A patient-focused summary of the ESMO Open clinical paper entitled:

"Epithelioid hemangioendothelioma (EHE), an ultra-rare cancer: a consensus from the community of experts"

THE EHE GROUP

EHE CONSENSUS PAPER – THE PATIENTS' VERSION

This document has been produced by the EHE Group (see page 44) to provide information for patients diagnosed with epithelioid hemangioendothelioma (EHE), wherever they live in the world, to help them understand this ultra-rare sarcoma and allow them to engage in more informed discussions and decision-making with their medical teams.

This document is a patients' version of the paper: **"Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts",** published in June 2021. This EHE consensus paper was produced in order to document and agree on key facts concerning the management of EHE, for which there was little or no agreed information.

The consensus was developed through the organisation of a global consensus meeting, held in December 2020 under the auspices of the European Society for Medical Oncology (ESMO), and chaired by Dr Silvia Stacchiotti from the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan. The meeting involved more than eighty experts from multiple disciplines from Europe, the United Kingdom, the USA, Canada and Asia. Patient advocates from the EHE Group and from Sarcoma Patients EuroNet (SPAEN) also took part.

We wish to thank all the clinical specialists for their time and care in participating in the collation of the consensus paper, and its subsequent drafting, review, and publication. For patients, carers or their medical teams who may want to read the full clinical consensus paper, this is available on the ESMO Open platform at:

https://www.esmoopen.com/article/S2059-7029(21)00130-7/fulltext

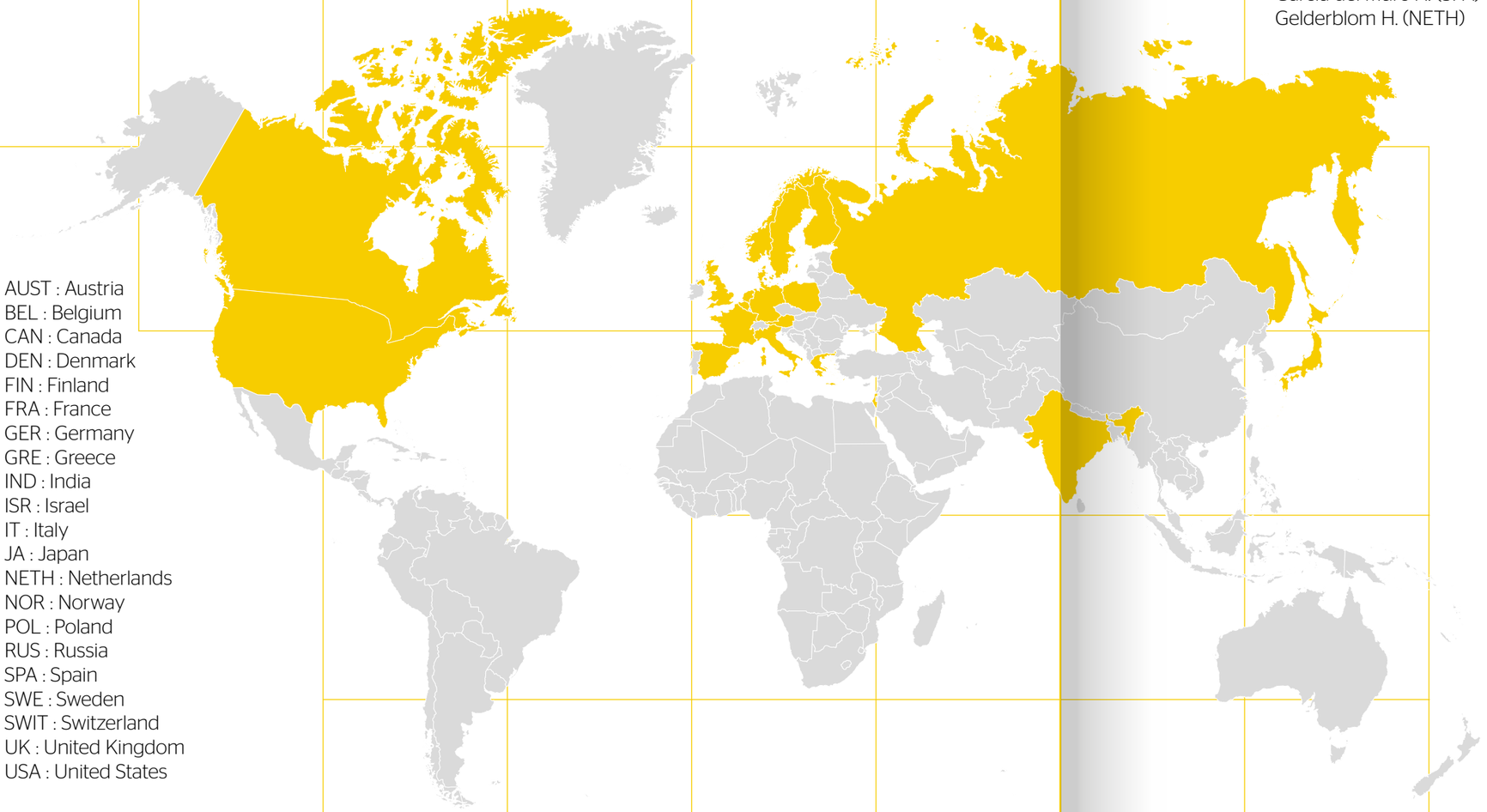
If having read this document you have any questions that have not been answered, or wish to discuss any aspect of EHE and its treatment, please contact any of the EHE Group organisations listed toward the rear of this document. We will do our best to answer your questions, and if we cannot, we hope we can direct you to somebody who can.

Epithelioid | hem | angio | endothel | ioma

cells | blood | blood vessel | inside surface of a blood vessel | tumor

THE COMMUNITY OF EXPERTS

Opposite is a list by discipline of the experts and patient advocates that took part in the consensus meeting and the subsequent preparation and publication of the paper. We thank them all for their continued focus and care for the EHE patient community.



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BEL : Belgium
CAN : Canada
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FIN : Finland
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GRE : Greece
IND : India
ISR : Israel
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1. INTRODUCTION

Epithelioid hemangioendothelioma (EHE) is an ultra-rare **vascular sarcoma**, with an unpredictable clinical course and often **metastatic** at the time of presentation. Given its rarity, there are still many open questions for the optimal management in EHE patients, and dedicated clinical practice guidelines are today lacking. In addition, advanced EHE has been reported to be poorly responsive to those treatment regimens usually recommended for other sarcomas and currently there are no potentially **active** alternative treatments approved specifically for this disease.

To address this shortcoming, a global consensus meeting was organized in December 2020 under the umbrella of the European Society for Medical Oncology (ESMO) involving over 80 experts from several disciplines from Europe, the United Kingdom, the USA, Canada and Asia, together with patient representatives from the EHE Group (a global, disease-specific patient advocacy group) and Sarcoma Patients EuroNet (SPAEN). The meeting was aimed at defining, by consensus, evidence-based best practices for the optimal approach to treating EHE. The consensus achieved during that meeting is the subject of this publication.

Global consensus meeting of over **80** experts

2. EXISTING EVIDENCE

Evidence for the treatment of EHE is mostly derived by case reports or limited **retrospective series**. To date, only two **prospective clinical trials** are available. On this basis, it is crucial that EHE patients are managed within **sarcoma reference centres** or **sarcoma networks**, by dedicated doctors with experience in the field of sarcomas.

The importance of sarcoma reference centres and sarcoma networks

For patients diagnosed with EHE, it is hard to over-emphasise the importance of being referred to a sarcoma reference centre or a sarcoma network. Sarcomas as a group are typically rare, and EHE is one of the rarest. Being under the care of a medical team with sarcoma experience is critical. If you want assistance in finding such groups, please contact your nearest EHE Group member, as listed on page 45 of this document.

GLOSSARY OF TERMS

In this paper certain terms are emboldened on each page. Definitions of these terms can be found in the yellow box on the same page. All such terms are also included in the Glossary of Terms at the end of the paper.

vascular: composed of neoplastic cells resembling blood vessels

sarcoma: cancer originating in connective tissues, including cartilage, fat, muscle, blood vessels, fibrous tissue

metastatic: spread from an initial or primary site to a different or secondary site

active: viable with possibility of success

retrospective series: studies including EHE patients looking backwards at their clinical history

prospective clinical trials: studies in which included patients are followed over time and data about them is collected as their characteristics or circumstances change

sarcoma reference centres, sarcoma networks: centres with a recognised expertise in the treatment of sarcomas

3.
EPIDEMIOLOGY/CLINICAL PRESENTATION

The rate of new EHE cases is 3.8 cases per 10,000,000 people per year. The total number of patients living with EHE is estimated at less than 1 per million. EHE is more common in women than in men and is very rare in children.

EHE can potentially arise anywhere in the body. It can present as a single lesion, as multiple **lesions** (known as "multifocal") in the same organ, or it can involve different organs. When EHE occurs as a single lesion, this is usually a mass in the soft tissues (such as muscles, fat, connective tissue, blood vessels). However, more than 50% of EHE at presentation affects the lung, and/or liver, and/or bone. The clinical presentation at the time of diagnosis is variable. Often patients are completely asymptomatic (i.e. having no symptoms) and EHE is found by accident, during consultation for a different medical condition. In symptomatic patients, symptoms can be pain (40%), a palpable mass (6%-24%), and weight loss (9%). EHE in a vessel may present with signs and symptoms of a blocked vessel (swelling, redness, pain).

3.8
cases per
10,000,000
people per year

4.
PROGNOSIS

Currently, there are no clearly proven clinical or biological factors for EHE that are able to predict how the disease will behave (ie, prognostic factors). There are characteristics such as tumor size and some microscopic features that have been proposed but need to be confirmed with more certainty. To estimate patient **prognosis** at the time of diagnosis, doctors look at the location, the extent of disease (tumor size and presence of metastasis), and the presence of specific signs and symptoms. For example, in patients with EHE involving the **pleura** and with evidence of fluid around the lungs the clinical course of the disease can be more aggressive, and the prognosis worse compared to those who do not show these signs.

The clinical behavior of metastatic EHE can be extremely variable, ranging from **indolent** variants to very aggressive disease. Also, symptoms such as non-infective fever, weight loss, and fatigue, which might be present at the onset or developed overtime, seem to correlate with a worse quality of life and survival.

So, to try to predict the course of the disease in a single patient and the best treatment strategy doctors carefully investigate the presence of **pleural effusion** or **ascites** weight loss, fever, fatigue, and tumor-related pain. There are currently no data to help in understanding the effect of pregnancy on the course of EHE. There are also current studies that are trying to investigate what the role of hormones and inflammation is in EHE and exploring the role of circulating blood inflammatory and hormonal molecules as potential markers of EHE aggressiveness, response to therapies, and potential hints for further EHE behavior.

epidemiology: the study and analysis of the distribution, patterns and determinants of health and disease conditions in defined populations

lesion: location of a tumor

prognosis: explanation and forecast of how a patient's EHE will progress and develop

pleura: lining of the lungs

indolent: naturally stable cases to very slow-growing

pleural effusion: fluid accumulating in the lining of the lungs

ascites: fluid accumulating in the abdomen

5.
GENERAL PRINCIPLES ON EHE MANAGEMENT

Due to the ultra-rare nature of EHE, patients should be managed in sarcoma reference centres or sarcoma networks by a dedicated sarcoma multidisciplinary team including several specialists, such as a pathologist, radiologist, surgical oncologist, orthopaedic surgeon, radiation oncologist, medical oncologist, and palliative care specialist who are familiar with the nuances of this disease. Other specialists, such as liver transplant (LT) experts, should be involved when requested.

6.
MOLECULAR BIOLOGY

EHE is a cancer characterized by a specific genetic alteration called a **translocation**. 90% of EHE are marked by the fusion of a gene called **WWTR1** and a second gene called **CAMTA1**, while approximately 10% have different gene fusions involving the gene **YAP1** and the gene **TFE3**. Other very rare translocations driving EHE have also been reported. Whenever an initial diagnosis is made outside a sarcoma centre, molecular testing and a review by a sarcoma centre pathologist are highly recommended to confirm the diagnosis and rule out other cancers. However, these translocations currently do not represent therapeutic targets and do not provide any form of prognostic or predictive value about a patient's EHE.

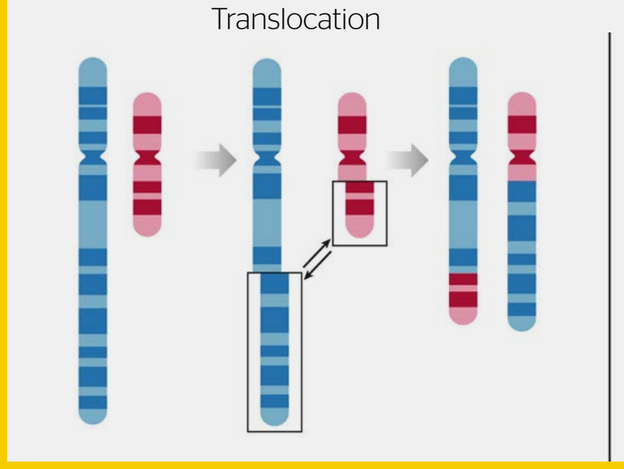
translocation: swapping of genetic material between two genes (see diagram below)

WWTR1: WW domain containing Transcription Regulator 1

CAMTA1: Calmodulin binding Transcription Activator 1

YAP1: Yes-Associated Protein 1

TFE3: Transcription Factor E3

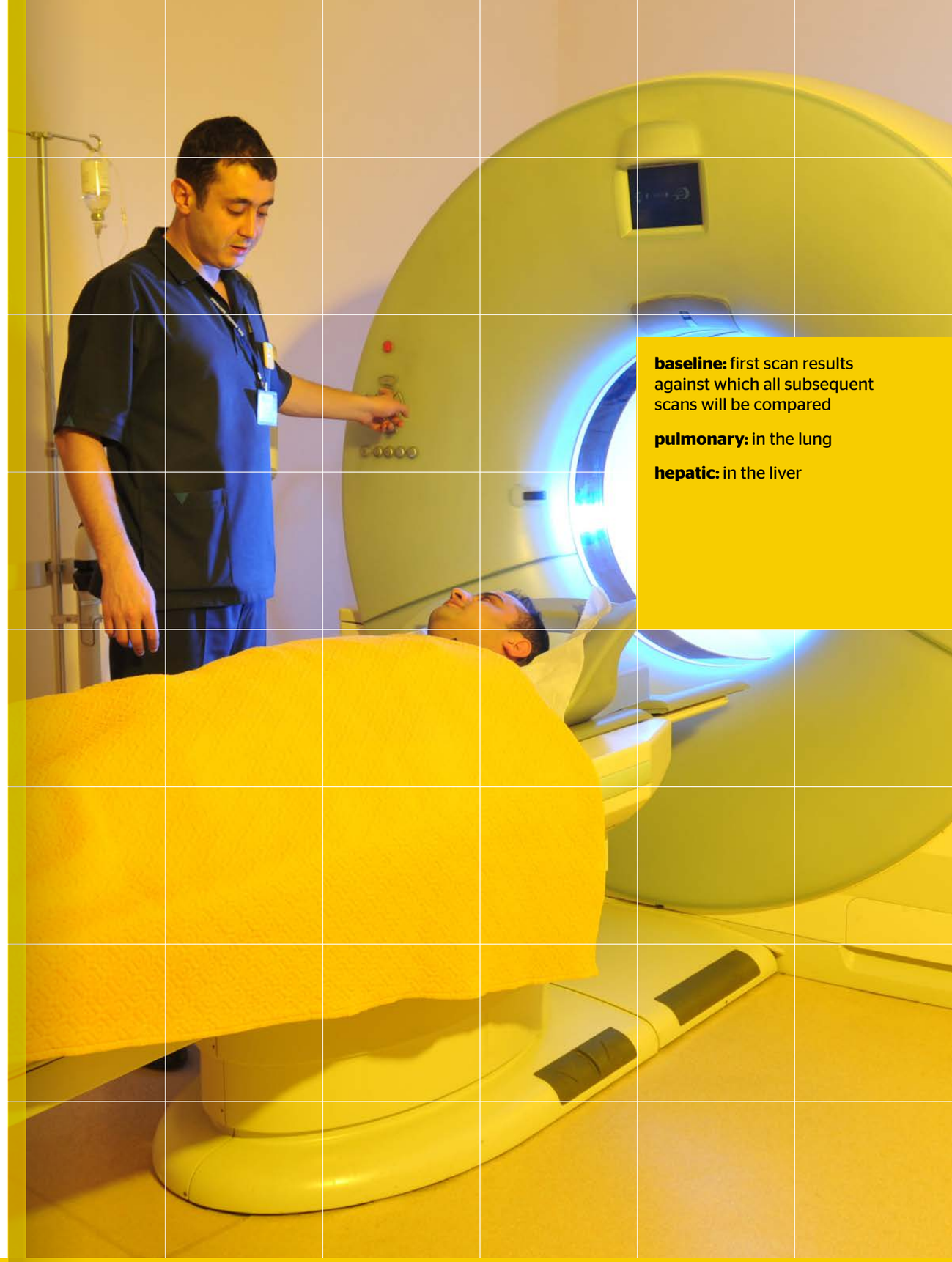


7.
RADIOLOGY

Upon initial diagnosis imaging for EHE consists of whole-body imaging by computed tomography (CT) or magnetic resonance imaging (MRI), or combinations of both modalities (e.g. chest CT and abdominal/whole-body MRI). A whole-body MRI, or whole-body FDG-PET/CT (including limbs) is advisable to detect bone and limb involvement. If whole-body MRI or PET/CT is unavailable, a bone scan is recommended to exclude bone lesions. FDG PET/CT scans use injected radioactive material (FDG) to determine how active a cancer is. FDG uptake in EHE is usually mild to moderate. There are reports suggesting that patients with particularly high uptake have a worse prognosis.

As a general rule, any relevant radiological study that was used at **baseline** to highlight the different sites of the disease should be used subsequently, to monitor the status of the disease while a patient is on treatment or surveillance.

Different scans can be used to complement one another. For example, CT or FDG PET/CT allows optimal assessment of **pulmonary** disease but MRI is recommended for the assessment of primary soft tissue disease and also for the monitoring of liver and bone involvement. Triple phase imaging of the liver is particularly helpful for **hepatic** involvement. This technique acquires images at 3 different time points, or phases, following the administration of contrast.



baseline: first scan results against which all subsequent scans will be compared

pulmonary: in the lung

hepatic: in the liver

7.1
Imaging features

Hepatic EHE usually presents as numerous often merged together nodules in a peripheral location of the liver. The liver is surrounded by a fibrous layer of tissue which is called a liver capsule. Irregularity (flattening or concavity) of the capsule is a characteristic feature of hepatic EHE. Other common features are the *"target"* appearance of tumors at a specific time after the administration of the contrast and the *"lollipop"* sign (a blood vessel tapering and terminating at the lesion).

Thoracic EHE can present with four main patterns: multiple small pulmonary nodules, **reticulonodular opacities**, thickening of the pleura (lining of the lungs), and a single mass in the lung. Sometimes pulmonary nodules may exhibit a surrounding halo, so-called ground-glass opacity. Patients with diffuse pleural thickening and pleural effusion seem to have a poor prognosis.

When EHE involves bones, the axial skeleton (including skull, vertebral column, and thoracic cage) and lower limbs are the most common sites. EHE spread to bones usually causes bone destruction.

7.2
Response assessment

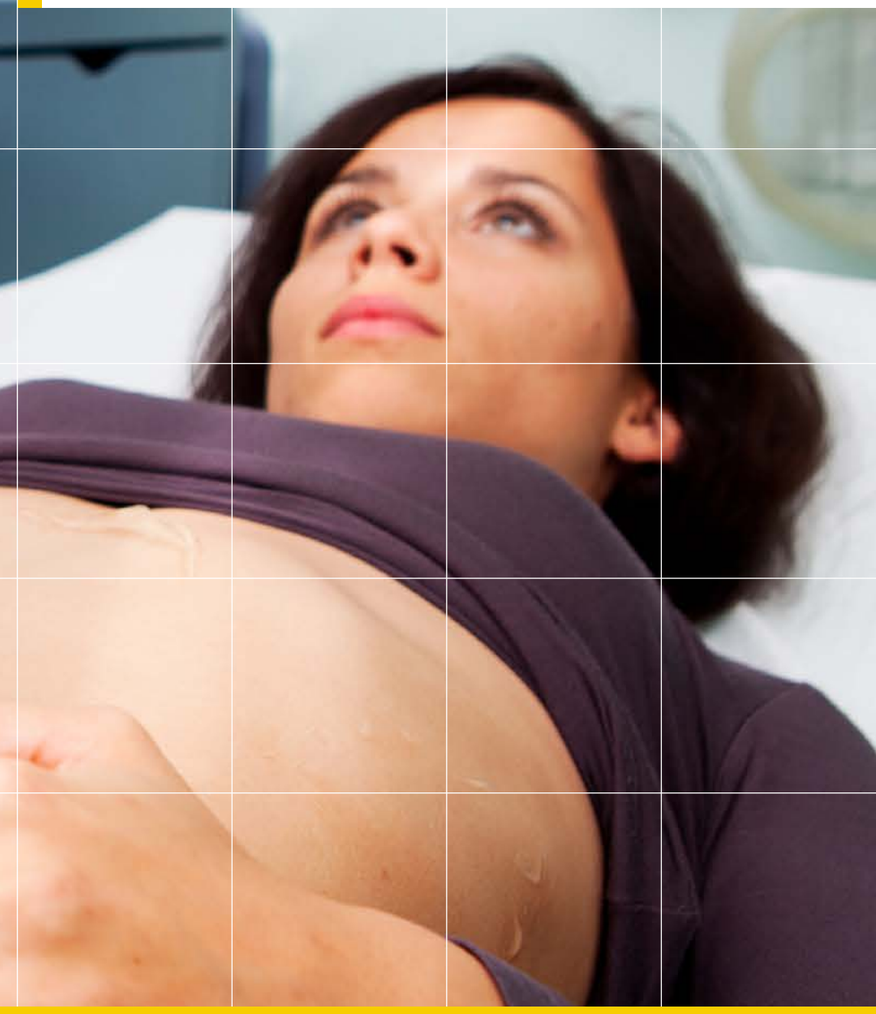
The imaging definition of progression and the assessment of treatment response are a challenge in EHE. The occurrence of pleural effusion or ascites and slow-growing subtypes makes the use of a common assessment criteria (increase/decrease in tumor size) of limited value. Improvement of pleural effusion/ascites, very limited reduction in size and improved symptom control should be taken into account when assessing treatment response. Similarly, worsening of symptoms, though not reflected by changes on scans, particularly for thoracic disease, should be carefully considered as a potential sign of progression. Therefore assessment of symptoms and QoL (quality of life) criteria are an essential component of progression/ treatment response assessment. Preliminary data suggest that changes in isotope uptake on FDG-PET/CT can also be of help in response assessment.

thoracic: in the chest cavity

reticulonodular opacities: a pattern resembling a net with small nodules

8.
DIAGNOSIS

EHE diagnosis must be confirmed pathologically. The recommended procedure to take tumor tissue, for diagnosis by pathologists is a core-needle biopsy (i.e. a procedure in which a needle with a hollow core is used). The needle should be large enough to collect an adequate tissue sample.



9.
TREATMENT

9.1
Surgery

The treatment of choice in EHE, when it presents with a single lesion that can be completely **resected**, is surgery. A full radiologic assessment to exclude distant metastasis needs to be performed before planning the resection of the single lesion. Imaging of the local lesion is also needed, usually by MRI, to confirm which is the best way to resect and approach the disease. Resection should be carried out in centres with experience in sarcoma surgery.

The primary aim of surgery is the complete resection of the tumor with **clear surgical margins**. When this is feasible, the probability of no further recurrence is very high, in the range of 85%-90%. Surgery can be complemented with radiation therapy (RT) before or after surgery, when the margins are close or when microscopic disease is seen under a microscope. When high-risk surgery is anticipated, or a complete resection with no residual disease is not possible, surgery can be substituted by RT or other local modalities such as **ablation**, or even **isolated limb perfusion** procedure.

The risk of EHE recurrence remains for a prolonged period of time after surgery, even after the complete resection of a tumor. For this reason, it is important that a regular follow-up plan with appropriate imaging is agreed and implemented.

Active surveillance (called “wait-and-watch”) is the initial recommended option in patients who cannot undergo surgery or present with multiple lesions. Although active surveillance has never been formally studied, it is common practice in experienced centres to keep asymptomatic patients on active surveillance before engaging in treatment should their disease begin to show signs of progression. Prolonged disease stabilities and occasional regressions in absence of any treatment have been reported.

resected: removed by surgery

clear surgical margins: the tumor is removed with a layer of normal tissue all around the tumor surface

ablation: treatment of tumors using different forms of targeted energy such as heat, cold or forms of microwaves

isolated limb perfusion: a treatment technique by which chemotherapy is only delivered in the affected region of the limb

9.1.1
EHE of soft tissue and bone

For EHE in which the tumor originates from the soft tissue, surgery must be planned by taking into account that the mass should be removed entirely without fragmenting the tumor and with clear surgical margins.

In tumors originating from large blood vessels, the part of the vessel where the tumor originated should be resected with the mass. The need for vascular reconstruction using synthetic grafts or blood vessels from other areas of the body depends on the vessel type (artery versus vein), and site and presence of additional blood supply. After **venous** resection, the vein is usually reconstructed if originally open and in the absence of additional adjacent blood vessels; otherwise, ligation (closing off) without reconstruction is acceptable. After **arterial** resection, the artery is usually reconstructed. Preoperative radiation therapy is preferred to avoid irradiation of the **vascular graft**.

The role of surgery in metastatic EHE of bone is unknown, but in the absence of alternative treatments, if feasible, surgery is an option. Such decisions should be considered on a case-by-case basis and take into consideration the pattern of tumor progression, fracture risk, site and number of lesions, expected risks, patient symptoms and availability of alternative local therapies, such as ILP (isolated limb perfusion), ablation procedures and/or radiation therapy.

venous: involving veins

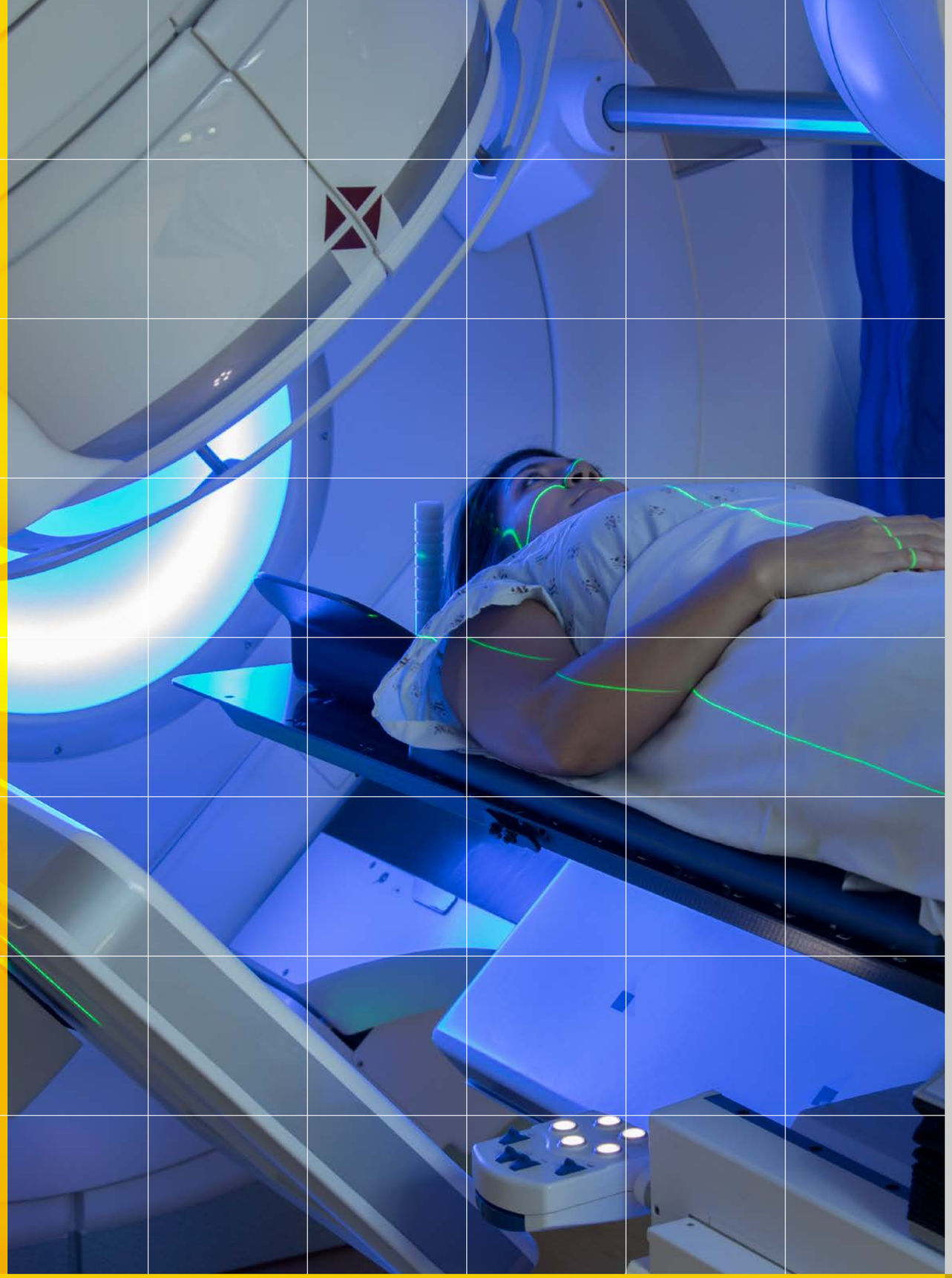
arterial: involving arteries

vascular graft: replacement of the removed segment of the vessel

multimodality: using different forms of therapy during a phase of treatment

For bone EHE, if surgery is used, the bone affected by EHE should be resected along with the involved surrounding soft tissues. In case of bone EHE, where a complete surgical resection cannot be proposed, it is possible to consider a curettage of the bone (removal of the tumor through a window in the bone using curettes to scrape the lesion) followed by RT.

Amputation (surgical removal of all or part of the limb) should be discouraged in patients who can be treated with a combination of surgical procedures, local treatments, and/or radiation therapy, provided the limb remains functional after **multimodality** treatment.



9.1.2
EHE of the liver

Treatment of hepatic EHE should take into consideration the anatomical location within the liver, tumor size, number of nodules, the presence of invasion of major blood vessels and the presence of **extrahepatic** disease.

After a period of observation to assess the biological behavior of EHE, surgical resection is considered the treatment of choice for stable/slowly growing single or several easy-to-access lesions. The goal is complete resection with no residual EHE cells at the resection margins. Based on the limited literature available, hepatic resections show no recurrence of EHE in at least 50% of patients. However, none of the studies contained information on the pace of disease growth before surgery.

In selected patients with unresectable hepatic EHE, in absence of extrahepatic disease, liver transplantation provides short- and long-term outcomes comparable to patients with other medical reasons for a transplant. Specifically, liver transplant has been associated with a 5-year post-transplant survival rate in excess of 50% of cases. Similar to the evidence available for hepatic resections, none of the studies provided information on the pace of disease before the transplant. It is well known that multifocal (multiple lesions) hepatic EHE can remain stable for many years without active treatment. On this basis, after full disclosure about the limitations of the current literature, liver transplantation should be proposed as a treatment modality for patients with unresectable EHE. It is also an option for patients with liver-only EHE who develop liver failure due to the tumor, but who are in

extrahepatic: anywhere in the body outside the liver

generally good condition, with an expected good survival after the transplantation.

The **median survival** in a study of 149 patients after liver transplant was 7.6 years. It is unclear, however, to which extent this is due to the natural history of stable EHE cases or, in part, to the impact of the complete removal of EHE by the replacement of the liver. Risk factors for post-transplant recurrence include tumor rupture, invasion of major vessels by the tumor and the presence of lymph node metastases in certain locations. History of tumor rupture should be considered a major **contraindication** to transplant. Liver transplant should not be proposed to patients with liver EHE and extrahepatic disease.

The role of transplantation for unresectable EHE requires further studies as the current evidence is based only on retrospective series, with a high risk of selection and reporting biases that may skew the data. Therefore, this indication is not universally supported by all transplant centres. Future studies with a long follow-up should provide data about the patient population mostly benefiting from liver transplantation.

Stereotactic body radiation therapy (SBRT), radiofrequency ablation (RFA) and microwave ablation (MWA) are therapeutic options for patients with single or several lesions who are not surgical candidates and for patients with recurrent liver nodules after liver resection/ transplantation and/or as bridge treatments while patients are waiting for a transplant.

9.1.3
EHE of the thorax (chest)

Thoracic EHE is predominantly found in association with liver and/or bone EHE. The presence of EHE in the pleura (lining of the lungs) is associated with a worse prognosis.

Amongst the four different types of EHE in the chest, the lung multinodular pattern is associated with longer survival, whereas the shortest survival is observed in cases with a nodule/mass with pleural involvement. There appears to be no significant difference in survival between EHE in the chest and other locations.

Surgical resection is the treatment of choice in cases with a single tumor or with several tumors that are technically resectable, after a period of observation. Procedures such as **pleural stripping** and or **pneumonectomy** may be considered on a case-by-case basis. Local ablative techniques can also be considered when EHE involvement is isolated to the lungs.

median survival: a statistic that refers to how long the majority of patients survive with a disease in general or after a certain treatment

contraindication: reason not to receive a particular treatment or procedure

pleural stripping: surgical removal of pleural layers

pneumonectomy: surgical removal of the lung or a part of the lung

9.2
Radiation therapy

9.2.1
General principles

There is limited evidence evaluating the role of radiation therapy alone in EHE, although EHE is considered relatively **radiosensitive**. The potential role of radiation should be based upon individualized case considerations. This will primarily depend on the ease by which the tumor can be resected, and the risk of recurrence and/or the feasibility of further surgery in the event of relapse.

Surgery remains the mainstay of treatment in cases of single resectable tumors. The risk of recurrence following complete surgical resection is in the range of 10%-15%. The role of radiation therapy in EHE is based on the principles and management of other soft tissue sarcomas. Post-surgery, radiation therapy can be recommended in selected cases where there is concern regarding the risk of recurrence. There are no reported cases evaluating the role of preoperative radiation therapy for EHE, but following basic soft tissue sarcoma principles, it is reasonable to consider preoperative radiation therapy in cases where complete resection is not feasible. For inoperable cases, definitive radiation therapy has been recommended to shrink and or control the local disease.

9.2.2
EHE of bone

Post-operative radiation therapy has been shown to offer excellent local control at 2 years in skeletal EHE. In the management of spinal EHE, radiation therapy has been also utilized in the preoperative setting, as a primary treatment for inoperable lesions and for symptoms management.

radiosensitive: potentially responsive to radiation

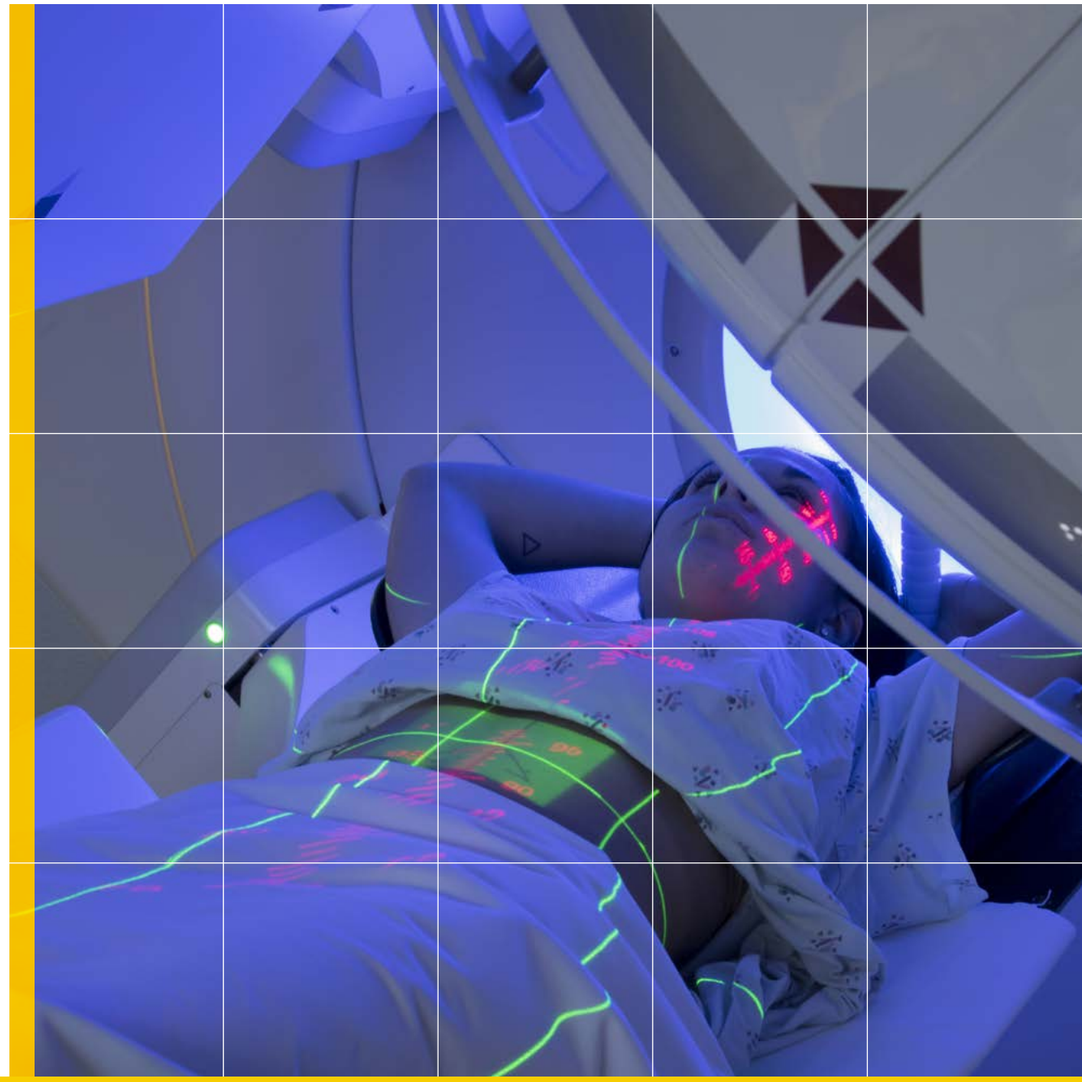
9.2.3
EHE of liver

Local ablative techniques including SBRT (stereotactic body radiation therapy), RFA (radiofrequency ablation) and MWA (microwave ablation) can be considered in unresectable single/several EHE lesions. The most suitable ablative technique is best determined by a multimodality team and is based on such factors as the size and anatomical location of the lesion (e.g. proximity to vessel or bowel must be taken into account).

SBRT delivers very high (ablative) radiation doses with high precision sparing surrounding tissue. It can be considered in suitable cases at prescribed doses as for other soft tissue sarcomas when other treatment options are not indicated.

9.2.4
EHE of the lung

Pulmonary EHE commonly manifests as multiple nodules. In this case, radiation therapy is generally considered only for symptoms management.



9.3
Other locoregional treatments for EHE localized to one organ

Data on **locoregional treatments** as an alternative to surgery and/or radiation therapy in EHE are limited and do not allow definitive conclusions on the specific role of any of these approaches. They include various types of ablation, **transarterial chemoembolization**, **radioembolization** and **isolated limb perfusion**. No data are available on other local therapies such as high-intensity focused ultrasound in EHE.

Retrospective data suggest that radiofrequency ablation (RFA) and microwave ablation (MWA) can be safe and useful to treat single/several small EHE lesions with curative intent. Nevertheless, prospective confirmatory data are necessary to make any definitive recommendations.

Prospective data are needed to confirm that transarterial chemoembolization (TACE) is superior to surgical modalities in advanced EHE. In extrahepatic disease (lymph node, lung, bone) a trend toward better survival and a better quality of life was seen in four patients who received TACE compared with five patients who underwent resection or liver transplantation, suggesting that TACE could be considered as a palliative option in most advanced cases. The role of pre-transplant TACE is not established and warrants further investigation. Data on Selective Internal RT (SIRT) (radioembolization) are lacking. A single case report described significant remission of a multifocal, diffuse, non-resectable EHE 2 months after carrying out SIRT.

EHE localized to the extremities can be treated by isolated limb perfusion (ILP). However, although there is a shared consensus among experts that this treatment can be highly active in EHE, there are no published data reported to confirm this. It remains unclear whether surgery should be carried out to resect residual disease post ILP, or whether patients should continue active surveillance, delaying further treatments to the time of progression.

locoregional treatments: treatment not reaching every part of the body, but only the single treated site

transarterial chemoembolization: delivering chemotherapy combined with blocking the blood supply to the tumors

radioembolization: radioactive beads deliver a small amount of radiation to the tumor and block blood supply at the same time

isolated limb perfusion: a treatment technique by which chemotherapy is only delivered in the affected region of the limb

9.4
Systemic treatment

In patients with resectable EHE located in one organ, there is no evidence supporting the use of systemic therapies before and/or after the surgery.

For patients with asymptomatic metastatic disease that is not possible to remove completely without potential complications, the wait-and-watch approach should be the preferred initial strategy in order to limit the risk of over-treatment.

Patients with pleural effusion or ascites (fluid in the thorax or abdomen) and/or significant symptoms tend to have a rapidly progressive course, therefore in this case, an early start of systemic therapy should be considered, even in absence of clear evidence of disease progression.

Patients with metastatic disease and clear evidence of disease progression and/or worsening of symptoms and/or organ dysfunction are candidates for systemic treatment, even though a standard medical approach is currently not established. Chemotherapy commonly used for other sarcomas appears to have very limited activity and its use should be limited to more aggressive EHE cases. Anti-tumor activity has been seen retrospectively with interferon, thalidomide, anti-angiogenic drugs and mechanistic target of rapamycin (mTOR) inhibitors. Amongst them, the highest clinical activity (most successful) has been reported for mTOR inhibitors. The panel agrees that these represent the preferred treatment option for patients with clearly progressive disease. No formal prospective comparison, however, has been carried out and the selection of drugs should factor in **comorbidities** as well as patient preferences.

As with other ultra-rare cancers, as far as costs of treatment being covered is concerned, in many countries, EHEs are merged with more common sarcomas, even though most trials that led to the approval of drugs commonly used in sarcomas have never included patients with EHE. We strongly advocate treatments for EHE based on the best available clinical evidence, even though the best evidence is limited to small trials and case series.

EHE patients should be considered for clinical studies when available and participation in clinical trials is encouraged.

The MEK-inhibitor trametinib is currently under investigation in the disease. In addition, also eribulin, is under assessment in patients with EHE within a clinical study currently ongoing in the US. Ongoing efforts are trying to clarify the role of hormonal stimulation and inflammation in EHE **pathogenesis**, with the aim of possibly identifying new treatment targets.

comorbidities: the simultaneous presence of two or more diseases or medical conditions in a patient

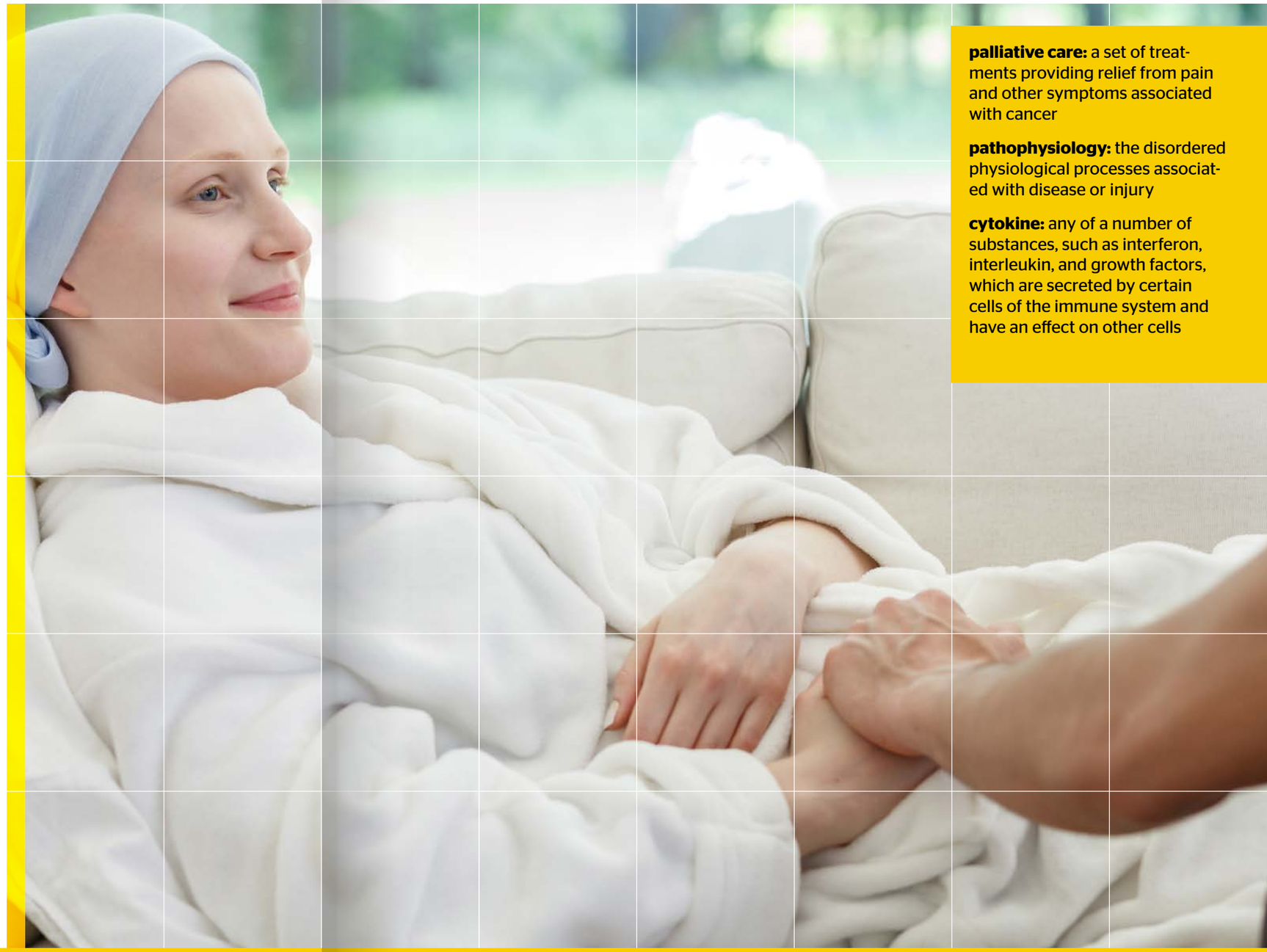
pathogenesis: development of a disease

9.5
Palliative care

Palliative care should be an integral part of the care of EHE patients. Early palliative care referral can be particularly useful for symptomatic patients. Identifying clinical and psychosocial support needs for patients and their family caregivers as early as possible across the changing pattern of the disease is crucial and requires an interdisciplinary palliative care approach and research effort. Systematic symptoms screening and assessment should be formally presented in clinical records and registries.

EHE pain **pathophysiology** is not well understood. Tumor related pain, as well as other symptoms often experienced by EHE patients, may be related to **cytokine** release from the tumor itself, which may also be responsible for limited response to common opioid pain medications. This clinical observation requires specific research efforts.

Some aspects of pain control for EHE are highly challenging, such as predicting the response to the most commonly used painkillers. Palliative care for EHE patients should be personalized and should follow state-of-the-art multimodal approaches, using nonsteroidal anti-inflammatory drugs (NSAIDs), neuropathic pain medications such as gabapentin, when indicated, and opioids. Pain related to EHE can be severe, with spontaneous flares that are difficult to treat with opioids and in some cases sensitive to NSAIDs. Anesthesiologists' and pain specialists' expertise may be needed when interventional procedures are considered. Localized surgical and radiation therapy can be necessary for pain management of symptomatic lesions. New pharmacological strategies would be of great benefit.



palliative care: a set of treatments providing relief from pain and other symptoms associated with cancer

pathophysiology: the disordered physiological processes associated with disease or injury

cytokine: any of a number of substances, such as interferon, interleukin, and growth factors, which are secreted by certain cells of the immune system and have an effect on other cells

10.
FOLLOW-UP

Due to limited data, routine follow-up schedules in EHE patients differ across institutions. The experts that participated in this consensus, have agreed that in patients in which the tumor has been completely resected an MRI of the primary tumor site and a whole-body CT scan can be suggested every 6 months for the first 4 to 5 years after diagnosis. Thereafter, if no disease progression is observed, MRI and whole-body CT scans could be done yearly. A more frequent disease assessment is however needed in patients who are on active treatment or have suspected tumor growth.

11.
FUTURE PROSPECTIVE

There are several unmet needs that require clinical studies in EHE. The main challenge for the studies is that EHE behaviour is variable across patients and difficult to predict. For that reason, patient registries should be encouraged. In such an ultra-rare entity, even small studies, case series analyses, and even case reports can contribute to the available evidence. Global collaboration will be critical to advance our knowledge.

Global collaboration will be critical to advance our knowledge

Acknowledgments

Dr Silvia Stacchiotti:

The EHE Group wishes to thank Dr Stacchiotti for her drive and dedication to the treatment and care of sarcoma patients, including those with EHE. We thank her for recognising the importance of developing the first consensus paper on how to treat EHE, even though there is much about this disease that is still not known, and for coordinating the consensus process under the auspices of the European Society for Medical Oncology (ESMO). There is much still to do, and many questions to be answered, but the first consensus paper is now a published, openly-available reality.

The European Society for Medical Oncology:

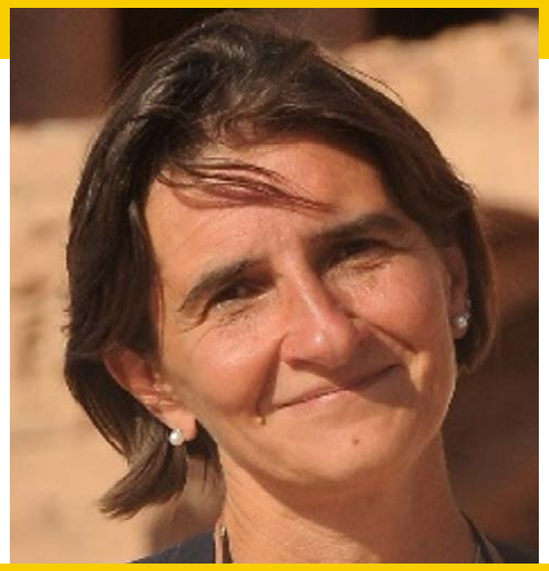
We also want to extend our gratitude to **ESMO** for providing the platform and structure through which the consensus process was organised. Without this, the ability to bring together a very significant community of clinical experts experienced in the treatment of EHE, from multiple countries both in and outside Europe, would not have been possible. We thank you for your invaluable support of the consensus-building process, not just for EHE, but for other cancers and sarcomas too.

Community of Experts:

We are also deeply grateful to the Community of Experts, listed near the beginning of this document, who together gave their time and energy to a detailed and extensive discussion of EHE; to the collation of consensus positions on multiple issues; and to the ultimate review and agreement of the Consensus Paper itself. As patient advocates we are all too well aware of the extreme demands on your time. We will never take your care and dedication for granted, and thank you deeply for your support.

The EHE Community:

We must also recognise the wonderful support that the EHE Group has received from the global EHE community. We thank you for your almost limitless drive to contribute patient experience, disease information, fundraising, and the inspiration, encouragement and help to spearhead critical initiatives, such as the international consensus-building effort represented by this document.



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

We will never take your care and dedication for granted.

The editorial team

We must thank a small group who all contributed to the development of this patient-focused version of the original paper. Special thanks to:

Dr Silvia Stacchiotti (IT)
Overall review of patient-focused document

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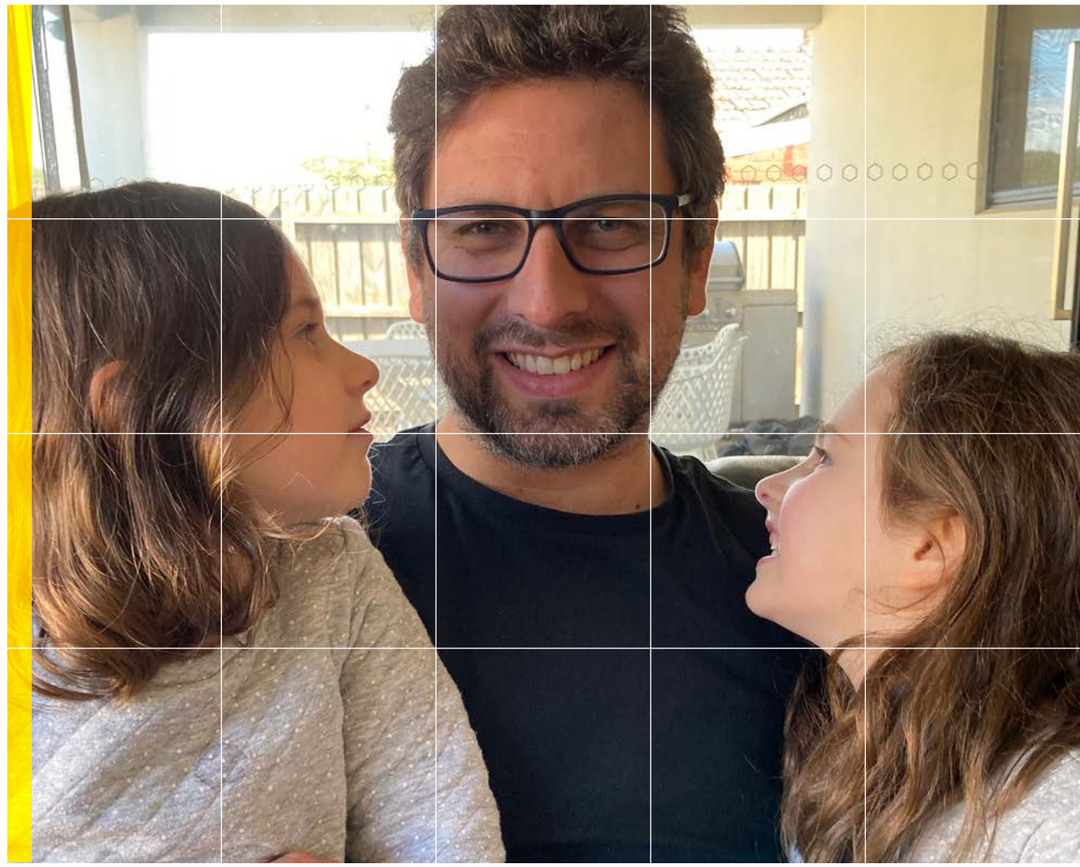

Glossary of terms

ablation:
treatment of tumors using different forms of targeted energy such as heat, cold or forms of microwaves

active:
viable with possibility of success

arterial:
involving arteries

ascites:
fluid accumulating in the abdomen

baseline:
first scan results against which all subsequent scans will be compared

clear surgical margins:
the tumor is removed with a layer of normal tissue all around the tumor surface

comorbidities:
the simultaneous presence of two or more diseases or medical conditions in a patient

contraindication:
reason not to receive a particular treatment or procedure

cytokine:
any of a number of substances, such as interferon, interleukin, and growth factors, which are secreted by certain cells of the immune system and have an effect on other cells

epidemiology:
the study and analysis of the distribution, patterns and determinants of health and disease conditions in defined populations

extrahepatic:
anywhere in the body outside the liver

hepatic:
in the liver

indolent:
naturally stable cases to very slow-growing

isolated limb perfusion:
a treatment technique by which chemotherapy is only delivered in the affected region of the limb

lesion:
location of a tumor

locoregional treatments:
treatment not reaching every part of the body, but only the single treated site

median survival:
a statistic that refers to how long the majority of patients survive with a disease in general or after a certain treatment

multimodality:
using different forms of therapy during a phase of treatment

palliative care:
a set of treatments providing relief from pain and other symptoms associated with cancer

pathogenesis:
development of a disease

pathophysiology:
the disordered physiological processes associated with disease or injury

pleura:
lining of the lungs

pleural effusion:
fluid accumulating in the lining of the lungs

pleural stripping:
surgical removal of pleural layers

pneumonectomy:
surgical removal of the lung or a part of the lung

prognosis:
explanation and forecast of how a patient's EHE will progress and develop

prospective clinical trials:
studies in which included patients are followed over time and data about them is collected as their characteristics or circumstances change

pulmonary:
in the lung

radioembolization:
radioactive beads deliver a small amount of radiation to the tumor and block blood supply at the same time

radiosensitive:
potentially responsive to radiation

resected:
removed by surgery

reticulonodular opacities:
a pattern resembling a net with small nodules

retrospective series:
studies including EHE patients looking backwards at their clinical history

sarcoma reference centres, sarcoma networks:
centres with a recognised expertise in the treatment of sarcomas

sarcoma:
cancer originating in connective tissues, including cartilage, fat, muscle, blood vessels, fibrous tissue

thoracic: in the chest cavity

transarterial chemoembolization:
delivering chemotherapy combined with blocking the blood supply to the tumors

translocation:
swapping of genetic material between two genes

vascular:
composed of neoplastic cells resembling blood vessels

vascular graft:
replacement of the removed segment of the vessel

venous:
involving veins

About the EHE not-for-profit organisations

THE EHE GROUP

The EHE Group is the collective name we use to describe our alliance of independent not-for-profit organisations that are dedicated to supporting EHE patients while driving a dynamic program of EHE research. The original three organisations were all formed in 2015, in the USA, UK and Australia. Since then EHE organisations have been organised in Canada and Italy. All of these groups have their origin in the EHE Facebook page that provides global engagement for patients and their supporters, wherever they live, and has over 2,100 members spread across more than 75 countries.

The EHE Group has three key common objectives:

1

To support EHE patients wherever they live, regardless of gender, race, religion, ethnicity or any other characteristic that may be discriminatory;

2

To advocate for greater awareness, engagement and participation from governments, health organisations and commercial entities in the management of EHE and EHE patients; and

3

To raise the funds, and coordinate, promote and deliver multi-focused EHE research to discover new treatments for EHE in order to bring forward the day that an EHE diagnosis no longer needs to be feared.

If you are an EHE patient or a family or friend of a patient, and you are seeking information and advice about EHE, please don't hesitate to contact us through the contact information given opposite.

Contacts

In the USA:

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Using this document

The information in this document was developed for the patient community from the information presented in the clinical paper entitled:

"Epithelioid hemangioendothelioma (EHE), an ultra-rare cancer: a consensus from the community of experts on the diagnosis and management of EHE"

The original clinical paper was published on 1st June 2021 in the ESMO Open platform. It can be accessed at **https://www.esmoopen.com/article/S2059-7029(21)00130-7/fulltext**

This document has been produced for the global EHE patient community and is for general guidance only. If you need detailed medical advice on Epithelioid Hemangioendothelioma (EHE) cancer, please contact an appropriate specialist medical practitioner, ideally with experience of EHE and within a sarcoma reference centre or sarcoma network.

Under no circumstances should you use the information in this document to replace, or instead of, the advice that can and should be given by an experienced medical practitioner relating to your treatment decisions.

We have tried to ensure that the information in this document is accurate. The information has been compiled in good faith and with input and review by clinical experts experienced with EHE, and we believe it represents a fair summary of the original EHE consensus paper described above. While this paper is not intended to provide medical advice, we hope that it will provide patients with a greater understanding of and information about EHE which will allow them to engage in a more informed and therefore useful discussion with their medical teams, about treatment options. If after reading this document you have any further questions about EHE, then please also contact us using the EHE Group contact details in this document and we will try and answer them for you.

THE EHE GROUP