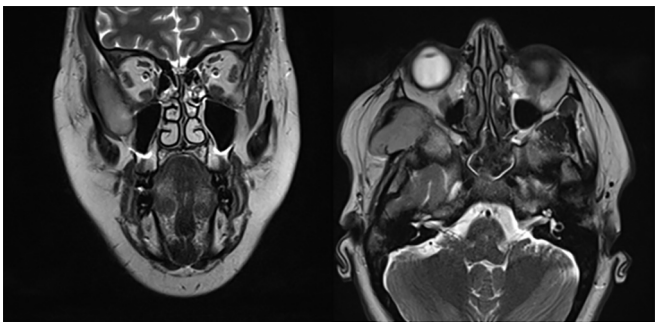

Fig. 1. Coronal and axial T2-weighted MR images depicting a lobulated 3.7 × 3.4 × 1.5 cm synovial sarcoma in the right temporalis region causing remodeling of the posterolateral orbital wall. This 42 year old woman's sarcoma was detected due to the socially sensitive location of the tumor leading to recognition of a non-resolving lump. She was successfully treated with pre-operative radiotherapy, 50 Gy in 25 fractions, followed by surgical resection.

occur in other anatomic areas (Fig. 1). This likely contributes to more prompt detection and workup of these tumors and consequently smaller size of primary tumors relative to extremity STS.

Initial workup involves a detailed history and physical examination with a particular focus on local symptoms and signs. Choice of imaging modality depends on the clinical indications, but MRI and CT scans are often employed and can complement each other, especially when evaluating for bone invasion in addition to soft tissue extent. Any suspicion for base of skull, orbit, or neural involvement would likely prompt an MRI for better evaluation, as should disease that originates in the sino-nasal complex. PET imaging is not standard in many centers, but utilized on a case-by-case basis with its main contribution being identification of distant metastases. Evaluation for metastatic disease normally includes a CT scan of the chest, since approximately 10% of patients present with metastatic disease at the time of diagnosis [17].

Based on the rarity of these tumours, and their numerous types and subtypes, they frequently pose a diagnostic challenge for pathologists. It is therefore important that these tumours be reviewed by pathologists with subspecialty training in sarcoma, with access to advanced diagnostic assays (e.g., molecular testing) [18–20]. It is also important to plan the biopsy carefully; given the rarity and varied presentation of these tumors, unplanned biopsies or surgeries are not uncommon [21]. If this occurs, subsequent treatment can be complicated or compromised. Sarcomas have a tendency to form implant metastases at the site of biopsy or surgical procedure, sometimes requiring wider surgical resection than would have otherwise been planned and/or larger radiation therapy target volumes; additionally, there may be an increased risk for distant metastatic disease [22]. Therefore, referral to specialized centers with multidisciplinary (pathology, radiology, surgery, radiation oncology, medical oncology, and allied health professionals among others) expertise in sarcomas is optimal at suspicion for STSHN before biopsy. STSHN also require further specialized care addressing support needs from speech language pathology, nutrition, dentistry, ophthalmology, voice rehabilitation, and social support [23]. A study of 4205 patients with STS, of which 12% had head and neck primaries, found that patients treated in a high-volume center had better survival and functional outcomes [24].

Obtaining local control of STSHN is important for two primary reasons: 1) compared to extremity sites, rates of local failure after treatment are relatively high while rates of distant metastases are low, and 2) failure in the head and neck can be especially morbid and may result in death from local disease progression. Mendenhall et al performed a literature review of STSHN and found that local control rates were approximately 60–70% after surgery alone or combined with radiotherapy [25]. This is substantially lower than rates of local control in extremity STS which are close to 90% [26]. Additionally, rates of distant metastases at 5 years were 10–30% and overall survival rates were approximately 60–70% [25].

The reasons for the inferior local control in STSHN compared to those of the extremity have not been well studied but can be rationalized. Although it is possible that the underlying biological behaviour differs, it is thought that alike tumors behave similarly in the head and neck and other anatomical locations. The difference probably stems from the compromised ability to deliver necessary radical oncologically sound treatment in the head and neck due to proximity to critical anatomic structures; this can affect the extent of surgical resection as well as the dose and volume of radiotherapy, which can be applied adjuvantly or neoadjuvantly, and occasionally in combination with chemotherapy or hyperthermia. Also, outcomes may be affected if patients are not treated in a high-volume center with multidisciplinary care. If, however, proper multidisciplinary care is able to deliver appropriate treatment, it is felt outcomes would be similar to those expected in a comparable extremity sarcoma population [27].

3. Primary tumor size

Reports of primary tumor size are mainly based on retrospective data. Granularity of data is limited as most reports classify tumors according to the previous TNM staging classifications, into those <=5 cm and >5 cm. In fact, as early as 1965, it was reported that STSHN present with smaller sizes relative to those of the extremity [28]. In this report of 139 sarcomas, tumors were documented into the following "size" categories: "cherry", "egg", "fist", and ">fist"; 60% of head and neck sarcomas were either sized as cherry or egg, presumably both categories representing tumors <5 cm, and only 5% as >fist. Kraus et al. analyzed a prospectively collected database between 1982 and 1989 [8]. Of the 60 patients evaluated, 72% had tumors <=5 cm. Results from Massachusetts General Hospital and the University of Iowa also show a majority

Table 2
Selected series reporting primary tumor size of head and neck soft tissue sarcomas according to first author and publication data.

Descriptive characteristics	Kraus 1994 [8]	Willers 1995 [29]	Le 1997 [35]	Barker 2003 [30]	Penel 2004 [31]	Chen 2005 [32]	De Bree 2006 [33]	Huber 2006 [34]	Park 2015 [16]
Number of patients	60	57	65	44	28	39	38	110	122
Mean age (y)	49	55	55	62	46	43	51	66	46
Site (%)									
Scalp	13	28	14	25	10	8	5	72	39
Face	33	30	25	NA	3	33	8		
Neck	15	32	12	NA	38	26	18	5	15
Orbit	5	5	NA	NA	NA	NA	NA	NA	NA
Sino-nasal complex	12	5	26	18	34	26	39	8	28
Oral cavity	22	NA	15	23	3	NA	NA	4	NA
Larynx/pharynx	NA	NA	NA	16	3	NA	30	8	NA
Other	NA	NA	8	18	7	8	NA	4	18
Grade									
Low	42	28	27	45	7	26	29	44	25
Intermediate	NA	53	15	NA	28	NA	26	6	43
High	58	16	58	55	55	74	45	11	18
Tumor size (%)					Mean size 2.7 cm				
<=5 cm	72	55	46	64	NA	67	66	82	74
>5 cm	15	31	54	36	NA	33	34	11	25
No data	13	14	NA	NA	NA	NA	NA	7	NA

of tumors <=5 cm (55% and 64%, respectively) [29,30]. The majority of other series show similar results (Table 2) [16,31–35].

The 5 cm cut-off introduced in the 1st TNM staging system for all soft tissue sarcomas was largely based on a report by Suit et al. [10,11]. In this study of 100 patients, tumors were categorized as "small" if <=5 cm and "large" if >5 cm. Recurrence rates were 8% versus 18% for small and large tumors, respectively, although this difference did not reach statistical significance. Comparing sub-categories of the large tumors, there was no difference between tumors >5 cm and <10 cm versus those >=10 cm. Disease-free survival was influenced by tumor size and grade: for small tumors (<=5 cm), disease-free survival for grades 1, 2, and 3 tumors was 92%, 69%, and 30%, respectively, whereas for large tumors (>5 cm) disease-free survival was 72%, 33%, and 7%, for grades 1, 2, and 3 tumors, respectively. Notably, this series that formed the basis of the 1st AJCC TNM edition, only examined patients with sarcomas of the extremities or torso and included no head and neck sarcoma cases.

4. Grading of soft tissue sarcoma

Histologic grade has consistently been found to be an independent predictor of distant metastases and prognosis for cancer specific mortality [36–38]. The effect is so prominent that it was included in the 1st edition of the AJCC TNM for soft tissue sarcomas in 1977, despite being better suited as a prognostic factor and not as an anatomical staging factor [1,10]. Moreover, a report from the Mayo Clinic that comprised one of the references in the original 1st edition AJCC Cancer Staging Manual [10], described 199 patients treated between 1910 and 1968, and indicated that only grade had a significant association with survival, while tumor size did not [39].

Several grading systems exist, but the most widely used, and the one recommended by the College of American Pathologists and the UICC/AJCC today, is the three-tiered system of the French Federation of Cancer Centres/Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC), instead of the traditional 4 grade system [6,40]. The strengths of the French system are its relative ease of use and wide adoption, as well as balance of components, which include differentiation score (scored from 1 to 3), mitoses (scored from 1 to 3), and necrosis (scored from 0 to 2). The grade is then assigned as follows: GX – grade cannot be assessed; G1 – total score = 2–3; G2 – total score = 4–5; or G3 – total score = 6–8. In a 2006 review, Deyrup and Weiss highlight several limitations for grading of STS [41]. In particular, grade does not always provide added value beyond the histologic subtype, such as well-differentiated liposarcoma. Additionally, grade is not always associated with outcome, such as for malignant peripheral nerve sheath tumors [41]. Lastly, not all histologies have traditionally been considered "gradable", such as epitheliod and clear cell sarcomas.

5. Lymph node metastases

The presence of regional lymph node metastases in patients presenting with STS of the head and neck is relatively rare and estimated to be no more than 10% [17,33,42,43]. While the prognostic significance of lymph node metastases is well established in rhabdomyosarcoma, its significance in other soft tissue sarcomas is less clear [44].

De Bree et al reported their experience treating STSHN between 1983 and 2004. Forty-one patients were reviewed and multivariate analysis showed lymph node metastases to be one of the most important prognostic variables, along with surgical margin status [33]. In contrast, Smith et al evaluated the Surveillance, Epidemiology, and End Results (SEER) database to identify cases of STS categorized based on head and neck versus non-head and neck location [43]. Only cases with surgical and pathologic nodal staging were included. While node-positivity was significantly associated with disease-specific mortality in the non-head and neck group ($p < 0.001$), disease specific mortality was similar irrespective of nodal status in the head and neck group ($p = 0.59$). However, the sample size of the head and neck group was only 25 out of the total 183 cases, and such comparisons are fraught with known limitations of small retrospective reviews as well as limitations of SEER database analysis such as unrecorded variables and incomplete treatment data.

6. Other prognostic factors

The TNM system provides a robust backbone for the staging of cancer, but other prognostic factors are also important for prognostication and should be part of any prognostic model, thereby building on the TNM backbone [1,2]. Surgical margins are an important consideration for local control and multidisciplinary management of STS, although surgical margins do not represent a true baseline variable since surgery must first be undertaken. The ability of radiotherapy to, in essence, "extend the surgical margin" was first demonstrated in the practice changing randomized trial of limb amputation versus limb sparing surgery and adjuvant radiotherapy [45]. This was further solidified in two further randomized trials of adjuvant radiotherapy with conservative surgery, where the addition of adjuvant radiotherapy significantly improved local control [46,47]. A thorough pathologic assessment of surgical margins is our best estimate at predicting risk of residual microscopic disease representing the disease characteristic being targeted by adjuvant radiotherapy. Involved pathologic surgical margins for STS portend inferior local control, which holds equally true for tumors arising in the head and neck [35]. STSHN are unique relative to extremity sarcomas, as local failure is difficult to salvage due to anatomic constraints and can cause death from locally progressive disease [48].

In addition, not all surgical margins have the same impact. There exists a significant difference between a planned, isolated, and small positive surgical margin versus an unplanned positive margin. In extremity STS, we previously reported a blinded study from a prospective database that showed that rates of local recurrence were low at 3.6% (95% CI 0–10.4) if the surgical margin was planned to be positive and kept small, provided adjuvant radiotherapy was delivered [49]; in contrast, unplanned positive margins with potentially significant local contamination, had substantially higher local recurrence rates of 31.6% (95% CI 10.7–52.5). While recognizing that these data originate from experience with extremity sarcomas, there is a rationale to employ similar concepts to head and neck tumors in an effort to spare critical functional or cosmetic structures.

Tran et al evaluated 164 patients with STSHN between 1955 and 1988 and found that local control was 52% in those receiving surgery alone compared to 90% for those receiving multimodality therapy with radiation [50]. Tumors adequately controlled with surgery alone were small, low-grade, and surgically excised with negative margins, whereas other situations warranted adjuvant radiotherapy. Contemporaneously, we had also reported similar rates of local control between STSHN with negative surgical margins and those with microscopically positive margins, but who received adjuvant radiotherapy [48].

Despite the clear prognostic importance of surgical margin status, it is difficult to incorporate margin data from reported series into prognostic models because questions about adjuvant treatments, extent of the surgical margin, and a goal to accept an up-front planned positive margin are crucially important and provide context on how to interpret the margin. These nuances merit

multidisciplinary discussion in the decision algorithm. However, margin status could reasonably be applied in a prognostic system for prediction of outcome for individual patients who have already undergone resection using calculators or nomograms [38,51].

7. Staging system evaluation

The evaluation of the performance of a staging system is a complex task that requires thoughtful attention. Our group originally proposed 4 criteria that a staging system should meet [3,52]:

1. "Hazard consistency" – within a given group of a staging system, the subgroups of TNM combinations that make up the parent group should have similar survival rates.
2. "Hazard discrimination" – different groups should have different survival rates.
3. "Outcome prediction" – the prediction of cure. This was measured in two ways – a) the percent of the variance in survival rates explained by the stage group scheme, allowing censored data to be used for cure prediction, and b) "slope" – the mean probability of cure assigned to those not cured minus the mean probability of cure assigned to those who were cured (in hindsight).
4. "Balance" – to maximize statistical power in each group, the distribution of patients throughout the groups should be balanced.

Subsequently we recommended modifications to augment this process [53]. In the original description, 3-year disease-free survival was used as a surrogate for cure and required non-censored data points; therefore, patients lost to follow-up or those dead from other causes within three years were excluded. Moreover, since staging systems have largely been based on historical data, clinical factors such as treatment and smoking, for example, should be included in the evaluation criteria as they may strongly affect survival. Therefore, in addition to slight modifications of the methods to evaluate hazard consistency and hazard discrimination, outcome prediction can be evaluated by "explained variation" and "likelihood difference", both of which better incorporate censored data and are adjusted for significant clinical variables [54].

An example of a new staging system created using these evaluation criteria is the 8th edition TNM staging system for HPV-related oropharyngeal cancer developed by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) [54]. In this effort, a large, high quality, prospectively collected database was used as a training dataset and data pooled from 6 other institutions served as a validation cohort. Recursive partitioning analysis and adjusted hazard ratios were used to generate hazard ratios for death for every T and N combination; importantly, age, smoking, and treatment were adjusted for in the modeling. The best performing classification was chosen based on evaluation of hazard consistency, hazard discrimination, explained variance, sample size balance, and likelihood difference.

While the ICON-S staging methodology for HPV-related oropharyngeal cancer represents a reality close to ideal, the opposite could be said for STSHN. The rarity of the disease and lack of high quality data renders this approach nearly impossible. However, one of the major strengths of the TNM system has been its applicability and practicality, and it is in this spirit that the updated STSHN TNM staging has been developed.

8. The 8th edition TNM staging of soft tissue sarcomas of the head and neck

In attempts to improve staging of STSHN, the 8th edition proposes a head and neck site-specific categorization [6]. Of note, the 8th edition places greater emphasis on anatomic primary site of the soft tissue sarcoma in general, with separate chapters for extremity and trunk, head and neck, visceral sites, and retroperitoneum, which also infrequently have a primary tumor size <5 cm [6]. The new system aims to address the primary tumor size limitation of the previous staging system by pragmatically employing tumor size cut-offs more commonly found in squamous cell carcinomas of the head and neck. The new system, which uses cut-offs of 2 cm and 4 cm, was proposed arbitrarily and without guidance from the literature since such a classification did not exist due to a paucity of data. This follows the size cut-offs that head and neck specialists are familiar with and their use overcame the problem noted earlier that most cases fall below the traditional 5 cm cut point that has limited relevance in STSHN. In the new system, T1 tumors are those <=2 cm, T2 for >2 cm but <=4 cm, and T3 for >4 cm; T4 tumors are locally advanced tumors defined similarly to squamous cell carcinomas requiring specific identified anatomic involvement that may override the size criteria used for lesser T-categories (Table 3). The grading system to be utilized is the 3 level French system, and was recently incorporated in the UICC/AJCC TNM system, but can be expected to remain an important variable in prognostication and stage groupings; similarly the importance of very extensive lesions (T4 disease) seems intuitive but remains unevaluated for outcome assessment.

Table 3
8th edition of the Tumor, Node, Metastases (TNM) staging system for soft tissue sarcomas of the head and neck [6].

T Category		
	T1	<=2 cm
	T2	>2 but <=4 cm
	T3	>4 cm
	T4	Invasion of adjoining structures
	T4a	Invasion of the orbit, skull base, dura, central compartment viscera, pterygoid muscles, or facial skeletal involvement
	T4b	Invasion of brain parenchyma, involvement of the central nervous system via perineual spread, invasion of prevertebral muscle, or carotid artery encasement
N Category		
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
M Category		
	M0	No distant Metastasis
	M1	Distant metastasis

The importance of the stated size criteria, the impact of the traditional 4 grade system, and the adverse impact of lymph node involvement were examined in June 2015 using the National Cancer Data Base (NCDB) for the period 1995–2013, excluding angiosarcoma, rhabdomyosarcoma of embryonal and alveolar subtypes, and dermatofibrosarcoma protuberans. The 8th edition size cut-offs, evaluating the categorized continuous variable size data captured in the NCDB, performed well with respect to survival, as did regional lymph node status and the 4 grade system (personal communication with Dr. Snehal Patel). However, as yet no stage grouping based on outcome is possible, as this requires application of the more commonly used French 3 grade system, and the very extensive lesions (to be categorised as T4 disease) remain without description in the NCDB. The supporting data from the NCDB prompted a recommendation from the AJCC expert committee on soft tissue sarcoma, with support from the head and neck expert committee, to introduce the new classification.

9. Conclusion

STSHN comprise an even rarer subgroup of an already uncommon disease. This entity represents an "orphaned disease" with reported series being overwhelmingly retrospective and small.

Much of the treatment of STSHN is based on extrapolation from extremity sarcomas, expert opinion, and institutional protocols. Our literature review of all publications relating to STSHN, with exclusion of STS histologies not included in the AJCC 8th edition, yielded four prospective studies and one randomized trial [8,27,55–57]. The randomized trial included patients with sarcomas of the head, neck, breast, and trunk (excluding retroperitoneal sarcomas) [55]. While a commendable effort, only 31 patients were randomized and of these, 22 had sarcoma of the trunk. While prospectively collected data provides a higher quality of evidence than retrospective series, the numerous histologies included and the variable inclusion criteria in these series make it extremely difficult to abstract guiding principles for stage classification. A search of ClinicalTrial.gov yielded only a single trial currently recruiting patients where inclusion criteria included STSHN [58]. However this trial, evaluating the benefit of concurrent pazopanib and radiotherapy for non-metastatic sarcoma patients, also includes patients with sarcomas of the extremity, trunk, and chest wall, and has a targeted accrual of 50 patients; there will likely be very few STSHN patients accrued.

The new TNM staging system for STSHN is a useful change following 40 years of a site agnostic soft tissue sarcoma staging system. The new system was not born from data, but rather from its dearth. Important prognostic information, such as tumor histology and distance to margins, is still absent from the staging system and would pose an extreme challenge to create independent prognostic groups, but the 8th edition changes represents progress none-theless. Whether the new system adds prognostic value through stage groupings and whether the optimal cut-offs for primary tumor size were chosen, as well as the contribution of the new T-category for locally advanced disease (i.e. T4 disease) remains to be determined. The new system also provides a framework in which upcoming data can be reported and highlights the need for specific consideration for anatomical site of origin. Ultimately, more high quality data are needed to best prognosticate and guide treatment for patients with STSHN, and to create the foundation of data required for future staging advancements.

As we look to the future, the UICC and AJCC have advocated for the development of sound prognostic classifications that would allow inclusion of all relevant factors in a manner sensitive to the state of knowledge and availability of new treatments [2]. These need to be developed on a backbone of the anatomical TNM stage which probably remains the strongest and most enduring prognostic factor, but which now needs to be validated for STSHN. Inevitably, such models would need to consider important statistical methods such as competing risk assessment, sensitivity analysis, and validation. They should also respond to the needs of personalized approaches involving new technologies, such as machine learning, artificial intelligence, and neural networks for large data sets that can be used to predict outcomes in individual cancer patients as more genomic, biological, and radiomic data become available.

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Conflict of interest

None.

Declarations of interest

None.

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