JOURNAL OF PLASTIC SURGERY AND HAND SURGERY
2021, VOL. 55, NO. 2, 96–104
https://doi.org/10.1080/2000656X.2020.1838914

REVIEW ARTICLE

# Epithelioid sarcoma of the hand: a wolf in sheep's clothing

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**ABSTRACT**

Epithelioid sarcoma (ES) of the hand is a rare, aggressive cutaneous malignancy with high rates of recurrence, metastases and mortality. With an incidence rate of 0.4 cases/y per one million population, which compromise for approximately 1–1.4% of all soft tissue sarcoma, ES accounts for 10% of soft tissues sarcomas of the hand and foot. Its aggressiveness and propensity to spread and metastases without being noticed, makes it unique and potentially lethal. Missed or delayed diagnosis are often encountered as this tumor can mimic variety of different entities and due to the infrequent nature of this lesion, treatment options are still controversial. The authors provide systemic review of the current literature on epidemiology, etiology, pathogenesis, management and outcomes of this disease as well as a case presentation and a proposed treatment algorithm. The choice of treatment option depends on disease characteristics, staging at presentation, regional lymph node involvement, comorbidities and performance status of the patient. Emphasis on a multidisciplinary coordinated care is crucial as early diagnosis and treatment can decrease morbidity and mortality rates.

**ARTICLE HISTORY**
Received 11 June 2020
Revised 27 September 2020
Accepted 14 October 2020

**KEYWORDS**
Sarcoma; epithelioid; hand; soft tissue

## Introduction

With tens of different types and subtypes, soft tissue sarcomas (STS), it compromises only 1% of all malignancies [1]. STS often involves the extremities. However, they are less common than malignancies of the overlying skin [2].

First described by Enzinger [3] in 1970, epithelioid sarcoma (ES) is a unique entity. It is slow growing but high-grade-STS and is more common in young adults. ES is a fairly rare malignancy, with an incidence rate of 0.03 cases per 100,000 people [4], which compromise for approximately 1–1.4% of all STS [5]. ES accounts for 10% of soft tissues sarcomas of the hand and foot [6] and more than 15% of all tumors seen in the hand [7]. It is one of the most common STS in the hand [2,8–10] and the upper limb [11]. These tumors are more commonly found distally with a decreasing distribution as you go proximally. This distinctive malignancy is a high-grade tumor with a propensity to progress, both locally and distally throughout the lymphatic system.

Traditionally, ES is divided in two subtypes: The classic form (distal-type) and the proximal-type. The classic form is seen more in teenagers and young adults. The proximal-type ES is a rarer form, which mainly affects adults and is often presented as a more aggressive and mainly affects adults [12].

Immunohistochemical studies can help in ES diagnosis. Most importantly INI1 expression as ES is one of the several tumors that lack expression of the SMARCB1/INI1 [13]. However, ES has a unique with a combination of positive expression of EMA, vimentin and CD34 and negative expression of other markers as well such S-100, neurofilament protein, carcinoembryonic antigen, factor VIII-related Antigen and CD-311 [14,15].

Despite its progressive nature and tendency to recur, ES is frequently misdiagnosed as a benign process. Because of its ability to mimic other lesions, both macroscopically and under the eyes of experience pathologists. In his original series of 62 cases, Enzinger counted the commonly misdiagnoses [3]. Sixteen of the cases were initially diagnosed granulomatous inflammation, followed by nodular tenosynovitis, nodular fasciitis, chronic ulcers, fibroma/fibromatosis and reactive fibrosis. Only three cases were diagnosed as histiocytoma/histiocytosis.

Like other STS, ES is associated with high mortality rate. After following ES cases between the years 2009 and 2015, the American Cancer Society published a 5-year relative survival rate for localized, regional and distant disease of 81%, 57% and 16%, respectively [16].

Therefore, it is important to raise clinician's awareness and assemble a multidisciplinary panel as early as possible to ensure high quality coordinated management. Treatment options and prognosis depend on patient's and disease's characteristics, staging at presentation, regional lymph node involvement and presence of metastases.

We present an up to date literature review and a treatment algorithm (Figure 4) for ES of hand as well as a case presentation that was misdiagnosed twice for benign histiocytoma before achieving a final diagnosis.

We believe our work on this rare yet fatal tumor is crucial, as early diagnosis and treatment can decrease morbidity and mortality rates.

## Case presentation

A 36-year-old Caucasian male was referred to our hand surgery clinic due to reoccurring palpable mass on his dominant right-

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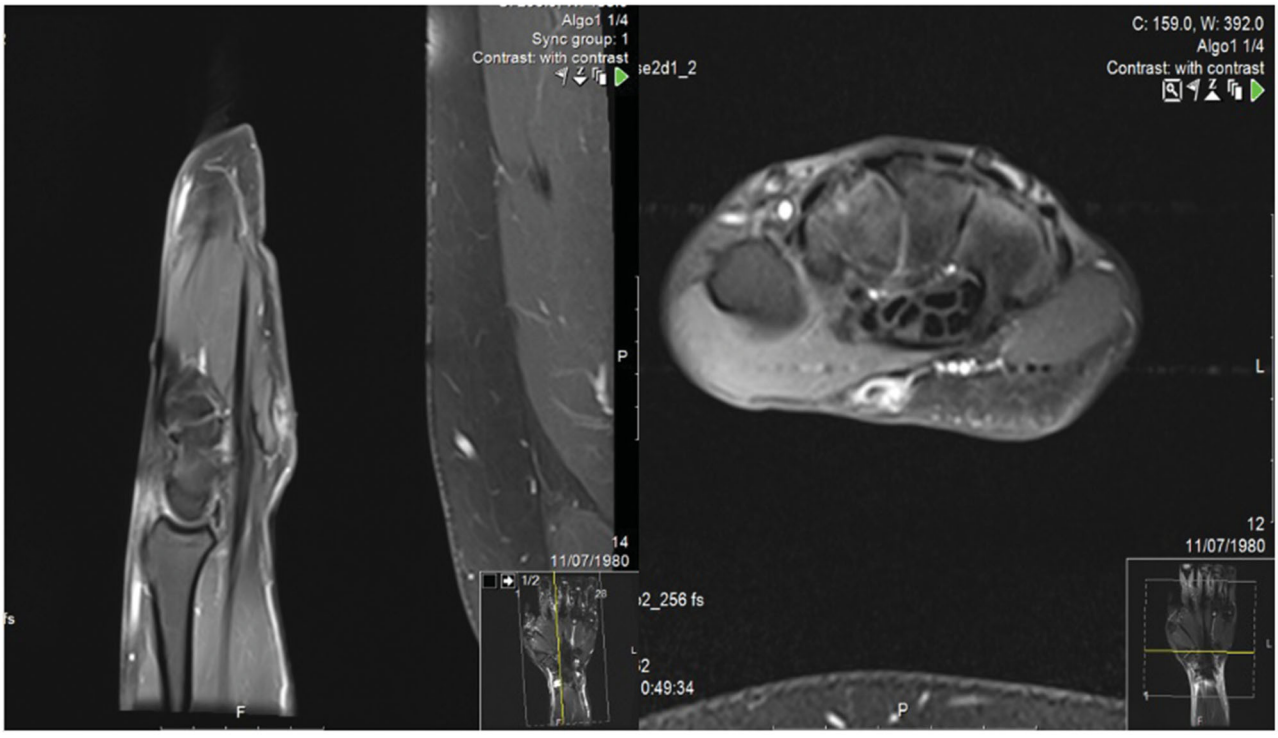


Figure 1. Sagittal (left) and axial T1-weighted MR images with contrast, presenting an epithelioid sarcoma (ES) lesion confined to the thenar region of the hand.

hand thenar eminence which already underwent two surgeries for excision in a different hospital.

His medical history was positive for hypothyroidism controlled by Levothyroxine treatment. No history of smoking or excessive alcohol consumption. No family Hx of any malignancy.

The patient reported a 1 $cm^2$ non-tender palpable mass on his right-hand thenar eminence, 5 years before his first assessment.

Due to the benign appearance of the lesion, ultrasound examination of the soft tissues was made and identified avascular soft tissue lump without and definite diagnosis.

Differential diagnoses of Keloid and Neuroma were suggested.

After 3 months, with no progression of the lesion's size, the patient had the mass surgically removed under general anesthesia in an intralesional approach. Surgery report noted the dermal and subdermal location of the lesion, without penetration of the thenar sheath. The patient did not attend his schedule follow-up meetings at the hospital's clinics, but rather went to a follow-up examination at his community clinic. One year after his surgery, the patient noticed recurrence of the mass at the same location. Follow this finding, a second surgery was performed. In the second surgery, the macroscopic description of golden localized mass suggested a diagnosis of Giant Cell Tumor. The mass was locally resected and was sent to a pathologic examination. The pathologic report was similar for both surgeries, stating that the morphological features consistent with benign fibrohistiocytic tumor.

This diagnosis was based on a cellular proliferation which involved the dermis and the subcutis and composed of fascicles of spindle cells with storiform pattern of growth mixed with CD68 positive, large polygonal and rounded histiocytic cells. Touton-type multinucleated giant cells were also seen, as well as scattered inflammatory cells, particularly lymphocytes and few plasma cells. Mitotic rate was 0–1/10 HPF. Immunohistochemical tests found Ki67 positive cells, mainly inflammatory cells as well as S100 positive staining in scattered dendritic cells.

The patient was not adherent to the follow-up schedule. Two years after his second surgery he turned to his GP due to surgical site pain and was referred to a hand specialist who detected a recurrence of the mass at the same location. MRI exam of the hand identify an $8 \times 5$ mm subdermal oval mass, with high signal intensity after administration of IV Gadolinium (Figure 1). Due to the differential diagnoses of primary STS or metastasis, a chest CT was done without any pathology to mention. The patient underwent a third surgical intervention to remove the recurrent lesion. Surgical approach included wide surgical resection with healthy margins. Histopathologic findings suggested a reticulohistiocytoma. However, the high mitotic activity precluded this diagnosis. After repeated assessments of the specimens and multiple discussions, it was concluded that the samples showed similar features that are undoubtedly those of a malignant lesion. Due to the lack of specific immunophenotyped findings, the tumor was labeled as a high grade undifferentiated malignant epithelioid and spindle cell neoplasm. Despite lacking a clear evidence of a specific line of differentiation, the fact that the lesion has recurred repeatedly over five-year period, in the absence of any primary tumor elsewhere, favored this being a primary mesenchymal neoplasm, rather than some unusual metastasis from another site.

Due to this exceptional case, a sarcoma multidisciplinary team was gathered including representatives of the orthopaedic hand surgery unit, radiology department, plastic surgery department, oncology and an onco-orthopaedic specialist. The joint decision was to address this subdermal lesion as a high grade epithelioid STS. The patient underwent a PET-CT scan, which did not show any nodal involvement, after which, a surgical plan was conducted. Treatment included wide resection (over 2 cm margins), followed by a reconstruction procedure with proximally based

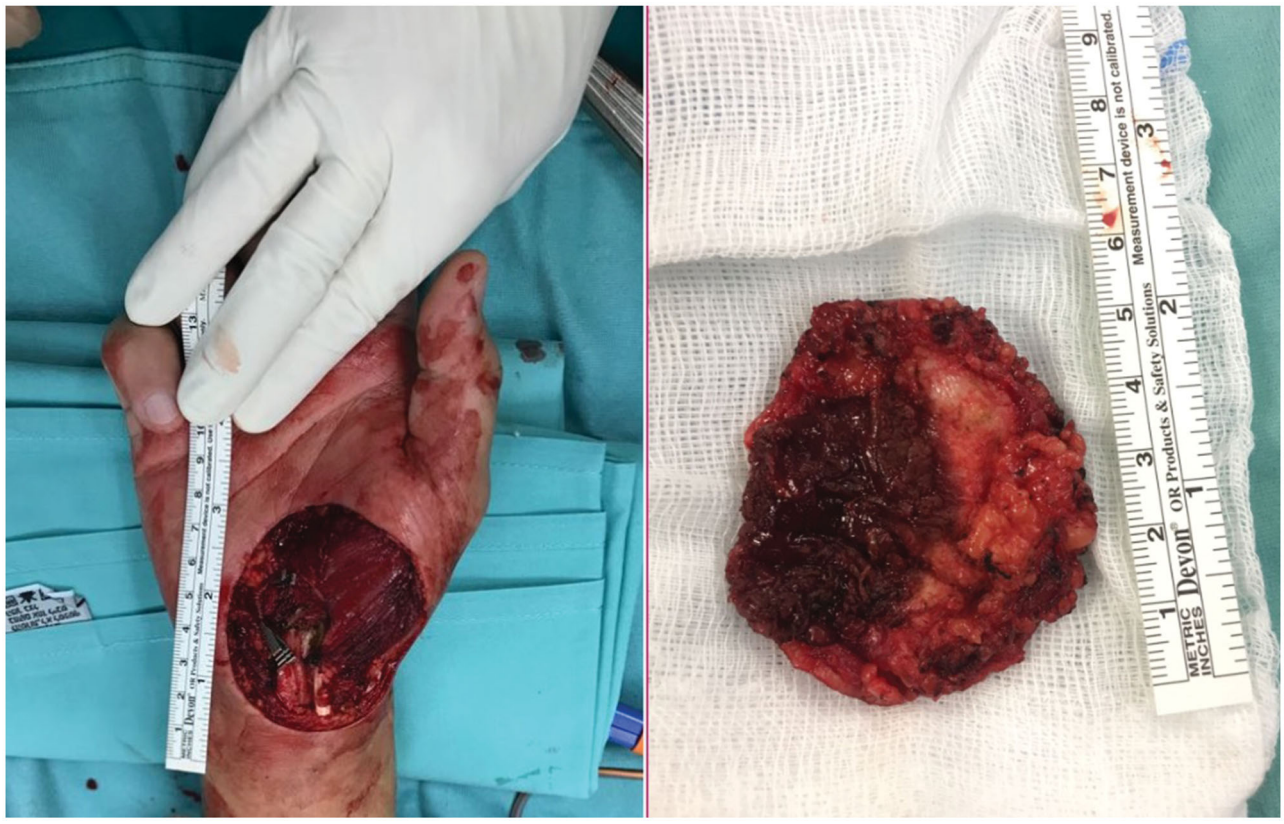


Figure 2. Intraoperative image of 5 × 4 cm ES resection from the thenar region of the hand. Tumor location was superficial to the abductor pollicis brevis and the transverse carpal ligament. Partial resection of the above structures was made in order to decrease chance of reoccurrence.

thenar flap (flexor pollicis brevis and abductor pollicis brevis) and split thickness skin graft (Hip) placed on a MatriDerm® (Figures 2 and 3). A local adjuvant radiotherapy treatment was given post-op. Final pathology report concluded that the specimen's characteristics are of epithelioid STS. The patient is disease free, four years after the day of resection, with an incorporated skin graft.

## Discussion

ES is a rare high-grade STS with a propensity to slowly progress and spread with lung and regional lymph nodes the most common sites for metastases [17]. This tumor is more common in the extremities and can involve the skin as well as the more deep tissues including fascial planes, aponeuroses and tendon sheaths [18]. Fingers are the most common primary site followed by a decreasing prevalence proximally along the extremities.

This tumor is more commonly found in young adult males, usually in the third or fourth decade of life, however, no age group is immune with some reports of ES in the older and pediatric population [19].

### *Presentation*

A firm painless mass is the presenting symptom in all reported case series. Other symptoms may include signs of nerve compression (i.e. ulnar nerve compression which can present with numbness of the respective distribution) or clinical picture of chronic ulcer/infection. A prior local trauma was also described by patients before lump diagnosis [2,20]. Due to the scarce symptoms, patients tend to ignore the slow growing mass and avoid medical assessment, which often result in late diagnosis, sometimes

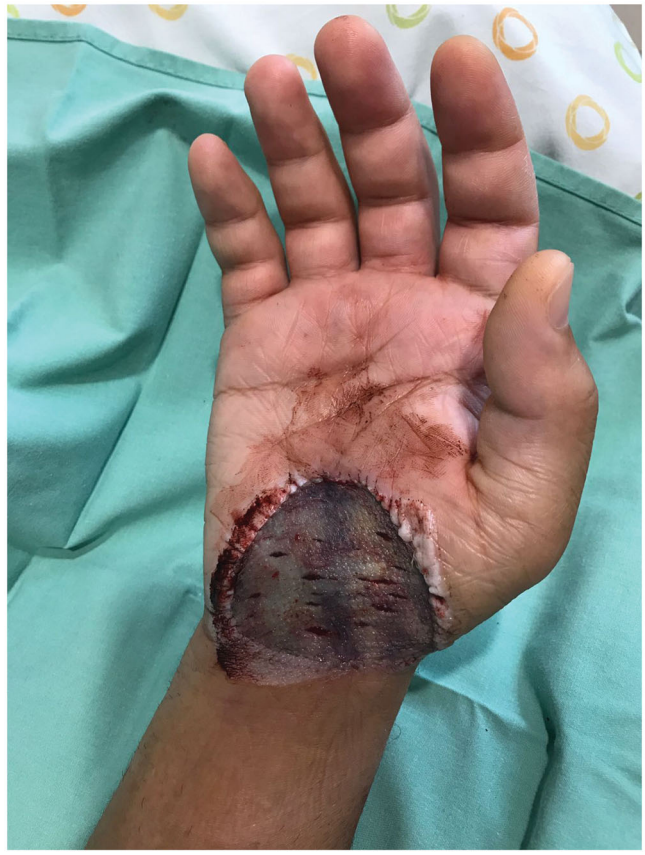

Figure 3. Status post ES resection involving the thenar region of the hand. Reconstruction was made using a proximally based thenar flap (flexor pollicis brevis and abductor pollicis brevis) and split thickness skin graft (Hip) placed on a MatriDerm®.

Writers' recommendations: When approaching a patient with a suspected lesion, a thoroughly assessment of the medical history (including family history of malignancies) and symptoms must be held. These must include past surgeries and/or traumatic events, red flags such as fever, weight loss or night sweats and current history of the lesion. Physical examination should include focal assessment of the suspected lesion, neurovascular assessment of the affected limb for potentially mass related symptoms such as nerve compression and palpation of regional lymph nodes.

up to several years. However, based on the current literature, the duration of symptoms does not seem to affect overall survival [2].

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### The role of imaging studies

In the absence of distinctive anamnestic features, characteristic physical examination findings or laboratory tests, diagnostic imaging serves not only as the most productive diagnostic tool but also as a major instrument for staging and treatment planning [21]. While X-ray imaging plays an important role in bone malignancies and aggressive penetrating processes of some sarcomas [22], its role in the slowly progressive ES is limited. X-ray imaging might reveal intralesional calcification and involvement of the adjacent bone when present. Ultrasonography (US) is an inexpensive and available modality which is often used to assess new palpable masses. Even though it can help identify some benign (i.e. ganglion cyst) or aggressive processes (i.e. rapidly growing masses, poorly defined margins or hypervascularity when doppler is used), in the case of ES which lacks specific morphological features, it might misdirect the work-up. Nevertheless, if a needle biopsy is recommended it can help as a guiding tool [22].

CT is an important diagnostic tool with an ability to identify malignant lesion. It helps assessing lesions which are too deep for US evaluation (it is the modality of choice for initial pelvic or intrathoracic tumor evaluation) [22]. However, with the improvements in quality and accessibility of the MRI, its role in soft-tissue sarcomas of the extremities is only secondary. Nevertheless, in the case of a suspected ES, it still holds an important role for lung involvement, and is part of the initial work-up protocol.

Writers' recommendations: Adequate imaging of primary site is indicated for all suspected lesions. We recommend a plain X-Ray and cross-sectional imaging (MRI with and without contrast ± CT with contrast). Imaging studies are crucial for lesion evaluation, including its size and its contiguity to nearby visceral structures and neurovascular landmarks.

Magnetic resonance imaging (MRI) is the method of choice when radiological assessing soft tissue mass is needed. MRI can identify subtle changes which suggest expansion or invasion of a mass [22,23]. The utility of MRI is even greater when assessing recurrent lesions. In their case series, Herr et al. [2] reported the positive predictive value of MRI In patients who underwent prior lesion resection was 100%, with a negative predictive value of 83%. Even though their series only counted 28 patients, to this day it is one of the largest published reports focusing on hand ES. Nevertheless, its magnetic resonance appearance is often indeterminate and necessitates further assessment.

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### Histopathology

Definitive diagnosis is made by histopathological evaluation and must include both immunohistochemical and immunocytochemical confirmation [24]. Even though tissue sampling can be made by either fine-needle aspiration (FNA) [25] or by tumor resection, and despite favorable cost-effectiveness and high sensitivity in sarcoma diagnosis [26], in the case of ES diagnosis is more challenging as it can mimic many other pathologies, both benign and malignant. Tissue sampling can yield different features if the sample is taken from the margins or center of the lesion. Compared to FNA, excision can yield more tissue and enable more thoroughly assessment of the lesion. For this reason, and for the potentially mass-related symptoms, we advise using full thickness core/excision biopsy as the mainstay of sampling method. Macroscopically, its appearance is indeterminate as well. ES nodules are often well circumscribed but can also present with infiltrating borders. While some may suggest that the nature of histologic pattern of this tumor is biphasic, unlike Synovial sarcoma, ES are not truly biphasic by nature as the transition from the spindle cells to the polygonal is continuous [15]. Their color is commonly described on the spectrum between white, tan and golden. Histologically, their classical appearance consists of nodules which are formed by epithelial and spindle cells. Central necrosis within the nodule is also a common finding (Figure 5). Nevertheless, this nodular pattern can vary significantly and can mimic the features of other tumors such as can mimic other processes such as benign granulomatous or synovial sarcoma [3].

Writers' recommendations: For tissue sampling, we recommend a planned core needle biopsy after adequate evaluation. The biopsy should respect the future resection axis, with great care to hemostasis and minimal soft tissue dissection. The biopsy should establish grading, histologic subtype and give us the initial prognostic factors for the patient.

Several attempts were made to identify some cytogenetic features have been made. These features include alteration in different genes such as 8q, 18q11 and 22q11 [17]. However, no conclusive and significant statements were made to this date.

Immunohistochemical studies have shown that ES cells typically positive for vimentin, cytokeratins (low molecular weight cytokeratin\CAM5.2 and CK7), CD34, Epithelial membrane antigen (EMA) [27]. Other positive findings have also been reported (i.e. positive CA125) but maybe of more importance is the absence of

nuclear staining for SMARCB1/INI1 in ES cells, which represent the inactivation of this tumor suppressor gene [28] and is found in 90% of the cases [29]. Having said that, despite its unique presentation of both epithelial and mesenchymal markers, the histogenesis of ES is still unknown [17,30]. On many occasions, however, especially when the first impression is that of a benign process, this panel of tests will not be held, and this entity would only be suggested when the mass reappears. Due to its unique nature, some advocate the use of patient-derived primary cultures in attempt to better understand the biology and natural history of this often-misdiagnosed tumor [31,32].

Writers' recommendations: To complete the staging, systemic imaging should take place in the form of chest CT without contrast. Care givers should consider abdominal/pelvic CT as well, in question for other primary lesion and or associated lymph nodes. PET/CT scan may be of hand in staging, prognostication and grading. In the case of suspected or proven malignancy or recurrence of a lesion, physical and radiological lymph node evaluation is advised. Regional lymph node FNA or Sentinel lymph node biopsy should become part of the preoperative evaluation and staging procedure for patients with ES [25].

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## Treatment

Writers' intake: Gamboa et al. [28] reviewed 909 patients from the US sarcoma collaborative data who underwent resection of high grade soft-tissue sarcoma. They showed that postsurgical lung surveillance with chest X-ray did not result in worse overall surveillance in comparison to a chest CT scan. Nevertheless, further studies are needed done before unequivocal recommendations are given. We advise that when it comes to follow-up assessment of chest involvement, the radiological modality of choice should be decided by the multidisciplinary team based on experience of the radiologist and oncologist [35].

Due to high recurrence rate, late diagnosis with lymph nodes involvement and metastases, ES treatment is often challenging.

Despite some specific characteristics, for practical reasons, when deciding on treatment protocol, ES should be addressed as unclassified STS of the extremities. We present our management algorithm (Figure 4) which is based on the National Comprehensive Cancer Network's (NCCN) STS clinical guidelines (Version 2.2018) [33] the latest literature and our clinical experience. This protocol is based primarily on the tumor staging (AJCC 8th edition [34]).

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The second most important factor is the possibility for lesion resection while sustaining the patient's functional status. The latter is especially important for treatment of hand sarcomas.

### Stage I disease

The mainstay of treatment is wide resection followed by margins involvement evaluation. We advise surgical margins to be at least 2 cm and an intact fascial plane.

Failure to obtain clean margins in stage I disease necessitates further intervention by either re-resection or adjuvant radiotherapy course. After achieving healthy margins for stage I disease, follow-up examinations are routinely made with history and physical examination every 3 to 6 months for 2 to 3 years and then annually. Postoperative MRI with and without contrast and/or CT with contrast of the primary tumor site is recommended based on estimated risk of locoregional recurrence. Chest imaging is recommended every 6 to 12 months.

Writers' intake: For stages II, III and IV disease, follow-up include history and physical examination, imaging of the chest and other known areas of metastasis every 2 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually. Postoperative MRI with and without contrast or CT with contrast of the primary tumor site should take place.

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### Stages II and III disease

The first question should be our capability to obtain oncologically appropriate margins and the second question is what would be the functional impact of wide resection. This in turn can help us to decide whether to use neoadjuvant therapy (by either radiotherapy, chemotherapy or chemoradiation) or not. After appropriate treatment which enables tumor resection with acceptable margins, stage III tumors or stage II tumor that underwent preoperative neoadjuvant treatment, should get postoperative adjuvant treatment which should be decided by sarcoma specialists.

Cases of stages II and III tumors in which appropriate margins were not obtained despite neoadjuvant therapy, should receive an adjuvant treatment, followed by either re-operation, recurrent follow-up examination if asymptomatic or amputation. Palliative surgery should also be considered. Multidisciplinary panel should guide each and every step. Treatment decision should be done by the patient after understanding all the circumstances and effect of the chosen method.

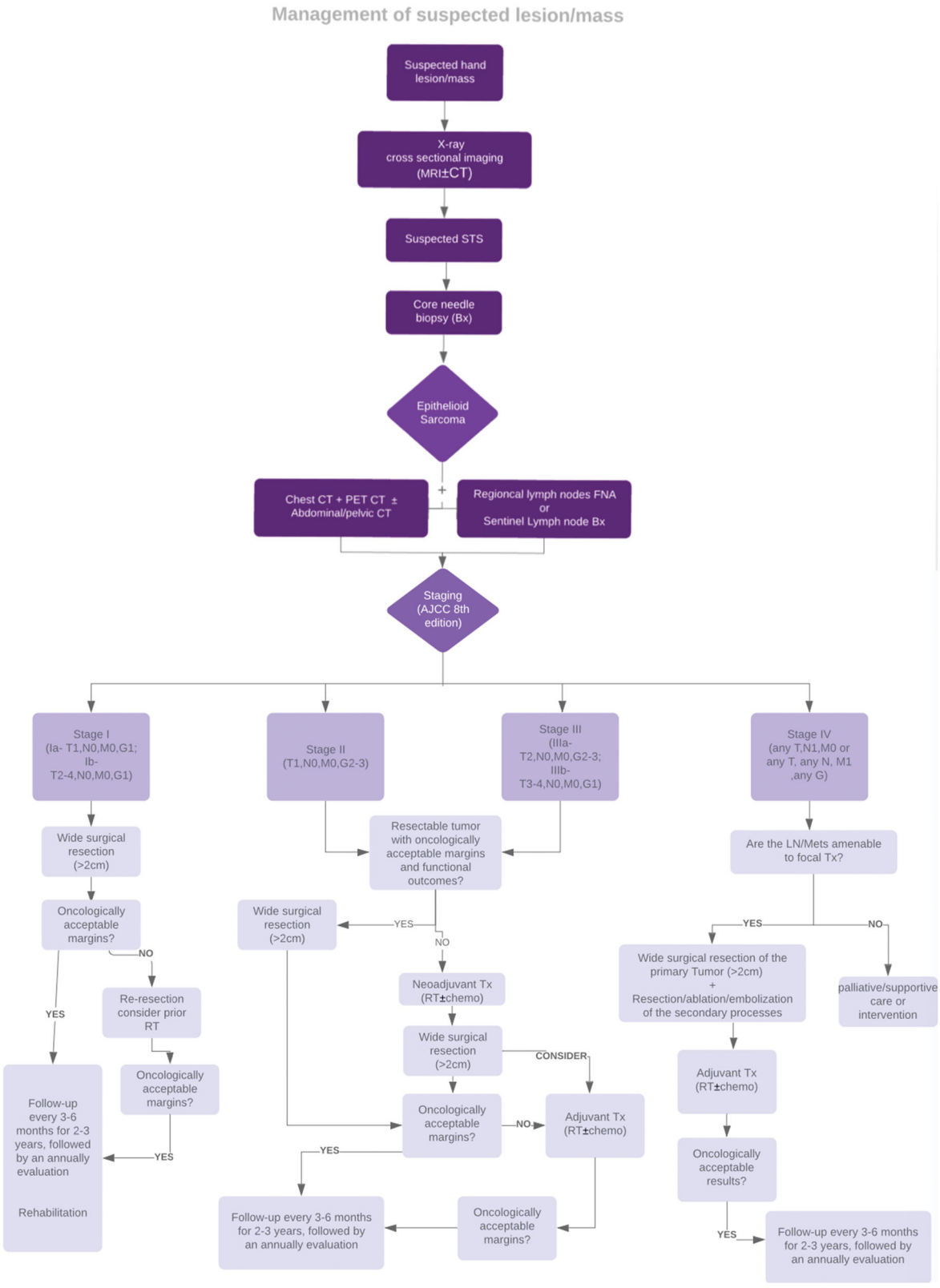


Figure 4. Our proposed treatment algorithm for ES.

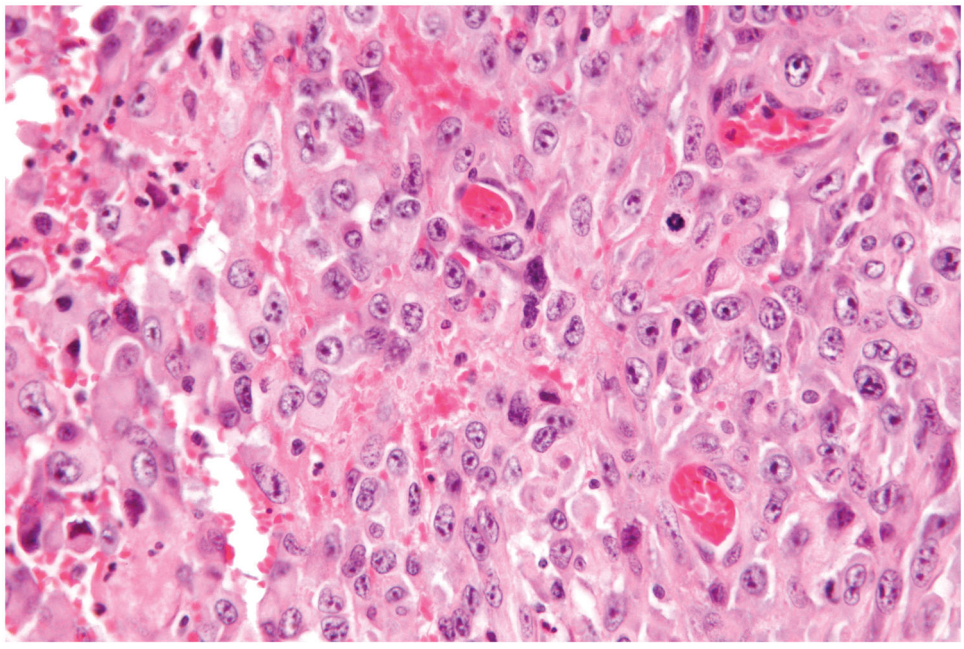

Figure 5. H&E Staining of ES. Epithelioid morphology and spindle morphology (predominant pattern dependent on location), +/– prominent nucleolus, zonal necrosis and irregular borders. By the courtesy of Wikimedia Commons (https://upload.wikimedia.org/wikipedia/commons/6/6d/Epithelioid_sarcoma_-_very_high_mag.jpg).

### *Stage IV disease*

When diagnosing stage IV disease, the main question whether the lymph nodes involvement or metastases are amenable to focal treatment. If so, this could be done by either surgical intervention (resection, ablation, embolization, etc.) ± adjuvant/neoadjuvant therapy. If not, palliative supportive treatment is advised. ES is considered moderately sensitive to chemotherapy and extrapulmonary metastases can respond to systemic treatment [36]. Jones et al. reported satisfactory results in patients who received palliative systemic chemotherapy [14]. As stated earlier, local recurrence is one of ES most characteristic features. Where recurrence is witnessed, care givers should follow the same protocol. However, in the case of recurrence, we advise thorough work-up and challenging the staging as this malignancy can be mischievous and metastases might be missed. Radiotherapy was showed to be effective in controlling local recurrence and limited metastases [36].

Writers' intake: For stages II, III and IV disease, follow-up include history and physical examination, imaging of the chest and other known areas of metastasis every 2 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually. Postoperative MRI with and without contrast or CT with contrast of the primary tumor site should take place.

While some evidence of moderate-positive results for anthracycline-based and gemcitabine-based chemotherapy regimens [37] or Tazemetostat which was found beneficial in cases with SMARCB1/INI1 deletion [29], surgical resection remains the mainstay of treatment [30]. Removal of the tumor is recommended by either radical excision as limb salvage procedures or by limb amputation. Even after an appropriate surgical resection, ES tend to recur, both locally and distally [38]. Recurrence is often accompanied by multiple nodules or multifocal infiltration and spread. Pre-operative or postoperative Radiotherapy showed to benefit patients in combination with more conservative surgery [18,39]. Limb amputation is generally reserved for refractory cases with multiple modules, in order to achieve control over the malignant process. Lymph node involvement is associated with worse prognosis. However, it was previously suggested that the high rate of metastases in these cases represent a stage in dissemination of the tumor rather than a truly local or regional involvement [39]. With this in mind, in the case of lymph node involvement with no evidence of metastases, therapeutic resection is indicated. Due to the radical surgical options, reconstructive surgeries are usually part of the treatment and some consideration must be taken into account when planning the resection.

### *Prognosis*

Jawad et al. assessed the outcomes and prognosis of 441 cases and found that at 5 and 10 years, survival was 68% and 61%, respectively [5]. Several factors were found to affect the prognosis of ES. Tumor size of over 5 cm was found to be significantly associated with distant failure and low overall survival, due to which effective systemic therapy is advised for patients with larger tumors [39]. Lymph node involvement is associated with less favorable prognosis [40] while localized mass, as well as more peripheral tumors have shown more favorable prognosis. Younger age (<16 years) and operability of the tumor were also found to independently predict survival [5]. Some reports noted that females were diagnosed in a younger age and had better outcomes [2]. Jawad et al. however, refuted any gender effect [5]. While both distal metastases and nodal involvement are considered to be bad prognostic factors [5], resection of nodal metastasis is still a matter of debate as it has shown to have low impact on patient's survival [41].

## Conclusion

ES is a rare malignancy of the soft tissues with a potential poor prognosis. Its aggressiveness and propensity to spread and metastases without being noticed, makes it unique and potentially lethal. Missed or delayed diagnosis is often encountered as this tumor can mimic variety of different entities. In light of our

observations, it is clear that the most crucial step of treatment is early diagnosis. We advise a treatment algorithm based on the latest literature and our experience. We believe that this algorithm, led by an experienced multidisciplinary team, will help achieving earlier diagnosis and in turn, adequate treatment and follow-up that will potentially decrease morbidity and mortality rates.

## Informed consent

The patient gave his informed consent after receiving all the information regarding this publication. No identifiers which could reveal the patient's identity were included.

## Disclosure statement

All authors declare that they have no conflict of interest relevant to this case or paper. Other disclosures are provided on the disclosure form.

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