

# Distal and proximal epithelioid sarcoma — differences in diagnosis and similarities in treatment

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## Abstract

Epithelioid sarcoma (ES) comprises two subtypes, distal and proximal. Initially, the distinction between these variants was based on tumor location, but subsequent research highlighted numerous functional differences between them. Proximal ES is distinguished by the molecular deletion of INI1, while classic ES is characterized by retained dysfunctional INI1 expression. Classic ES features elevated expression of GLI3, FYN, and CXCL12, along with overactive Notch/Hedgehog pathways and class 1 human leukocyte antigens (HLA). In contrast, proximal ES demonstrates MYC overexpression and upregulation of genes associated with the cell cycle, chromatin metabolism, and protein synthesis. The differences in clinical presentation underscore the necessity for tailored treatment approaches for each ES subtype. New therapeutic strategies are crucial, especially for the aggressive proximal variant. Tazemetostat, an oral selective inhibitor of the histone methyltransferase enhancer of zeste homolog 2 (EZH2), has recently gained FDA approval as a first-line treatment for ES patients.

**Keywords:** sarcoma, epithelioid, INI, surgery, chemotherapy, tazemetostat

## Introduction

Epithelioid sarcoma (ES) is a malignant epithelioid soft tissue tumor of yet undefined etiology. It was first reported by Laskowski in 1961 [1] and then described and named by Enzinger in 1970 [2]. Epithelioid sarcoma is rare with 0.02–0.05 cases per 100 000 people. The reported incidences of epithelioid sarcoma are collected, among others, in the Surveillance, Epidemiology, and End Results (SEER) database supported by the National Cancer Institute of the United States

and in the RARECAREnet database in Europe. The RARECAREnet collection gathers data on cancer diagnosed in patients in 27 countries of the European Union. Collected data on ES age-adjusted incidence rates differ in the United States (0.05/100 000) and in the European Union (0.03/100 000) [3].

Epithelioid sarcoma often resembles benign entities in histopathology and therefore initial misdiagnosis is common. Epithelioid sarcoma has high recurrence and metastasis rates (around 70% and 50%, respectively), and poor prognosis [4]. The average survival rate in the absence of distant metastases is estimated at 88 months and 8 months for patients with distant metastases [5, 6]. Metastases are diagnosed in 40% to 50% of cases and mostly localized in regional lymph nodes, lungs, bone, brain, and liver [7], and

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early diagnosis may improve survival for ES patients. Epithelioid sarcoma affects mainly adolescents although it may also be diagnosed in adults (18–79 years old) [4, 8]. Several studies revealed male predominance in ES diagnoses [3, 5]. The most common localization of ES is the upper or lower limb [4, 5]. Typically, ES is diagnosed as a nodule within the subcutis or in deep soft tissues. The nodules grow slowly over the years particularly in the hand and forearm area [9, 10]. Tumors localized in distal extremities are defined as the distal type of ES. The proximal type of ES, less frequent but with a more aggressive clinical course, was described within the perineum and genital region first time in 1997 [11]. The proximal type of epithelioid sarcoma usually accounts for one-third of all ES cases [12]. These two variants of ES differ from each other in localization, epidemiology, and pathological features.

### Macro- and microscopic characteristics of distal and proximal types of epithelioid sarcoma

Distal epithelioid sarcoma, also called conventional or classic, most often occurs in the extremities. It affects different distally located anatomic sites of fingers, hands, and arms in particular in association with tendons or aponeuroses, rarely with bones [2, 9, 13]. Distal ES less often affects the lower leg [14]. The second variant of ES, i.e. the proximal type, also described as the axial or large-cell type, tends to affect soft tissues of the perineum, pelvis, genital tract, head, neck, proximal extremities, and other sites [11, 15–17].

Distal epithelioid sarcoma commonly occurs as a small, solid, superficial, and slowly growing potentially ulcerated nodule or a cluster of nodules. The nodules may be well-circumscribed as well as fused into lobulated masses [3]. Generally, it often grows slowly and is asymptomatic. Histological examination revealed that distal ES is composed of spindle, polygonal, and polyhedral (as in the epithelium) epithelioid cells, containing deeply eosinophilic cytoplasm and often with loss of cellular connections [7, 9]. Polynuclear giant cells occasionally are found in histological preparations [18]. Central palisaded hyalinizing necrosis of the nodule with possible calcification is frequently observed [2, 3]. Tumor tissue of the distal ES contains large numbers of inflammatory cells, hyalinized collagen, vascular invasion, and the deposition of hemosiderin, fibrin, or mucin [2, 3, 7]. Binucleated cells are observed in the smears obtained from lymph node metastases [19].

Proximal ES has a different clinical picture. It forms nonspecific soft tissue masses deep in trunk organs or the proximal part of a limb, commonly with hemorrhage and necrosis [11]. Epithelioid sarcoma presents in histopathology as disintegrated large

and round epithelioid cells containing eccentrically located vesicular pleomorphic nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm, with or without paranuclear globules of intermediate filaments characteristic of the rhabdoid phenotype [7, 11, 19, 20]. In the microscopic image, binucleated and multinucleated cells are observed [20]. Mixed multinucleated osteoclast-like cells and signet cells are in aggregations next to the epithelioid cells [20]. The aggregations are separated by fibrous septa [20]. Images of cells in the tumor tissue in proximal ES show greater atypia compared to the distal type [18, 20]. Mitoses are more frequent in proximal ES [20].

### Epidemiology and prognosis of distal and proximal types of epithelioid sarcoma

Distal ES is rare in children and older people but commonly occurs in adolescents and young adults (20–40 years of age, median age 26 years) with a predominance in men [10, 21]. The proximal subtype affects older adults more often than the distal subtype; they are between 20 and 65 years of age, with a median age of 40 years, at diagnosis and a slight predominance of men [7, 9, 19, 21]. Proximal ES comprises fewer than one-third of ES cases [22]. Trauma is cited in 20–25% of ES cases as the cause of tumor appearance [23].

The type of ES is one of the prognostic factors in a clinical rating [8, 24]. The proximal variant of ES is considered more aggressive, and it metastasizes earlier than the distal type [9, 19, 25]. The poorer prognosis in proximal ES may be caused by inadequate surgical resectability associated with the tumor's deeper and more proximal location [7].

Other prognostic factors concerning both ES variants include age, tumor size, vascular invasion, deep location, higher mitotic rate and lack of lymphocyte infiltrate in the primary tumor [5, 9, 25, 26]. A better prognosis is associated with a diagnosis age below 55 years and adequate surgery [4], tumor size below 2 cm (in tumors greater than 2 cm necrosis and vascular invasion are observed) [27], absence of metastasis and low grade (I and II) [4]. Positive prognostic factors are a single localized disease stage and no regional spread [28]. The presence of distant metastases is a poorer prognostic factor compared to the finding of metastasis in regional lymph nodes [29]. Conflicting evidence was reported in terms of an association between sex and prognosis [29, 30]; however, a large study of the SEER database showed no differences in survival between male and female ES patients [31]. Pediatric patients have a better prognosis due to more frequent diagnoses of distal ES and low metastasis rate [21]. Patients who underwent any surgery had a better prognosis, confirming that

surgery is a positive prognostic factor [14, 25, 31]. The postoperative prognosis depends on radicality of local resection [29]. The median local recurrence rate, measured as time from the date of diagnosis to the occurrence of relapse in the primary tumor after surgical treatment, was 13 months (range 6–82 months) in 35% of cases [5]. In patients diagnosed with ES, lymphatic spread is also observed (20–45% of ES cases) [10, 32, 33].

### Immunohistochemical profile of distal and proximal types of epithelioid sarcoma

Analysis of immunoreactivity weakly confirms the difference between distal and proximal variants of epithelioid sarcoma (Tab. 1 [2, 3, 12, 15, 17, 18, 20, 25, 34–41]). Both proximal and distal variants of ES show great immunophenotypic similarity. Consequently, the distinction between the two variants of epithelioid sarcoma is unclear. Therefore, proximal and distal types of epithelioid sarcoma are also considered a continuum of the same disease [21].

Tumor tissue of ES possesses a unique immunophenotype, expressing epithelial and mesenchymal markers [3, 18]. The most common epithelial

antigens expressed in epithelioid sarcoma are cytokeratins (Fig. 1), i.e. proteins building the intermediate filament cytoskeleton in epithelial cells. Cytokeratins are expressed in both the distal and proximal variants of epithelioid sarcoma (88.2%), especially cytokeratin 8 and 18 [3, 7, 12]. These keratins typically are co-expressed in normal epithelial cells. Moreover, cytokeratin K8 and K18 are the first to be expressed during embryogenesis [42]. Cytokeratins K8 and K18 are also expressed in most carcinomas and therefore are useful markers in immunohistochemical analysis of tumors. Cytokeratins of high molecular weight, K5 and K6, are usually not detected in ES tumor tissue [17].

Epithelioid sarcoma tumor tissue also shows strong expression of the epithelial membrane antigen (EMA) [12, 18, 20], a member of a family of transmembrane mucin glycoproteins, which is localized on the apical cellular surface of normal epithelial cells. Expression of E-cadherin, a protein that creates epithelial cellular connections was not observed in tumor tissue of distal and proximal ES [12]. Samples of both types of ES tissue overexpress CA125 [12, 34]. Moreover, the serum glycoprotein CA125 level depends on the progression of both tumor variants, tumor growth, and clinical treatment [34, 43]. Epithelial tissue has been reported as one of the main sources of CA125 [44]. Expression of serum antigen CA125 and lack of E-cadherin expression may be useful ES diagnostic epithelial markers. Serum and tissue CA125 level analysis is recommended for monitoring the course of the proximal ES variant [43].

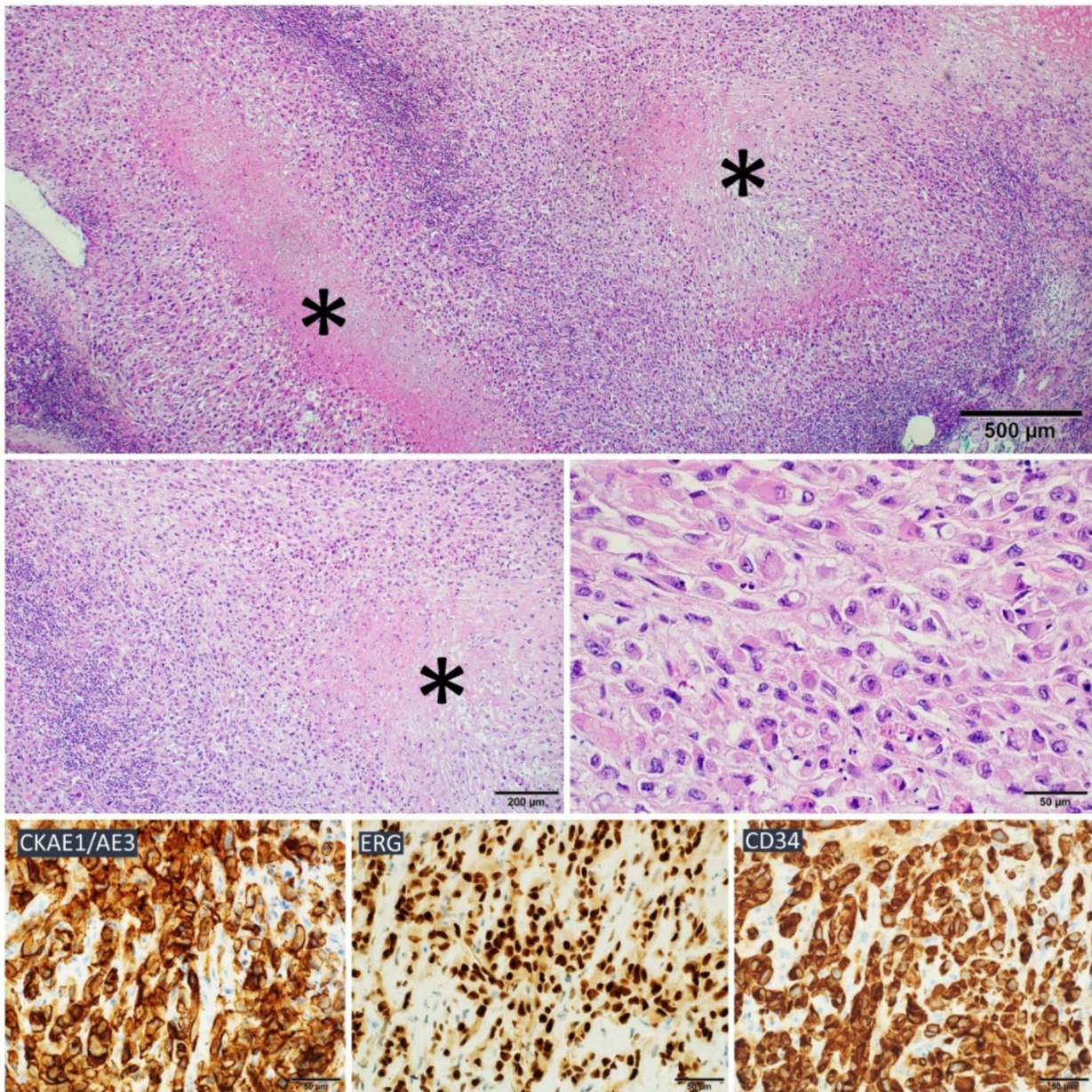
Mesenchymal antigens detected in ES tumors include, among others, vimentin and CD34. Vimentin is a building protein of intermediate filaments in cells of mesenchymal origin and is used to confirm the mesenchymal origin of these tumors. It is expressed in both variants of ES [15, 18, 20, 35–37]. Transmembrane phosphoglycoprotein CD34 is expressed in ES [3, 12, 18, 38]. High expression of angiogenesis factors VEGF-A and VEGF-C has been detected in both ES variants, while proximal ES often shows overexpression of MYC, a proto-oncogene involved in cell cycle regulation. Immunohistochemistry for MYC can be positive in proximal ES [12]. Smooth muscle actin and desmin were usually negative in ES tissue, as was expression of the S-100 protein [3, 18, 20].

In distal and proximal variants of epithelioid sarcoma nuclear positivity for ERG, an ETS-family transcription factor, was detected [39]. ERG represents endothelial markers. It controls endothelial cell differentiation and is used as a marker of endothelial cell neoplasms [39]. The role and origin of ERG in epithelioid sarcoma is unknown. Expression of other endothelial markers such as adhesion molecule CD31, claudin 5, or another transcription factor Prox1 was

**Table 1.** Biomarkers used in the diagnosis of distal and proximal epithelioid sarcoma (ES) types

	Distal type	Proximal type	References
<b>Epithelial markers</b>			
Cytokeratin 5	–	–	[17]
Cytokeratin 6	–	–	[17]
Cytokeratin 8	+	+	[7, 12]
Cytokeratin 18	+	+	[7, 12]
EMA	+	+	[12, 20]
E-cadherin	–	–	[12]
CA125	+	+	[12, 34]
<b>Mesenchymal markers</b>			
Vimentin	+	+	[15, 18, 20, 35–37]
CD34	+	+	[3, 12, 18, 38]
VEGF-A	+	+	[12]
VEGF-C	+	+	[12]
Smooth muscle actin	–	–	[3, 18]
Desmin	–	–	[3, 18]
<b>Endothelial markers</b>			
ERG	+	+	[39]
CD31	–	–	[39]
Claudin 5	–	–	[39]
<b>Gene expression markers</b>			
SMARCB1	–	–	[12, 17, 20, 25, 40]
EZH2	+	+	[41]

EMA — epithelial membrane antigen



**Figure 1.** Histopathological images of epithelioid sarcoma (ES); tumor composed of malignant epithelioid cells, with geographical necrosis (\*) and infiltration by inflammatory cells, mainly lymphocytes; cytokeratins [CKAE1/AE3, CK8/18 and epithelial membrane antigen (EMA)] and vascular markers (CD34 and ERG) are usually positive

not detected in either variant of endothelial sarcoma [39]. Melanosomal glycoprotein HMB45 was not detected in ES [18, 37]; this is useful in its distinction from malignant melanoma [18].

The most diagnostically useful finding is the lack of SMARCB1 (known as integrase interactor INI-1, hSNF5, or BAF 47) protein expression in ES tumor cells [12, 17, 20, 25, 40]. The INI1 protein is a subunit of the Switch/Sucrose Non-Fermentable (SWI/SNF) complex, which plays a crucial role in regulating gene expression by altering the structure of chromatin. SMARCB1/INI1 expression loss is commonly used as

a marker of ES [45]. SMARCB1/INI1 is a protein of the BRG1/BRM-associated factor (BAF) complex engaged in remodeling chromatin by nucleosome repositioning, and it suppresses tumor development [46]. SMARCB1 loss has been identified as the sole mutation leading to the initiation of tumor development [46]. The loss of expression of INI1 is characteristic both of classic and proximal ES. In particular, deletion of INI1 is found in proximal ES, while classic ES is characterized by retained dysfunctional INI1 expression. Moreover, classic ES is also characterized by high expression of glioma-associated oncogene

family zinc finger 3 (GLI3), tyrosine-protein kinase fyn (FYN), as well as stromal cell-derived factor 1, also known as C-X-C motif chemokine 12 (CXCL12) [40]. Moreover, proximal ES exhibits MYC overexpression and genomic patterns influencing cell cycle, chromatin metabolism, and protein synthesis. Conversely, classic ES displays heightened activation of Notch/Hedgehog pathways and immune regulation, associated with elevated expression of class 1 human leukocyte antigens (HLA) and enhanced immune infiltration [47].

### Genetic characteristics of distal and proximal types of epithelioid sarcoma

The loss of SMARCB1 (abbreviation of the full gene name SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily B, Member 1) expression in ES tumors presented above has a genetic cause. SMARCB1 is ubiquitously expressed in the nuclei of all normal cells. Moreover, SMARCB1 is a tumor suppressor gene located on chromosome 22 at band 22q11. It encodes BAF47, a subunit of the SWI/SNF (Sucrose Non-Fermentable, SNF) complex which regulates genes, the cell cycle, and signaling pathways [3, 17, 21, 48]. Therefore, inactivation of SMARCB1 leads to genomic instability, cell cycle progression, and abnormal signaling pathway activation [17]. The loss of SMARCB1 has been associated with induction of metaplasia [46]. Both variants of epithelioid sarcoma are characterized by peculiar chromosomal translocations caused by new gene fusions, and numerous rearrangements and deletions. Deletion of *SMARCB1* has been reported in classical and proximal types of ES [26, 49]. Both homozygous and heterozygous deletions of at least two exons in the *SMARCB1* gene were observed in proximal and distal ES variants [26, 49, 50]. The loss of SMARCB1 may also be due to silencing of *SMARCB1* gene expression caused by point mutations, interaction with microRNA, or epigenetic mechanisms [3, 51, 52]. Moreover, it was reported that the loss of SMARCB1/INI1 expression in the tumor cells is related to persistent activation of various pathways engaged in tumor progression, such as phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway, the sonic hedgehog signaling pathway, or the Polycomb pathway [51, 53, 54]. Activation of these pathways leads to induction of cellular proliferation, motility, and survival [51, 53]. Within the tumor tissue, there is a subpopulation of cells exhibiting pluripotent embryonic stem cell characteristics, called cancer stem cells (CSCs), that are not involved in tumor initiation, proliferation, recurrence, metastasis, or drug resistance [55]. Successful tumor initiation and proliferation is based on transformation of normal progenitor cells into cancer stem cells. Analyses

of sensitive CSC biomarkers are currently being conducted for use in personalized treatment [55]. The interaction between inactivation of *SMARCB1/INI1* and upregulation of enhancer of zeste homolog 2 (EZH2), a member of the polycomb group genes, which are epigenetic regulators of transcription in ES tumorigenesis, has been demonstrated [56]. The role of EZH2 in cancer initiation, progression, and metastasis has been described [56]. Therefore, EZH2 is an important therapeutic target for treating epithelioid sarcoma [17].

The BAF complex mutation has been found in 25% of cancers. BAP1 (BRCA1-associated protein 1) mutations gene have been reported in some cases of epithelioid sarcoma. Moreover, alterations in the *cyclin-dependent kinase inhibitor 2a (CDKN2A)*, and *neurofibromin 2 (NF2)* genes, encoding for tumor suppressor proteins, have been identified in epithelioid sarcoma cases [46, 57].

Epithelioid sarcoma biomarker gene expression analysis identified slight differences between distal and proximal ES samples [40] (Tab. 2 [2–4, 7–9, 11, 12, 15, 16, 18–21, 24–26, 40, 45, 49, 58, 59]). The source of distal and proximal ES dissimilarity may be differences in translocations: t(8;22)(q22;q11) in the distal ES variant and t(10;22) in the proximal ES variant [21]. The genetic differences are associated with expression patterns of certain genes related to SMARCB1/INI1 [40]. RNA sequencing profiling conducted on proximal and distal ES samples identified MYC pathway overexpression in the proximal ES variant and Sonic Hedgehog and Notch pathway overexpression in the distal ES variant [3].

### Diagnosis of distal and proximal types of epithelioid sarcoma

Diagnosis of epithelioid sarcoma is often incorrect and delayed due to its rarity, slow growth, and unalarming benign signs. Epithelioid sarcoma, especially the distal variant, mimics numerous diagnoses such as fibrosarcoma, synovial sarcoma, fibrous histiocytic sarcoma, malignant rhabdoid tumor, epithelioid hemangioendothelioma, anaplastic carcinoma, melanoma, or rheumatoid nodules [3, 7, 60, 61]. Nodules of ES slowly extend into deeper tissues reaching sometimes a size greater than 20 cm, causing pain, muscle weakness, movement restriction, paresthesia, and fever of unknown origin [20, 37, 61, 62]. Initial misdiagnoses of ES also relate to its proximal variant. Worse diagnosis of proximal ES may be caused by its rarity and deeper and more proximal location of the tumor. This often leads to a subsequent increase in ES size and risk of metastases. Appropriate and timely diagnosis management is crucial to restrict ES recurrence, metastasis, and mortality. Metastases to lymph

**Table 2.** Comparison of distal and proximal types of epithelioid sarcoma (ES)

	<b>Distal epithelioid sarcoma</b>	<b>Proximal epithelioid sarcoma</b>	<b>Reference</b>
Place of occurrence	Extremities; distal sites of hands and feet, particularly associated with tendons or aponeuroses	Soft tissue of perineum, pelvis, genital tract, head, neck, proximal parts of extremities	[11, 15, 16, 18]
Incidence	More frequent	Less frequent (approximately one-third of all ES cases)	[11, 12]
Demography	Predominantly affects male adolescents and young adults	Tends to affect older individuals	[8]
Macroscopic image	Superficial, slowly growing, solid nodule or cluster of nodules. Potentially ulcerated	Nonspecific tissue masses deep in healthy tissues. Hemorrhage and necrosis are common	[3, 11]
Histological features	Pseudogranulomatous appearance. Spindle, polygonal, polyhedral epithelioid cells with deeply eosinophilic cytoplasm. Often the loss of cellular connections. Occasionally polynuclear giant cells. Often central palisaded hyalinizing necrosis with possible calcification. Numerous inflammatory cells. Hyalinized collagen, vascular invasion, deposits of hemosiderin, fibrin, or mucin. Binucleated cells in the smear of nodal metastasis	Disintegrated large and round epithelioid cells with abundant eosinophilic cytoplasm, eccentric vesicular pleomorphic nuclei, and prominent nucleoli. Possible paranuclear globules of intermediate filaments and rhabdoid phenotype. Multinucleated osteoclast-like and signet cells are aggregated adjacent to the epithelioid cells and separated from each other with fibrous septa. Absence of granulomatous appearance. Atypia and mitotic rates are greater compared to the distal type	[2, 3, 7, 9, 11, 18–20]
Molecular characteristics	Common: Loss of SMARCB1/INI-1 expression		[26, 45, 49]
	t(8;22)(q22;q11), Enrichment in Sonic Hedgehog and Notch pathways	t(10;22), Overexpression of MYC pathway activity signature	[3, 4, 21]
	Trend toward lower dysadherin expression	Trend toward higher dysadherin expression	[58]
	Higher expression of <i>FYN</i> , <i>CXCL12</i> , <i>NID2</i> , <i>KRT7</i> , <i>SMARCB1</i> , <i>MMP2</i> , <i>BASP1</i> , <i>VASN</i> , <i>ACTA2</i> , <i>THBS1</i> , <i>ICAM2</i> , <i>ABCA8</i> , <i>TGFBR2</i> , <i>PDE2A</i> , <i>EPHA4</i> , <i>CD44</i> and <i>CDH5</i> genes than in proximal ES	Higher expression of <i>SHC1</i> , <i>C19orf33</i> , <i>RIPK4</i> , <i>EPHA2</i> , <i>SLCO4A1</i> , <i>THBS3</i> , <i>AC091180.3</i> , <i>RRAS</i> , <i>ITGA2B</i> , <i>APLP1</i> , <i>KRT8</i> , <i>FBXL6</i> , <i>FJX1</i> , <i>CACNG6</i> , <i>KRT18</i> , <i>CENPV</i> , <i>MUC1</i> and <i>MAP2K2</i> genes than in distal ES	[40]
Course of the disease	Poor prognosis, 10-year OS for patients with localized disease is approximately 50%, and 10% for patients who developed distant metastases	Increased risk of developing distant metastases and worse overall survival, compared to the distal type	[8, 9, 19, 24, 25]
Response to the treatment	Moderate activity of anthracycline — and gemcitabine-based regimens	Trend toward a higher response rate to anthracycline-based regimens, with a lower response rate to gemcitabine-based regimens, compared to the distal type	[59]

OS — overall survival

nodes, lungs, pleura, and skin have been documented in patients with epithelioid sarcoma [9, 38].

Correct diagnosis requires the use of many diagnostic tools including computed tomography scan, magnetic resonance imaging, X-ray, ultrasound-guided biopsy, and histological and immunohistochemical analysis [20, 37, 63, 64]. However, it should be noted that immunohistochemistry is not a substitute for microscopic histological images and should be analyzed in parallel with them [65]. The use of molecular genetics methods for diagnostic ES detection is increasingly indicated. A methodological approach following the World Health Organization (WHO) instructions should form the basis for further therapeutic management [66]. This approach requires changes in

diagnostic management such as integration of morphology with immunochemistry and molecular genetics and involvement of sarcoma expert pathologists and clinicians [66]. Tumor appearance and location on preoperative imaging using computed tomography scans and magnetic resonance imaging allow determining the anatomical site of the tumor, its volume, percentage of tumor necrosis, areas of hemorrhage, bone and neurovascular bundle involvement [6, 67]. Collection of tumor tissue material by biopsy allows analysis of microscopic images of cells, immunohistochemical evaluation, and DNA sequencing [19]. Using these methods allows the identification of epithelioid sarcoma and the determination of its variants, proximal and distant.

## Therapy of distal and proximal types of epithelioid sarcoma

The therapy for both variants of epithelioid sarcoma is still controversial. Surgical management with or without adjuvant/neoadjuvant radiotherapy and chemotherapy is still the most acceptable and effective method [63, 68]. The location and size of the ES tumor, presence of metastases, and the patient's age determine further treatment management. When the mass is localized, complete surgical resection (amputation or resection with wide margins — R0) with high-dose radiotherapy and chemotherapy is usually recommended, aiming at low local recurrence rates [7]. Some clinicians suggest ultrasound examination and sentinel node biopsy to check for undiscovered lymph node metastasis [24, 67]. Flap reconstruction and isolated limb perfusion are sometimes used [3, 24].

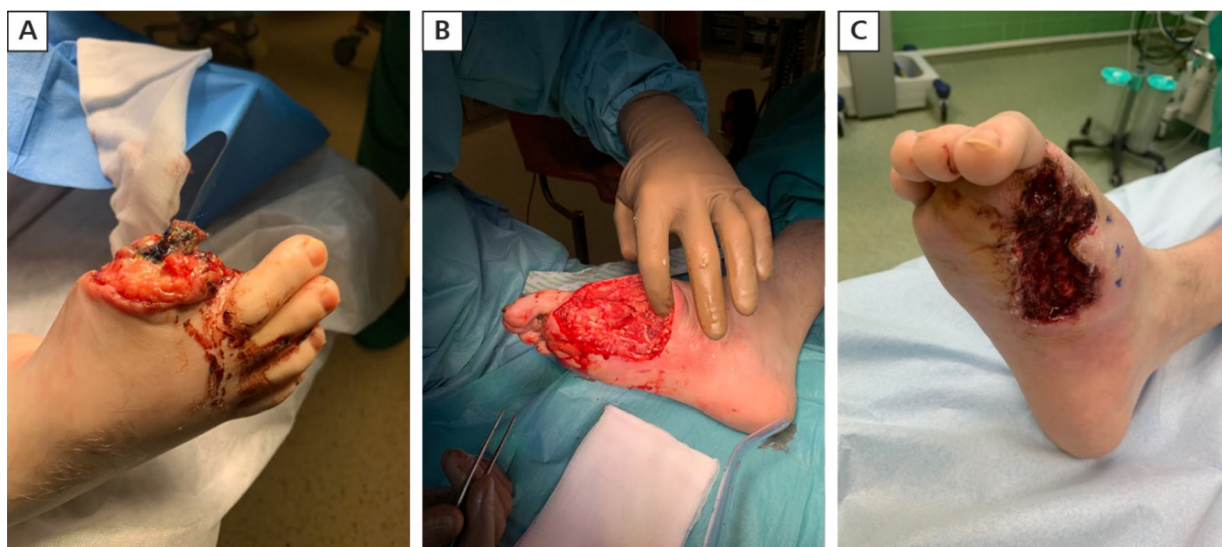
Presurgical embolization can help reduce tumor vascularity, and neo-adjuvant or adjuvant radiotherapy is useful in reducing the local recurrence rate [69]. To obtain cytoreduction allowing the decrease of tumor size and immediate treatment of metastases, neoadjuvant chemotherapy may be applied [67]. In addition to primary tumor resection, lymph node surgery may be required, and an appropriate lymph node basin should always be evaluated with imaging before surgery [67]. R1 and R2 resections are associated with high risk of recurrence and shorter overall survival (OS) [3]. Radiation therapy aims to prevent recurrence, especially after microscopically and macroscopically incomplete surgical ES resection

[24]. Conventional fractionation, as well as hypofractionated radiotherapy, may be used [24, 70]. However, even complete surgical excision with clear margins does not prevent tumor recurrence, as even the first report by Enzinger indicated a local recurrence rate of 85% [7, 71].

## Surgical management in the treatment of distal and proximal types of ES

Surgery is a potentially curative treatment for localized ES, in case of both primary and recurrent tumors [14]. Misdiagnosis of ES delays the treatment process and can lead to significant proliferation of tumor tissue and metastases. Therefore, patients should be referred to specialized sarcoma centers that are equipped with NGS and may provide gene fusion analysis. Figure 2 shows photographs of the foot of a misdiagnosed patient unsuccessfully treated for two years for ulceration of the toe at a chronic wound clinic and a local orthopedic clinic where a full-thickness skin graft was used. The graft was rejected due to proliferation of tumor tissue. Subsequently, resection of the distal phalanx and amputation of the first phalanx were performed, after which the pathological tissue was excised. Due to the rapid recurrence of the tumor and the diagnosis of distal ES, the patient underwent amputation of the lower limb in our Institute (Fig. 2).

R0 surgical resection with a wide tumor-free margin is crucial for the treatment of both proximal and distal ES types [29]. Surgery of the distal sarcoma type depends on the size and localization of the tumor and most often amputation of the finger or limb



**Figure 2.** Patient with acral epithelioid sarcoma misdiagnosed as a toe ulcer and treated for two years with a full-thickness skin graft, which failed, in a chronic wound clinic and at the local orthopedic service. This was followed by resection of the distal phalange and first-ray amputation, after which the resected pathology specimen was diagnosed as non-radical resection of the epithelioid sarcoma. Due to fast relapse, the patient underwent lower leg amputation; **A.** Failed skin graft after resection of the distal phalange; **B.** Intraoperative image of the first ray amputation; **C.** Preamputation image of the foot with recurrence in the postoperative wound

in which the tumor is located is performed, although a neoadjuvant multidisciplinary treatment approach may enable limb sparing surgery [10, 61]. Achieving R0 margins (i.e. margins free of tumor cells on microscopic evaluation), when removing a tumor, is often difficult due to its spread via the synovial space routes, especially in the distal type of ES [29, 61]. The presence of tumor tissue in surgical margins on macroscopic or microscopic pathological evaluation (R2 or R1 margins) has been associated with high risk of recurrence and reduces the survival rate of ES patients. In several studies, researchers have observed that amputation of lesioned limbs does not increase the survival rates of ES patients compared to sparing surgery with R0 resection [29]. However, when multiple local recurrences of tumor occur, removal of the affected limb becomes a necessity [29]. It is worth adding that even complete surgical excision with clear margins does not always prevent ES recurrence; the course of both ES types is unpredictable, and late recurrences were also reported [7]. Epithelioid sarcoma staging may often be supported by sentinel lymph node biopsy (SLNB), as SLNB is indicated in patients suffering from sarcomas with high risk of regional lymphatic spread such as ES [72]. However, retrospective analysis including 217 patients undergoing ES therapy showed that prophylactic removal of most or all of the lymph nodes draining the area around the primary ES tumor significantly increased overall survival rates and tumor-specific survival rates [73].

### The role of systemic treatment in es management

Chemotherapy for ES uses a broad spectrum of cytostatics, such as doxorubicin, ifosfamide, vincristine, cyclophosphamide, actinomycin D, and gemcitabine [3, 24, 67]. However, cytostatics are not highly effective in reducing ES growth. Increasing knowledge about the role of lack of SMARCB1 in developing epithelioid sarcoma makes it possible to design new, more effective personalized ES therapy [46]. Lack of SMARCB1 is associated with the BAF complex loss and upregulation of EZH2, which is a catalytic subunit of PRC2 (Polycomb repressive complex 2) [46]. Inhibition of EZH2 leads to regaining control of gene expression regulation [74]. Tazemetostat is an oral selective inhibitor of the histone methyltransferase — enhancer of zeste homolog 2 (EZH2) approved as the first-line treatment for ES. EZH2 is a histone methyltransferase that catalyzes the trimethylation of histone H3 at lysine 27 (H3K27me3) and plays a role in the regulation of gene expression by modifying chromatin structure. Tazemetostat specifically targets and inhibits the activity of EZH2. By doing so, it interferes with the addition of methyl groups to histones, and

this inhibition leads to changes in the expression of genes involved in cell growth and survival and enables inhibition of the growth of ES cells. For example, repression of the INK4A-ARF locus, which encodes the p16INK4a and p14ARF tumor suppressors, is a well-documented effect of EZH2, so inhibition of EZH2 upregulates these tumor suppressors. EZH2 has also been implicated in promoting epithelial-mesenchymal transition (EMT) — a process associated with increased cell motility and invasiveness, which is again stopped by EZH inhibition [25, 74].

New chemical compounds targeting mTOR and c-MET signaling pathways are also studied [67]. Novel therapeutic strategies are needed to treat highly aggressive epithelioid sarcoma, especially for the proximal ES variant [64, 75]. Differences in the clinical presentation of patients with different ES types indicate the need for different treatment procedures. Analyses of sensitive CSC biomarkers are currently being conducted for use in personalized treatment [55]. Use of pazopanib, a tyrosine kinase inhibitor, was also reported in ES tumor cases, but the results were also not satisfactory [3]. Dasatinib (multi-kinase inhibitor) efficacy in ES was investigated in the SARC0009 single-arm trial and multiple immunotherapy trials are ongoing including studies with immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway as well as CTLA-4/CD80/86 signaling. Pembrolizumab, as well as a combination of nivolumab with ipilimumab, were investigated in ES [76].

### Conclusions

There are two subtypes of ES — distal and proximal [23, 66]. The differences in the functional structure of these two variants described in the scientific literature have resulted in an update of the WHO classification of soft tissue tumors [23]. Initially, distal and proximal terms were related to the location of the tumor. It is now known that there are many more differences between the two types of ES (Tab. 2). However, it should be noted that both proximal and distal ES variants also show great similarity, mainly in the immunophenotype and genotype, therefore, both ES types are also considered a disease continuum [21]. At the molecular level, deletion of INI1 is found in proximal ES, while in classic ES is characterized by retained dysfunctional INI1 expression. While classic ES has high expression of GLI3, FYN, and CXCL12, along with overexpression of the Notch/Hedgehog pathways and class 1 human leukocyte antigens (HLA), proximal ES exhibits overexpression of MYC and genes involved in the cell cycle, chromatin metabolism, and protein synthesis [40, 47]. Differences in the clinical presentation of patients with different ES types indicate the need for different treatment approaches. New therapeutic



strategies are needed to treat highly aggressive ES, especially for the proximal variant of ES. Tazemetostat is an oral selective inhibitor of the histone methyltransferase EZH2 recently approved by the FDA as the first-line treatment for ES patients.

## Article Information and Declarations

### Author contributions

A.M.C., P.R.: conception and design; B.S., A.S.-C.: figures; all authors: writing and editing.

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### Conflict of interest

All authors declare no conflict of interest.

### Supplementary material

None.

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