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Epithelioid Hemangioendothelioma: Challenges in Diagnosis and Management

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Abstract

Epithelioid hemangioendothelioma (EHE) is an ultra-rare endothelial neoplasm with intermediate malignant potential and markedly variable clinical behavior. Historically regarded as within the spectrum of vascular tumors between epithelioid hemangioma and epithelioid angiosarcoma, EHE is now recognized as a distinct, molecularly defined entity, most commonly driven by *WWTR1-CAMTA1* or *YAP1-TFE3* gene fusions. The liver, lungs, and bones are the most frequently involved sites, whereas involvement of the heart, spleen, breast, and the head and neck region is uncommon. Given the frequent hepatic involvement and the clinical relevance of rare primary gastrointestinal presentations, this review synthesizes current evidence on the epidemiology, molecular pathogenesis, diagnosis, prognostic assessment, and management of EHE, with particular attention to hepatic and gastrointestinal manifestations, liver-directed strategies, and emerging therapeutic approaches.

Keywords: Epithelioid hemangioendothelioma, vascular neoplasms, gene fusion, molecular pathogenesis, immunohistochemistry

Introduction

Epithelioid hemangioendothelioma (EHE) is an ultra-rare endothelial neoplasm with intermediate malignant potential, accounting for less than 1% of all vascular tumors (1). It can arise at almost any anatomical site and shows a variable clinical course, ranging from indolent disease with prolonged periods of stability to aggressive progression. Because clinical and radiological findings are often non-specific, EHE is frequently misdiagnosed or inappropriately managed, which may adversely affect outcomes in a subset of patients. Notably, 50-76% of individuals are asymptomatic at the time of diagnosis (2). Accurate pathological confirmation is therefore essential.

Immunohistochemically, EHE typically expresses endothelial markers such as ERG and CD31, while CAMTA1 and TFE3 staining may provide additional diagnostic support. At the molecular level, the *WWTR1-CAMTA1* and *YAP1-TFE3* gene fusions are identified in approximately 90% and 10% of cases, respectively (3,4). These alterations have established EHE as a molecularly defined vascular neoplasm, and they are particularly valuable in distinguishing it from histologic mimics.

Because of its low incidence and unpredictable behavior, no universally accepted treatment strategy has been established. Complete surgical resection remains the preferred approach for localized resectable disease, whereas systemic therapy, radiotherapy, or liver-directed interventions can be used in selected clinical scenarios. Conversely, active surveillance is appropriate for some asymptomatic patients with indolent or slowly progressive disease. These management decisions are particularly relevant in hepatic EHE, one of the most common presentations, and in rare primary gastrointestinal cases that may mimic other gastrointestinal malignancies. Overall, the limited availability of prospective evidence continues to complicate therapeutic decision-making and highlights the need for individualized, multidisciplinary care (5).

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This narrative review was based on a literature search in PubMed/MEDLINE, Scopus, and Google Scholar for articles published through April 2026. Search terms included "EHE", "hepatic EHE", "gastrointestinal EHE", "*WWTR1-CAMTA1*", "*YAP1-TFE3*", "diagnosis", "systemic therapy", and "liver-directed therapy". Priority was given to consensus papers, population-based studies, real-world cohorts, and clinically relevant molecular or therapeutic reports. This review summarizes current evidence on the epidemiology, molecular pathogenesis, diagnostic evaluation, prognostic assessment, and management of EHE, with particular attention to hepatic/gastrointestinal relevance, liver-directed strategies, and emerging therapeutic approaches.

Epidemiology

A population-based analysis of U.S. National Cancer Registry data reported that malignant hemangioendothelioma is an ultra-rare vascular cancer, with an incidence of approximately 0.4 cases per million person-years (6). Although the disease is uncommon, outcomes remain poor in advanced stages, particularly among patients with metastatic disease, underscoring the need for improved therapeutic strategies (6).

EHE can occur across a wide age range, but most often presents in middle-aged adults, with a peak incidence in the fourth and fifth decades of life and a slight female predominance. Because many cases follow an indolent course and are detected incidentally, the true incidence may be underestimated. In a recent large single-center series of 115 patients, EHE showed a broad age distribution, slight female predominance, and diverse anatomical involvement, most commonly affecting the liver, lungs, and soft tissues (7). These findings indicate that EHE does not follow a uniform epidemiological pattern and may present across different patient populations and anatomical sites (7).

Clinical Presentation

EHE can arise in almost any anatomical location, but the liver, lungs, soft tissues, and bones are the most commonly affected sites. Many patients are incidentally diagnosed while asymptomatic. When symptoms occur, they are usually site-dependent and may include pain, a palpable mass, weight loss, fever, or fatigue. Pulmonary involvement can present with dyspnea, cough, hemoptysis, or chest pain, whereas osseous disease may cause pathological fractures or neurological deficits, particularly in cases with spinal involvement. Serosal disease, including pleural or peritoneal involvement, is frequently associated with effusions and a more aggressive clinical course (8,9). Hepatic EHE may be asymptomatic or present with non-specific abdominal pain, hepatomegaly, or abnormal liver function tests, whereas primary gastrointestinal involvement is rare and may mimic other gastrointestinal tumors, manifesting as bleeding, obstruction, abdominal pain, or mass-forming lesions.

A large multi-institutional retrospective study conducted by the Canadian Sarcoma Research and Clinical Collaboration (CanSaRCC) and multi-pronged Canadian research (PRO_CARE) EHE reported a median age at diagnosis of 51 years (range, 9-86), with an approximately equal sex distribution. Metastatic disease was present at diagnosis in approximately 45-47% of patients, and a substantial proportion of cases were identified incidentally. The most common primary sites were the liver (28%), the extremities (16%), and the lungs (14%) (9). Population-based analyses further indicate that EHE predominantly affects middle-aged and older adults, while pediatric cases remain rare. Tumors most commonly originate in soft tissue and skin, followed by abdominal and thoracic sites, and may present as multifocal or metastatic disease at diagnosis (10).

The clinical course ranges from prolonged stable disease to rapidly progressive and fatal outcomes. Systemic symptoms, pulmonary involvement, and serosal disease have been associated with worse prognosis (5,8). Therefore, clinical presentation should be interpreted together with disease distribution, symptom burden, and tumor kinetics when planning multidisciplinary management.

Histopathological and Molecular Features

EHE has distinctive histopathological features that support its recognition among vascular neoplasms. Histologically, it is composed of cords and nests of epithelioid endothelial cells embedded in a characteristic myxohyaline stroma. Tumor cells typically show abundant eosinophilic cytoplasm, round to mildly atypical nuclei, and hallmark intracytoplasmic vacuoles, some of which contain erythrocytes and reflect primitive vascular lumen formation. Mitotic activity is usually low; however, increased mitotic figures, nuclear pleomorphism, and necrosis may indicate more aggressive behavior. Immunohistochemically, EHE consistently expresses endothelial markers such as CD31, ERG, and FLI1, whereas CD34 expression is more variable (4,7).

At the molecular level, EHE is characterized by recurrent and highly specific gene fusions. The most common alteration is the *WWTR1-CAMTA1* fusion resulting from a t(1;3)(p36;q25) translocation, which is present in the majority of cases and represents a disease-defining event (4). A smaller subset harbors the *YAP1-TFE3* fusion, which is associated with distinct morphological features and strong nuclear TFE3 expression (3). These fusion proteins are thought to promote tumorigenesis through dysregulation of the Hippo signaling pathway and aberrant transcriptional activation (1).

The identification of these alterations has established EHE as a molecularly defined vascular neoplasm and has provided substantial diagnostic value, particularly in challenging cases. Although reverse transcription polymerase chain reaction and fluorescence *in situ* hybridization can detect these rearrangements, their limited availability in routine practice has supported the use of CAMTA1 immunohistochemistry as a practical adjunct in the diagnostic workup (1,4). The key histopathological, immunohistochemical, and molecular features used in the diagnostic evaluation of EHE are summarized in Table 1.

Imaging Features and Differential Diagnosis

Accurate staging of EHE requires comprehensive whole-body imaging because of its propensity for multifocal and systemic involvement. Cross-sectional imaging, particularly computed tomography (CT) and magnetic resonance imaging (MRI), forms the basis for baseline evaluation and is often complemented by functional imaging techniques (11). Contrast-enhanced CT of the chest, abdomen, and pelvis remains the preferred initial modality because of its wide availability and utility in assessing pulmonary and abdominal disease. In suspected hepatic involvement, multiphasic liver imaging improves lesion characterization, while MRI is particularly useful for evaluating hepatic, soft tissue, and bone lesions because of its superior soft tissue contrast resolution (12). Whole-body MRI or [18F]-fluorodeoxyglucose (FDG)-PET/CT, when available, can be valuable for detecting skeletal and soft tissue involvement. Bone scintigraphy may serve as an alternative in resource-limited settings. For follow-up, imaging modality used at baseline should preferably be retained to allow reliable longitudinal comparisons (11). Functional imaging may also provide prognostic information. Although FDG uptake in EHE is typically mild to moderate, higher standardized uptake values have been associated with more aggressive disease behavior, increased risk of progression, and inferior survival outcomes (13).

Radiological findings in EHE are broad and often non-specific, with substantial overlap with other vascular, hepatic, and metastatic malignancies. Characteristic features of hepatic EHE include multifocal, coalescent nodules with a peripheral, subcapsular distribution, often accompanied by capsular retraction and a "target-like" enhancement pattern on contrast-enhanced imaging. The "lollipop sign", defined as tapering and abrupt termination of a hepatic or portal vein at the margin of a lesion, may further support the diagnosis (14). However, neither target-like enhancement nor the lollipop sign is pathognomonic. These findings should be interpreted in the clinical context, particularly because hepatic EHE can radiologically overlap with intrahepatic cholangiocarcinoma, metastatic carcinoma, and epithelioid angiosarcoma.

Thoracic involvement may manifest with diverse patterns: multiple pulmonary nodules, reticulonodular opacities, diffuse pleural thickening, or mass-like lesions with pleural invasion, which can mimic malignant pleural mesothelioma (11). In some cases, pulmonary nodules may demonstrate a surrounding ground-glass halo resembling that seen in metastatic angiosarcoma. Osseous involvement most commonly affects the axial skeleton and long bones.

Table 1. Diagnostic, immunohistochemical, and molecular features of EHE

Feature	Typical findings	Diagnostic relevance
Histological architecture	Cords and nests of epithelioid endothelial cells embedded in a characteristic myxohyaline stroma.	Supports recognition of EHE among vascular neoplasms (4,7).
Cytological features	Abundant eosinophilic cytoplasm, round to mildly atypical nuclei, and hallmark intracytoplasmic vacuoles, some containing erythrocytes.	Intracytoplasmic vacuoles reflect primitive vascular lumen formation and support endothelial differentiation (4,7).
Adverse histological features	Increased mitotic activity, nuclear pleomorphism, and necrosis.	May indicate more aggressive tumor behavior and should be integrated with clinical and radiological context (4,7).
Endothelial markers	Consistent expression of CD31, ERG, and FLI1; CD34 expression is more variable.	Confirms endothelial differentiation and helps distinguish EHE from non-vascular mimics (4,7).
Fusion-associated IHC	CAMTA1 nuclear expression in *WWTR1-CAMTA1*-associated EHE; strong nuclear TFE3 expression in the *YAP1*-TFE3 subset.	Provides a practical diagnostic adjunct, particularly when molecular testing is unavailable or limited (3,4).
Molecular alterations	*WWTR1-CAMTA1* fusion in most cases; *YAP1-TFE3* fusion in a smaller molecular subset.	Disease-defining alterations that establish EHE as a molecularly defined vascular neoplasm and support distinction from histologic mimics (3,4).
Molecular testing	RT-PCR or FISH can detect fusion rearrangements.	Useful for confirming the diagnosis in challenging cases and for resolving equivocal IHC findings (1,4).
Differential diagnosis	Epithelioid angiosarcoma, metastatic carcinoma, intrahepatic cholangiocarcinoma, malignant mesothelioma in pleural presentations, and other vascular tumors.	Requires integration of morphology, endothelial immunophenotype, molecular confirmation, and site-specific imaging findings (11,14).

EHE: Epithelioid hemangioendothelioma, IHC: Immunohistochemistry, RT-PCR: Reverse transcription polymerase chain reaction, FISH: Fluorescence *in situ* hybridization

It typically appears as poorly defined lytic lesions, occasionally exhibiting sclerotic margins or mixed expansile features. On MRI, these lesions are generally hypointense on T1-weighted images and hyperintense on T2-weighted or short tau inversion recovery sequences, reflecting their vascular and cellular composition (15).

Despite these characteristic patterns, imaging alone is insufficient to establish a definitive diagnosis. The differential diagnosis includes primary or metastatic carcinomas, epithelioid angiosarcoma, intrahepatic cholangiocarcinoma, and malignant mesothelioma in pleural presentations. This limitation is particularly important because some imaging features of EHE, although suggestive, are not specific enough to reliably distinguish it from more aggressive vascular tumors or hepatobiliary malignancies. Therefore, histopathological confirmation remains essential. Immunohistochemical and molecular analyses, including the identification of *WWTR1-CAMTA1* or *YAP1-TFE3* gene fusions, are critical for confirming the diagnosis and distinguishing EHE from its histologic mimics.

Prognosis

EHE is an intermediate-grade vascular neoplasm with an unpredictable clinical course, ranging from prolonged disease stability to rapid progression and fatal outcomes (16). Prognosis is influenced by disease distribution, tumor burden, clinical presentation, histopathological features, and disease kinetics; however, no universally accepted prognostic model has been established.

Early insights from an international patient-based registry showed that male sex and age greater than 55 years were associated with poorer survival, whereas anatomical extent alone did not consistently predict outcome (16). This study proposed a clinical classification distinguishing pattern A, defined by localized and well-demarcated lesions, from pattern B, characterized by diffuse and infiltrative disease. This distinction emphasized the prognostic relevance of tumor growth pattern rather than disease extent alone. Pleural effusion, ascites, hemoptysis, and extensive bone involvement were also identified as adverse clinical features (Table 2) (16).

Subsequent studies have supported the prognostic importance of both disease burden and clinical context. Patients with localized disease, particularly those amenable to complete surgical resection, may achieve prolonged survival. In contrast, multifocal or metastatic disease, especially when involving the liver and lungs, is generally associated with poorer outcomes (5). Systemic symptoms, weight loss, and serosal involvement have also been linked to a worse prognosis. Conversely, some asymptomatic or incidentally diagnosed patients may follow an indolent course, even in the presence of radiologically evident metastases (5).

Histopathological parameters further contribute to risk assessment. Increased mitotic activity, nuclear atypia, and necrosis have been associated with more aggressive tumor behavior, although these features alone are insufficient for reliable prognostic stratification (8). Similarly, recurrent molecular alterations, including *WWTR1-CAMTA1* and *YAP1-TFE3* fusions, define EHE biologically and diagnostically but do not fully explain its clinical variability.

More recent data have refined the understanding of prognostic determinants. In a nationwide cohort of 57 patients confirmed by molecular and immunohistochemical analyses, Tomassen et al. (17) demonstrated that tumor

Table 2. Pattern A/B classification and associated clinical implications in EHE

Feature	Pattern A	Pattern B	Clinical interpretation
Growth pattern	**Localized, well-demarcated lesions**	**Diffuse, infiltrative disease**	**Growth pattern may provide prognostic information beyond anatomical extent alone.**
Prognostic concern	Generally lower clinical concern when stable and asymptomatic	Higher clinical concern, particularly when progressive or symptomatic	Pattern B may warrant closer follow-up and earlier multidisciplinary discussion.
Role of anatomical extent	Extent of disease alone may not reliably predict prognosis	Extent of disease alone may not reliably predict prognosis	Pattern should be interpreted together with disease distribution, symptoms, and tumor kinetics.
Associated adverse features	Usually assessed in the absence or presence of additional adverse features	May coexist with adverse features such as pleural effusion, ascites, hemoptysis, or extensive bone involvement	These adverse features have been associated with poorer outcomes.
Practical use	May support observation or local treatment in selected stable patients	May support earlier active intervention when accompanied by symptoms, progression, or high-risk features	The classification should complement clinical, radiological, histopathological, and molecular assessment.

The pattern A/B classification should be used as a complementary clinical framework rather than as a standalone prognostic model
EHE: Epithelioid hemangioendothelioma

size and mitotic activity were key determinants of clinical outcome, particularly among patients with unifocal disease. These findings suggest that intrinsic tumor biology may be more relevant than anatomical extent in selected clinical contexts. Large real-world cohorts, including the CanSaRCC/PRO_CARE EHE study, further indicate that baseline disease distribution alone cannot fully predict disease behavior, supporting the need to incorporate dynamic clinical factors into prognostic assessment (9).

Multivariate analyses have identified older age, pleural effusion, ascites, primary pulmonary involvement, and metastatic disease as independent predictors of poorer survival, with pleural effusion representing the strongest adverse factor (9). These observations underscore the prognostic importance of serosal involvement and highlight the need to interpret the anatomical extent of disease together with symptoms and tumor kinetics.

In clinical practice, the pattern A/B classification should be viewed as a complementary framework rather than a standalone prognostic model. Molecular classification is essential for diagnosis, but current evidence does not support using *WWTR1-CAMTA1* or *YAP1-TFE3* status alone to guide prognosis or treatment selection. Therefore, prognostic assessment should integrate clinical presentation, growth pattern, tumor burden, histopathological risk features, molecular confirmation, and longitudinal behavior. This multidimensional approach can help identify patients suitable for active surveillance and those who require earlier local or systemic intervention.

Treatment

The management of EHE is challenging because treatment decisions must account not only for anatomical extent but also for symptoms, tumor burden, resectability, and disease kinetics (5). No universally accepted standard of care has been established, and management is therefore best individualized within a multidisciplinary framework.

Current treatment approaches combine general soft tissue sarcoma principles, as outlined in the European Society for Medical Oncology (ESMO)-European Reference Network for Rare Adult Solid Cancers (EURACAN)-European Reference Network on Genetic Tumour Risk Syndromes (GENTURIS) Clinical Practice Guidelines, with EHE-specific expert consensus recommendations, particularly those proposed by Stacchiotti et al. (8). While the ESMO guidelines provide a broad framework for sarcoma care, disease-specific consensus emphasizes a more phenotype-driven strategy, distinguishing patients with indolent disease suitable for observation from those with symptomatic, progressive, or high-risk disease requiring active intervention (8).

Localized and Unifocal Disease

For patients with localized and resectable disease, complete surgical excision with negative margins (R0 resection) remains the cornerstone of treatment and offers the greatest likelihood of long-term disease control or cure, with reported cure rates of up to 70-80% in selected cases (8). Radiotherapy can be used in selected clinical settings, including close or positive surgical margins, unresectable lesions, and symptomatic disease requiring local control. Although EHE is considered moderately radiosensitive, radiotherapy is generally used adjunctively rather than as a curative treatment (8). For patients who are not candidates for surgery, local ablative approaches such as radiofrequency ablation, microwave ablation, or stereotactic body radiotherapy (SBRT) are potential options, although supporting evidence remains limited.

Multifocal and Metastatic Disease

A substantial proportion of patients present with multifocal or metastatic disease at diagnosis, which limits curative treatment options. In this setting, management should balance the risk of overtreatment against the potential for clinically meaningful progression. Importantly, metastatic disease alone does not mandate immediate systemic therapy. In asymptomatic patients with indolent or slowly progressive disease, active surveillance (watch-and-wait) is widely accepted as the preferred initial approach (9). In contrast, symptomatic disease, rapid radiological progression, serosal involvement such as pleural effusion or ascites, and substantial tumor burden favor earlier intervention, as these features are associated with poorer outcomes (9).

Systemic Therapy

Systemic therapy is generally reserved for patients with symptomatic, progressive, unresectable, or high-burden disease. Conventional cytotoxic chemotherapy has shown limited and inconsistent efficacy, and is not routinely preferred (8). Targeted and anti-angiogenic therapies, therefore, represent the main systemic options in current practice. vascular endothelial growth factor pathway inhibitors, including tyrosine kinase inhibitors such as pazopanib and sorafenib, are commonly used and more often lead to disease stabilization than to objective tumor regression. MammalianTarget of rapamycin (mTOR) inhibitors, particularly sirolimus, have also shown activity in selected patients (9). Other agents, including interferon-alpha and thalidomide, have demonstrated modest activity, although high-level evidence remains lacking. Overall,

systemic therapy in EHE should be viewed primarily as disease-modifying rather than curative. The available clinical outcomes of commonly used systemic agents are summarized in Table 3.

Liver-directed and Locoregional Therapies

Hepatic EHE warrants particular attention because the liver is one of the most frequently involved sites, and the disease may be multifocal at presentation. Surgical resection remains the preferred option for technically resectable, liver-limited disease when complete removal is feasible (8). In carefully selected patients with unresectable liver-limited disease, liver transplantation can be considered, particularly when tumor biology appears indolent and extrahepatic disease is absent or limited (8). For patients who are not candidates for resection or transplantation, locoregional strategies such as ablative techniques, SBRT, or transarterial therapies can be considered for local control, symptom palliation, or reduction of hepatic tumor burden. However, the evidence supporting these approaches remains limited and largely retrospective. Therefore, treatment selection should be individualized by a multidisciplinary liver tumor board or sarcoma board.

Table 3. Summary of systemic therapies evaluated in advanced epithelioid hemangioendothelioma (EHE)

Study	Treatment/ agent	Study design/ population	EHE patients, n	ORR/response	PFS/TTP	OS	Main clinical interpretation
Frezza et al. (18)	Paclitaxel	Same retrospective series; advanced EHE	11	PR 1/11 (9%); SD 6/11 (55%); PD 4/11 (36%)	Median PFS 2.9 months	Median OS 18.6 months	Limited response activity; may provide disease control in selected patients.
Frezza et al. (18)	Pazopanib	Same retrospective series; advanced EHE	12	PR 0; SD 3/12 (25%); PD 9/12 (75%)	Median PFS 2.9 months	Median OS 8.5 months	Activity was variable; in this series, pazopanib mainly produced disease stabilization in a minority of patients.
Frezza et al. (18)	Interferon-alpha-2b	Same retrospective series; advanced EHE	15	PR 1/15 (7%); SD 11/15 (73%); PD 3/15 (20%)	Median PFS 8.9 months	Median OS 64.3 months	Occasional durable disease control was observed, but evidence remains retrospective.
Stacchiotti et al. (24)	Sirolimus	Retrospective case-series; advanced/ progressive EHE treated within the Italian Rare Cancer Network	18 total; 17 EHE and 1 retiform HE	In EHE: PR 1; SD 12; PD 3; retiform HE also achieved PR	Median PFS 12 months	Median OS 16 months	Sirolimus demonstrated disease control in selected patients; activity appeared lower in patients with pleural/peritoneal effusions.
Chevreau et al. (25)	Sorafenib	Multicenter single-arm phase 2 trial; progressive EHE	15 enrolled	Two partial responses; 9-month progression-free rate 30.7%	2-, 4-, and 6-month progression-free rates: 84.6%, 46.4%, and 38.4%	NR	Sorafenib showed modest activity, with limited response rates and occasional clinical benefit.
Agulnik et al. (26)	Bevacizumab	Open-label multicenter phase 2 trial in angiosarcoma and EHE	7 EHE among 30 evaluable patients	In EHE: PR 2/7 (29%); SD 4/7 (57%); PD 1/7 (14%)	Median PFS 39.1 weeks in EHE	Median OS 142.6 weeks in EHE	Bevacizumab showed activity in a small EHE subset, but interpretation is limited by the mixed-histology design and small sample size.
Schuetze et al. (21)	Trametinib	Single-arm phase 2 trial; locally advanced or metastatic EHE	44 enrolled; 42 started treatment	ORR 3.7%	Median PFS 10.4 months	2-year OS 33.3%	Trametinib did not meet the ORR goal but was associated with reduction in EHE-related pain, suggesting palliative benefit in selected patients.
IAG933/IK-930 studies (22,23)	TEAD inhibitors	Early-phase trials in advanced solid tumors, including EHE or Hippo pathway alterations	EHE-specific efficacy not yet mature	NR	NR	NR	Biologically rational investigational strategy; clinical efficacy in EHE remains to be defined.

HE: Hemangioendothelioma, ORR: Objective response rate, PR: Partial response, SD: Stable disease, PD: Progressive disease, PFS: Progression-free survival, TTP: Time to progression, OS: Overall survival, NR: Not reported

Real-world Evidence and Treatment Heterogeneity

Real-world cohorts demonstrate substantial variability in the management of EHE. Surgical resection is most commonly used for localized disease, whereas systemic therapy is applied selectively in advanced cases and is generally associated with modest benefit (9). Observational strategies are also frequently used in asymptomatic or slowly progressive disease, including in some patients with metastatic lesions, indicating that radiological extent alone is insufficient to define treatment urgency.

In a large retrospective series from the World Sarcoma Network, Frezza et al. (18) reported that conventional chemotherapy had limited activity in advanced EHE, with low objective response rates and disease stabilization as the most common outcomes. Anti-angiogenic agents and targeted therapies, including pazopanib, sorafenib, and mTOR inhibitors, produced variable but occasionally durable disease control, supporting their use in selected patients with progressive or symptomatic disease. However, no systemic agent has demonstrated consistent superiority across all subgroups (18).

The nationwide NETSARC cohort of 267 patients, followed over 12 years, further illustrated the longitudinal nature of EHE management. Many patients were initially managed without systemic therapy, and treatment strategies were frequently modified over time according to evolving tumor behavior (19). Sequential use of systemic, surgical, and locoregional approaches was common in advanced disease, supporting a dynamic treatment model based on repeated clinical reassessments rather than a fixed upfront algorithm (19).

Guideline-practice Gap

Although ESMO-EURACAN-GENTURIS guidelines provide a broad framework for soft tissue sarcoma management, EHE-specific decision-making remains constrained by the absence of prospective evidence and validated treatment algorithms (8). This gap is most evident in three practical areas: the duration and intensity of active surveillance, the threshold for initiating systemic therapy, and the selection or sequencing of local, liver-directed, and systemic treatments in advanced disease.

In clinical practice, patients with asymptomatic metastatic EHE may remain under observation for prolonged periods, yet guidelines do not define optimal imaging intervals, surveillance duration, or radiological progression thresholds that should trigger treatment. Similarly, systemic therapy is often initiated for symptomatic, progressive, or high-burden disease, but no standardized criteria exist to determine the optimal timing for initiating treatment (9,19). Local and locoregional therapies are also used variably, particularly in hepatic-predominant disease, where resection, transplantation, ablative approaches, or transarterial strategies may be discussed according to disease distribution, tumor biology, and institutional expertise.

Another important gap concerns treatment goals. In real-world practice, systemic therapy is frequently used to delay progression or maintain disease control rather than to achieve objective tumor regression, reflecting the cytostatic activity of many available agents (18,19). These discrepancies highlight the need for a more disease-specific framework that integrates guideline principles with real-world evidence. Until stronger prospective data are available, management should preferably be conducted at specialized sarcoma centers or by multidisciplinary boards, with treatment decisions reassessed over time according to symptoms, tumor kinetics, anatomical involvement, and patient-specific factors.

Future Therapeutic Approaches in EHE

Future therapeutic development in EHE is increasingly focused on disease-defining molecular drivers, particularly the *WWTR1-CAMTA1* and *YAP1-TFE3* fusions and their interaction with TEAD transcription factors. Because TAZ and YAP are key mediators of Hippo pathway signaling and cancer progression, small molecules designed to disrupt YAP/TAZ-TEAD-dependent transcription represent a biologically rational strategy. Verteporfin, a porphyrin derivative, has been proposed as a potential inhibitor of the YAP/TAZ-TEAD interaction, thereby impairing downstream transcriptional programs. Similarly, stabilization of angiomotin family proteins through tankyrase inhibition has been suggested as an indirect approach to reduce nuclear localization and transcriptional activity of these fusion-driven proteins. However, these strategies remain largely preclinical and should be interpreted as hypothesis-generating rather than clinically established therapeutic options.

The potential sensitivity of fusion-driven signaling to upstream regulatory pathways has also generated interest in alternative approaches. Inhibition of mevalonate synthesis (for example, through statins) or modulation of extracellular matrix stiffness (with agents such as losartan) could theoretically suppress YAP/TAZ activity if these pathways are confirmed to be relevant in human EHE. Similarly, modulation of phosphoinositide 3-kinase/protein kinase B (AKT serine/threonine kinase) signaling may influence the glycogen synthase kinase-3-mediated phosphorylation of the phosphodegron motif, thereby promoting proteasomal degradation of fusion-

related proteins. These approaches aim to target oncogenic signaling at the protein or microenvironmental levels, but their clinical relevance remains unproven and requires validation in EHE-specific experimental models.

Biological therapies and immunotherapy are also areas of ongoing interest. The observation that TAZ and YAP can promote programmed death-ligand 1 expression and immune evasion in several cancers provides a rationale for exploring immune checkpoint inhibition in EHE. In addition, monoclonal antibodies such as TRC105, which targets endoglin, an endothelial cell surface marker highly expressed in EHE cells, have been evaluated as targeted biological therapies. In the longer term, small interfering RNAs (siRNA) directed against fusion transcripts or clustered regularly interspaced short palindromic repeats (CRISPR)-based gene-editing strategies may offer a theoretical means of suppressing or eliminating the oncogenic driver. At present, however, siRNA, CRISPR, and microenvironment-targeted strategies remain investigational and preclinical. Their successful development will depend on robust EHE-specific cell lines, genetically engineered mouse models, and improved characterization of downstream target genes (20).

Recent and Ongoing Clinical Trials

Recent and ongoing studies in EHE increasingly focus on pathway-directed therapies, reflecting the biological importance of WWTR1-CAMTA1 and *YAP1-TFE3* fusions in Hippo/YAP-TAZ signaling (20). However, most available evidence comes from early-phase or retrospective studies or from small patient subsets, and no systemic therapy has yet been established as a uniformly effective standard.

Trametinib, a MEK inhibitor, was evaluated in a single-arm phase 2 trial in patients with locally advanced or metastatic EHE. Although the objective response rate was low, treatment was associated with a reduction in EHE-related pain and a median progression-free survival of approximately 10 months, suggesting a potential palliative role rather than strong cytoreductive activity (21).

TEAD inhibitors are an important investigational strategy because TEAD transcription factors function as downstream effectors of YAP/TAZ-driven oncogenic signaling. Early-phase trials are evaluating oral TEAD inhibitors in advanced solid tumors, including EHE. IAG933 is being studied in a phase 1, first-in-human trial, while IK-930 has also been evaluated in a phase 1 study in advanced solid tumors with Hippo pathway alterations (22,23). These studies are biologically relevant, but their clinical efficacy in EHE remains to be defined.

Among established systemic options, sirolimus and pazopanib remain the most commonly used agents in clinical practice, although supporting evidence is largely retrospective. Sirolimus has demonstrated disease control in selected patients with slowly progressive EHE (24). Pazopanib and other anti-angiogenic agents have shown variable activity, generally leading to disease stabilization rather than objective tumor shrinkage (18). Earlier prospective studies also evaluated sorafenib and bevacizumab in vascular sarcomas, including EHE, and reported limited response rates with occasional clinical benefit (25,26).

Taken together, current and emerging data suggest that systemic therapy in EHE is most relevant for patients with progressive, symptomatic, or unresectable disease. Future trials should aim to define predictive biomarkers, clarify optimal treatment sequencing, and determine whether pathway-directed agents can improve outcomes beyond disease stabilization.

Conclusion

EHE is an ultra-rare endothelial neoplasm with distinctive molecular alterations and a broad clinical spectrum. Accurate diagnosis requires integration of histopathological findings, endothelial immunophenotype, molecular confirmation, and site-specific radiological assessment. Although *WWTR1-CAMTA1* and *YAP1-TFE3* fusions have substantially improved diagnostic precision, prognostic assessment remains challenging and should incorporate clinical presentation, disease distribution, tumor kinetics, histopathological risk features, and serosal involvement.

Management should be individualized within a multidisciplinary framework. Complete surgical resection remains the preferred approach for localized resectable disease, whereas active surveillance is appropriate for selected asymptomatic patients with indolent or slowly progressive disease. In hepatic EHE, liver-directed strategies, including resection, transplantation, or locoregional approaches, may be relevant in carefully selected cases. For progressive, symptomatic, unresectable, or high-burden disease, systemic therapies such as anti-angiogenic agents, mTOR inhibitors, and investigational pathway-directed agents can provide disease control, although objective responses remain uncommon and no standard systemic regimen has been established.

Future progress will depend on prospective registries, international collaboration, improved risk stratification, and biomarker-driven clinical trials. In particular, better integration of molecular classification with clinical behavior may help refine treatment selection and clarify the role of emerging targeted approaches in this rare and biologically distinctive malignancy.

Footnotes

Authorship Contributions

Concept: G.Ö., S.T., Design: G.Ö., S.T., Data Collection or Processing: A.F.A., Analysis or Interpretation: G.Ö., S.T., Literature Search: G.Ö., A.F.A., S.T., Writing: G.Ö., A.F.A., S.T.

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Reader Questions

Based on the manuscript: "Epithelioid Hemangioendothelioma: Challenges in Diagnosis and Management"

1. Which gene fusion is identified in the majority of epithelioid hemangioendothelioma (EHE) cases?

A. EWSR1-FLI1

B. WWTR1-CAMTA1

C. SS18-SSX

D. NAB2-STAT6

Correct Answer: B. WWTR1-CAMTA1

2. Which immunohistochemical marker is most consistently expressed in EHE?

A. CK20

B. CD31

C. S100

D. Desmin

Correct Answer: B. CD31

3. According to current expert recommendations, which strategy is appropriate for selected asymptomatic patients with slowly progressive metastatic EHE?

A. Immediate chemotherapy

B. Immediate radiotherapy

C. Active surveillance ("watch-and-wait")

D. Liver transplantation

Correct Answer: C. Active surveillance ("watch-and-wait")

4. Which organ is one of the most common primary sites or sites of involvement in EHE?

A. Pancreas

B. Liver

C. Thyroid

D. Prostate

Correct Answer: B. Liver

5. Which class of targeted agents is most commonly used for progressive or symptomatic advanced EHE?

A. EGFR inhibitors

B. VEGF pathway inhibitors (e.g., pazopanib, sorafenib)

C. PARP inhibitors

D. BRAF inhibitors

Correct Answer: B. VEGF pathway inhibitors (e.g., pazopanib, sorafenib)