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Collaboration that builds better understanding in epithelioid sarcoma

Recognizing and diagnosing epithelioid sarcoma (ES): **The critical role of pathology and Integrase Interactor 1 (INI1) testing**

This resource is for informational purposes only and is not intended to serve as a diagnostic tool or medical advice. It does not provide a comprehensive overview of all diagnostic options for ES. Healthcare professionals should rely on their clinical judgment and consult relevant guidelines or specialists when evaluating and diagnosing ES.

Understanding ES and its diagnostic challenges

What is ES?

ES is a rare, aggressive, malignant mesenchymal neoplasm that represents <1% of soft tissue sarcomas (STS).[1-5]

- Mostly found in **young adults** with **etiology unknown**[1-5]
- **Two subtypes:** distal and proximal[1-5]
- **Painless, slow-growing lump**, often mistaken for benign conditions[1-5]
- High rates of **recurrence** and **lymph node metastases**[1-5]

Diagnosing ES is challenging

STS including ES are considered one of the most challenging areas of diagnostic pathology.[6,7]

- In ES, delays in diagnosis and misdiagnosis are common[4,5,8] due to **lack of distinguishing clinical features** and **histological/morphological diversity**[2-5]

Early and accurate diagnosis may improve patient outcomes.[9-13]

Explore bridgES to learn more about the challenges of ES.

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Understanding INI1 and its critical role in ES diagnosis

What is INI1 (*SMARCB1*)?

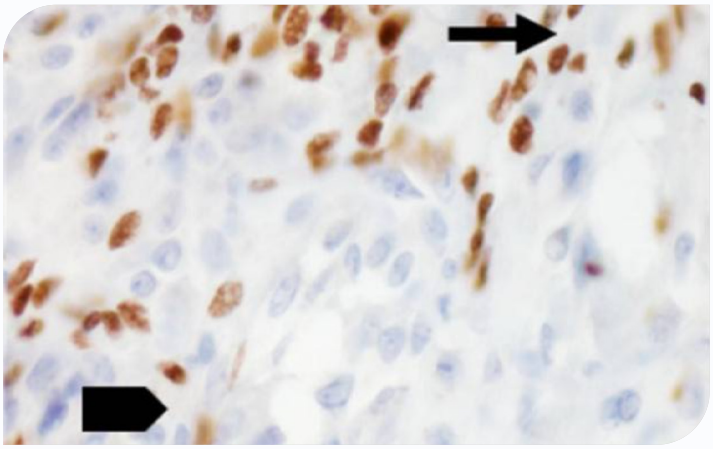
INI1 is a potent tumor suppressor protein encoded by the *SMARCB1* gene (also called BAF47 or SNF5).[1,14-16]

- **Loss of INI1** nuclear expression is the most common genomic alteration in STS and a **defining feature of ES**[1-5,14-17]
- While INI1 negativity on immunohistochemistry (IHC) staining is a key diagnostic marker of ES, results should always be interpreted **alongside clinical and morphological features**[2,3,5,14-22]

INI1 loss in STS[14]

	ES	Malignant rhabdoid tumor	Poorly differentiated chordoma	Myoepithelial carcinoma	Extraskeletal myxoid chondrosarcoma	Epithelioid schwannoma	Epithelioid malignant peripheral nerve sheath tumor
INI1 loss	90%	100%	100%	10%-40%	17%	40%	70%

Loss of INI1 nuclear expression in ES[3]



IHC stained section at 200× magnification. Arrowhead indicates loss of INI staining in tumor cells and arrow indicates internal control in endothelial cells. Image from Czarnecka A, et al. 2020[3]

Loss of INI1 as a defining molecular feature of ES[1-5,14-17] should always be considered alongside clinical and morphological features.[2,3,5,18-22]

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to learn more about INI1 as a key molecular characteristic of ES.

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Understanding the pathology workflow for ES diagnosis

A structured, multidisciplinary diagnostic approach

ES diagnosis requires a structured, multidisciplinary approach involving pathologists with expertise in sarcoma differential diagnosis.[2,6,19-21]

A coordinated diagnostic algorithm for early and accurate diagnosis[1,2,4,5,18-23]

Suspicion of STS or ES
Clinical assessment
Imaging

→

Biopsy and histopathology
Key histopathological features

→

Immuno-histochemistry
Diagnostic marker panel including INI1

→

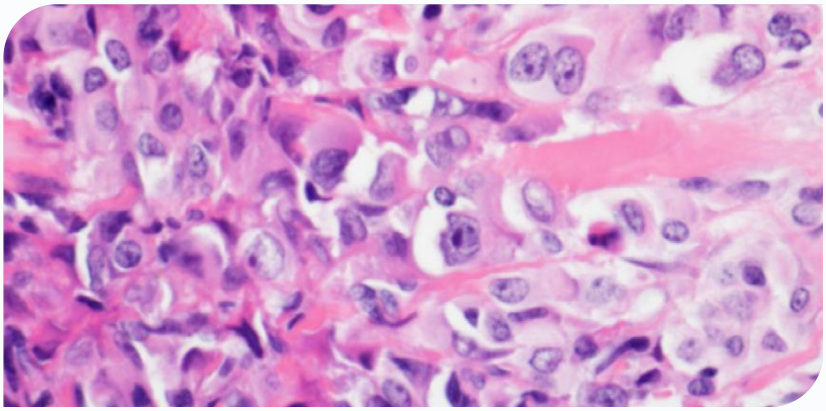
Molecular testing
Verification of diagnosis

Key histopathological features

Histopathology and morphology remain two cornerstones of diagnosis.[19,22]

ES histopathology:

Epithelioid cells with abundant eosinophilic cytoplasm, moderate nuclear pleomorphism, and a solid sheath arrangement, often with marked geographical necrosis[3]



Hematoxylin and eosin (H&E) stained section at 200× magnification.

Image from: Czarnecka A, et al. 2020[3]

Pathologists should identify **specific histopathological features** associated with **distal and proximal type ES**[1-5]

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Understanding the pathology workflow for ES diagnosis

Key histopathological features of distal and proximal ES[5]

	Distal type	Proximal type
Architecture and growth pattern	• Superficial, slowly growing, solid nodule or cluster of nodules • Potentially ulcerated	• Nonspecific masses deep in healthy tissues • Hemorrhage and necrosis common
Histological features	• Pseudo granulomatous with spindle, polygonal, or polyhedral epithelioid cells that have deeply eosinophilic cytoplasm • Central palisaded hyalinizing necrosis as a distinguishing feature, which may include calcification	• Disintegrated, large, round epithelioid cells with abundant eosinophilic cytoplasm, eccentric vesicular pleomorphic nuclei, and prominent nucleoli • Paranuclear globules of intermediate filaments and a rhabdoid phenotype may be present

IHC markers

Histology alone is insufficient for ES diagnosis and differentiation; pathological diagnosis relies on complementary IHC markers and morphological features.[1-3,7,18-22,24]

Careful antibody selection enhances diagnostic confidence and IHC presents many operational advantages, including rapid turnaround, cost-effectiveness, and consistent interpretation across pathologists and institutions.[7]

IHC diagnostic panel for ES[2,24]

Positive	Negative
• Cytokeratin • Vimentin • CD34 • ERG • CA-125	• **INI1 (>90%)** • CD31 • CD68 • S100 • Desmin • FLI1

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Understanding the pathology workflow for ES diagnosis

Molecular confirmation

Weak INI1 staining can be inconclusive and may not distinguish ES from other tumor types. In these cases, molecular confirmation is required to ensure diagnostic accuracy.[1,14,17,25,26]

The emergence of more accessible high-throughput sequencing technologies in recent years has enhanced our understanding of the molecular landscape of STS.[7]

Fluorescence in situ hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS) **to detect *SMARCB1* deletions or mutations**[1,6,14,19,21,22]

A multidisciplinary team (MDT) approach for comprehensive evaluation

Effective diagnosis of ES requires **close collaboration among pathologists, oncologists, radiologists, and surgeons** to review patient information and ensure accurate evaluation.[2,6,19-21,27]

By integrating clinical and imaging findings with histopathology and INI1 IHC results, specialists may ensure **a more accurate and timely diagnosis of ES**[5,6,19-21]

Pathologists play a crucial role in diagnosing ES by integrating morphological, IHC, and molecular features, which guides accurate classification and informs clinical decision-making.[6,19-21]

Explore bridgES to learn how integrating INI1 testing into pathology workflows may enhance confidence in borderline cases and support the precise classification of ES.[1-5,19]

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The critical role of INI1 testing in ES diagnosis

When to consider INI1 testing and the consequences of omission

Consider INI1 testing whenever clinical suspicion arises, particularly if histological evaluation reveals epithelioid morphology.[1-4,19]

When to consider INI1 testing

Consider INI1 testing if you observe the following:	
Suspicious clinical features	**Suspicious histopathological features**

• Tumor presenting as a soft tissue mass[1-5]
  • Distal: Superficial, slow-growing nodules in distal extremities, typically <5 cm[1,3-5]
  • Proximal: Deep, infiltrating masses in proximal limbs, up to 20 cm[1,3-5]
• Shiny, gray-white, gray-tan appearance with yellow-brown areas of necrosis and hemorrhage[1,3]
• Superficial bleeding, swelling, and ulceration[1-5]
	• Epithelioid morphology: Abundant eosinophilic cytoplasm and vesicular nuclei[1-5]
	• Rhabdoid features: Large cells with eccentric nuclei and prominent nucleoli[1-5]

Inconsistent application of INI1 testing contributes to significant delays and inaccuracies in ES diagnosis[28]

Failure to perform INI1 testing when ES is suspected may negatively impact clinical outcomes[1-5,9,10]

INI1 testing may transform ambiguous cases into actionable diagnoses[1-5]

Explore bridgES to learn how INI1 testing may bolster confidence in borderline cases and facilitate accurate classification of ES.[1-5,16,17,30]

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The critical role of INI1 testing in ES diagnosis

How to test for INI1 (*SMARCB1*)

To assess INI1 expression, IHC is performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections using antibodies targeting the INI1 protein.[29]

National Comprehensive Cancer Network (NCCN®) Guidelines* recommend IHC to support morphological findings[19]

INI1 IHC is associated with high sensitivity and specificity[30]

The NCCN® Guidelines* recommend molecular confirmation of IHC results in ambiguous cases, using methods such as FISH, RT-PCR, or NGS to test for the loss of the *SMARCB1* gene.[19]

Standardizing INI1 testing in pathology practice

Key steps to standardize INI1 testing:

- **Recognize morphological features**: Consider INI1 in STS with epithelioid or rhabdoid morphology[1-5]
- **Use INI1 IHC as an early diagnostic tool**: Loss of nuclear staining confirms INI1 deficiency, a defining feature of ES[1-5,16]
- **Implement reflex molecular testing for equivocal cases**: Utilize FISH, RT-PCR, or NGS to assess *SMARCB1* deletion/mutation when IHC results are unclear[1,5,19,21]
- **Enhance collaboration**: Work closely with oncologists, radiologists, and other specialists to integrate pathology findings into comprehensive case assessments[2,5,6,19-21]

* The NCCN® Guidelines are a copyrighted resource owned by the NCCN®. The full guidelines are available at www.nccn.org. The NCCN® has not reviewed or endorsed this material.

Developing a standardized approach to ES diagnosis may provide a consistent and reliable framework for clinical evaluation – helping to reduce variability, improve diagnostic accuracy, and enhance patient outcomes[6,7,13,31,32]

Explore bridgES to learn more about differentiating ES from other conditions.

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