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Original Research

Epithelioid hemangio-endothelioma (EHE) in NETSARC: The nationwide series of 267 patients over 12 years

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Abstract ***Epithelioid hemangioendothelioma: a nationwide study:*** Epithelioid hemangioendothelioma (EHE) is an ultrarare sarcoma whose natural history and treatment is not well defined. We report on the presentation and outcome of 267 patients with EHE in the NETSARC+ network since 2010 in France.

Patients and methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centres with specialised multidisciplinary tumour boards (MDTB), funded by the French National Cancer Institute (NCI), Institut National du Cancer (INCA). Since 2010, presentation to an MDTB and second pathological review are mandatory for sarcoma patients. Patients' characteristics are collected in a nationwide database regularly monitored with stable incidence since 2013. The characteristics of patients with EHE at diagnosis are presented as well as progression-free survival (PFS), overall survival (OS), and outcome under treatment.

Results: Two hundred and sixty-seven patients with EHE were included in the NETSARC+ database since 2010. Median age in the series was 51 (range 10–90) years, 58% were women. Median tumour size was 37 mm (4–220). Forty-eight percent, 42%, and 10% were visceral, soft parts, or bone primaries. The most frequent sites were liver (28%), lung (13%). 40% were reported to have systemic (i.e. multifocal or metastatic disease) at diagnosis. With a median follow-up of 20 months, OS and PFS rates at 24 months were 82% and 67%, with 10-year projected OS and PFS of 62% and 21% respectively. Male and M+ patients at diagnosis had a significantly worse OS, but not PFS. Local treatment was associated with a favourable survival in localised but not in patients with advanced stage at diagnosis. For 23 patients receiving medical treatment, PFS and OS were 50.2% and 33.2% at 60 months were respectively.

Conclusions: EHE is a frequently metastatic sarcoma at diagnosis with a unique natural history. This study shows in a nationwide series over 12 years that most patients progressed but are still alive at 10 years, both in localised and metastatic stages.

1. Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumour of intermediate malignancy but frequently metastatic, with a reported incidence reported of $0.38/10^6$/y on an exhaustive nationwide series with centralised expert pathology review [1]. On histopathological examination, EHE is characterised by the proliferation of endothelial cells with epithelioid morphology. Tumour cells often express markers such as CD31, CD34, and ERG. The molecular hallmarks of EHE are specific translocations, either WWTR1-CAMTA1 (in 90% of patients) or YAP1-TFE3 (10% of patients), but rarer translocations involving WWTR1 have also been described [2–6]. Diagnosis of EHE includes the evaluation of the expression of CAMTA1, and if negative TFE3, by immunohistochemistry [2].

The clinical presentation of EHE is highly variable, EHE may develop in various parts of the body, including the liver, lungs, bones, and soft tissues, and present with an indolent behaviour but may also rapidly progress as high grade sarcomas [2–7]. In soft tissues, EHE can present as a palpable mass, pain, and functional impairment as for other soft tissue sarcomas. In the liver, EHE is often asymptomatic and discovered incidentally on imaging studies performed for other reasons. Large liver tumours may cause abdominal symptoms and pain. In the lungs, EHE is also frequently asymptomatic but can cause shortness of breath, cough,

and pain. In the bones, it can cause bone pain, swelling, and fractures [1,2,7–13].

Predictive factors for progression of EHE are not well characterised. When confined to a single organ and when it can be completely resected, EHE has an excellent prognosis, with a five-year survival rate of over 90%. However, when EHE has spread to other organs or cannot be completely resected, a five-year survival rate of around 50% has been reported again from a limited number of retrospective series [2]. The treatment of EHE is not well standardised, though standard guidelines for localised sarcoma are often used [2,14–20]. When the tumour cannot be completely resected, when surgery would be mutilating, or in the presence of metastatic disease, other treatment modalities such as definitive radiation therapy, cytotoxic chemotherapy, or targeted therapy, in particular anti-angiogenics, may be considered [21–29]; only two small prospective studies evaluating medical treatments have been reported [22,23].

In this article is reported a unique nationwide series of EHE, with confirmed diagnosis upon central mandatory pathology review, obtained within the French NETSARC+ Network. It describes the very unusual natural histories of these sarcomas is an unbiased series and provides a benchmark for future clinical studies.

2. Patient, materials and methods

2.1. The network

The NETSARC+ network involves 26 expert sarcoma centres. Each NETSARC centre organises a multidisciplinary tumour board (MDTB) with sarcoma specialised pathologist(s), radiologist(s), surgeon(s), radiation oncologist(s), medical oncologist(s), and often molecular biologist(s), orthopaedist(s), paediatrician(s). All sarcoma or suspected sarcoma patient cases presented to the MDTB of these centres were recorded in the NETSARC+ database, by a dedicated team of Clinical research assistant (CRAs), supervised by three Coordinating centres (Centre Leon Bérard, Institut Gustave Roussy, Institut Bergonié). Patient files may be presented before any diagnostic procedure, before initial biopsy, before primary surgery, after primary surgery, at relapse, and/or in case of a possible inclusion in a clinical trial. A monitoring of centre's activity is performed by the three coordinating centres on a regular basis.

2.2. Pathological diagnosis of diagnosis

The diagnosis of EHE is reviewed by pathologists of the French Sarcoma Group in the NETSARC+ centres using the criteria reported in the most recent WHO classification of sarcoma [30], including immunohistochemistry investigating CAMTA1 expression or TFE3 expression (and if negative whole exome RNAseq) [31].

2.3. The NETSARC database and the CONTICABASE

The NETSARC database exhaustively describes the incident and prevalent population of all sarcoma patients in France, using a cross comparison of the pathological review database (pathology review of sarcoma is mandatory in France) and the clinical database. This database enables to monitor the diagnostic and initial treatment procedures, and patient outcome in particular survival and relapse. The database includes a limited set of data, on purpose, describing patients and tumour characteristics, surgery, relapse and survival [19,20]. The following parameters extracted from NETSARC+ were used in this work: centre, age at diagnosis, gender, previous history, previous radiation therapy, presence of metastasis at diagnosis, date of diagnosis, biopsy before surgery, imaging before surgery, date of presentation to a NETSARC MDT, date of surgery, site of surgery,quality of first surgery, reexcision and quality of reexcision (R.), date of systemic and/or RT treatments, date of progression, date of death, date of last contact, vital status at last contact. The database was extracted on January 2023 for the period from 1/1/2010–31/12/2022. Importantly this database is not that of a clinical trial; the documentation of the follow-up is variable across NETSARC+ centres. For these reasons the median follow-remains short in the entire series.

The CONTICABASE is a sub-set of NETSARC+ database which includes only patients managed since the initial diagnosis in one of the NETSARC+ centres, and all these patients. It contains more information on the clinical presentation (e.g. multifocality in one organ) the nature of medical treatment, responses and follow-up. It is regularly used for publications of the group [32,33]. The 72 patients with EHE from the Conticabase were analysed for progression-free survival (PFS) and overall survival (OS), with a focus on the 23 patients with documented systemic treatment were analysed.

These databases have been approved by the French Ethic Committee and Agency in charge of non-interventional trials: the 'Comite´ Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Sante´ (CCTIRS: number of approval 09.594)' and the 'Commission Nationale Informatique et Liberte´ (CNIL: number of approval 909510)'. The consent was obtained orally.

2.4. Statistical analyses

The categorical data were summarised by the frequencies and percentages, and the continuous covariates were summarised with median, range and numbers of observations. The statistical test used for comparison was a chi-square (or a Fisher) test for categorical covariates, without adjustment for multiple comparisons. For the analysis of the NETSARC+ database, the

diagnostic date was the date of histological diagnosis (biopsy or first surgery when no previous biopsy). OS was calculated from the date of diagnosis (or start of the treatment when surgery was the starting point for diagnosis) to the date of last follow-up or death. PFS was computed from the date of diagnosis, or the date of surgery (if not preceded by a biopsy), to the date of the last follow-up or the date of the first local relapse, metastasis progression or death, whichever comes first. For the analysis of response to medical treatment in the Conticabase, PFS was computed from the date of initiation of chemotherapy, to the date of the last follow-up or the date of the first local relapse, metastasis progression or death, whichever comes first.

Survival curves were plotted using a Kaplan–Meier method. Survival curves were compared using the log-rank test. The median follow-up of the series is 20 months. Multivariate analysis for OS included prognostic factors identified as significant in univariate analysis, e.g. sex, presence of metastasis, presence of bone lesions. Cox proportional hazard model was used for the multivariate analysis, introducing parameters correlated to survival with a p value $p < 0.10$ in univariate analysis. Factors included in the multivariate model were identified by a backward selection procedure which entails including all the covariates in the model and removing those whose p-value is higher than 0.10 one at a time. At each step of the model, all included variables were tested and removed if they were no longer associated with the outcome considering a 5% type one error (p-value ≥0.05). Therapeutic parameters (immediate surgery yes/no; immediate medical treatment yes/no) were subsequently introduced in the model along with independent clinical prognostic factors. All statistical tests were two-sided. All statistical analyses were performed using SPSS (version 22.0).

Table 1
Description of the patients.

	All[a]	Localised[a]	Metastatic[a]	p value
	N = 267	N = 160	N = 107	
Gender				
F	156 (58.4%)	91 (56.9%)	65 (60.7%)	0.52
M	111 (41,6%)	69 (43,1%)	42 (39.3%)	
Age (median range)	51 (17.8)	52.3 (17.7)	49.2 (17.9)	0.84
Sites				
Bone	26 (9.7%)	16 (10%)	10 (9.3%)	0.86
Soft part	112 (41.9%)	91 (56.9%)	21 (19.6%)	**0.000**
Visceral	129 (48.3%)	53 (33.1%)	76 (71.0%)	**0.000**
Liver	74 (27.7%)	32 (20%)	42 (39.3%)	**0.001**
Lung	34 (12,7%)	10 (6.3%)	24 (22.4%)	**0.000**
Pleura	20 (7.5%)	14 (8.8%)	6 (5.6%)	0.39
Deep seated	246 (92.1%)	141 (88.1%)	105 (98.1%)	**0.003**
Size (median, range)	37 (34)	34.8 (32.3)	41 (38)	0.774
Initial treatment[b]				
Surgery	109 (40.8%)	88 (55.0%)	21(19.6%)	**0.000**
Medical treatment	35 (13.1%)	16 (10.0%)	19 (17.8%)	0.06
No immediate treatment	127 (47.6%)	59 (36.9%)	68 (63.6%)	**0.000**
Years				
2010	9 (3.4%)	6 (3.8%)	3 (2.8%)	
2011	13 (4.9%)	8 (6.3%)	5 (4.7%)	
2012	14 (5.2%)	7 (4.4%)	7 (6.5%)	
2013	27 (10.4%)	15 (9.4%)	12 (11.2%)	
2014	20 (7.5%)	12 (7.5%)	8 (7.5%)	
2015	30 (11.2%)	18 (11.3%)	12 (11.2%)	
2016	23 (8.6%)	12 (7.5%)	11 (7.5%)	
2017	19 (7.1%)	9 (5.6%)	10 (9.3%)	
2018	21 (7.9%)	13 (8.1%)	8 (7.5%)	
2019	23 (8.6%)	13 (8.1%)	10 (9.3%)	
2020	22 (8.2%)	16 (10.0%)	6 (5.6%)	
2021	25 (9.4%)	17 (10.6%)	8 (7.5%)	
2022	21 (7.1%)	14 (8.8%)	7 (6.5%)	***0.89***

[a] Percentage per column.
[b] Four patients had neoadjuvant treatment then surgery.

3. Results

3.1. Description of the patients

Two hundred and sixty-seven patients with EHE were included in the NETSARC+ database since 2010 (Table 1), with an estimated annual incidence of 0.32/10^6/y, close to the one previously reported for the 2013–2016 period [1]. Median age in the NETSARC+ series was 51 (range 10–90) years, 156 (58.4%) were women. Median tumour size at diagnosis was 37 mm (range 4–220). One hundred and twenty-nine (48.3%), 112 (41.9%), and 26 (9.7%) were visceral, soft parts, or bone primaries. The most frequent sites were liver (N = 74 [27.7%], 42/74 [56.7%] multifocal), lungs (N = 34 [12.7%], 24/34 [70.5%] multifocal), thigh (N = 17 [6.4%, four [23.5%] metastatic), pleural (N = 20 [7.5%], six [30%] metastatic). Two hundred and forty-six (92.1%) were deep seated. Three (1.1%, all three positive for CAMTA1 expression) arose in previously irradiated fields. One hundred and seven (40.1%) were reported by investigators as 'metastatic' that is, multifocal or systemic at diagnosis. Thirty (18.8%) patients with localised disease relapsed later on distant sites only, nine (5.6%) relapsed both local and distant sites. Metastases of EHE can present as multifocal in a single organ (e.g. liver, lung), versus a classical multiple organs presentation. This information is not captured in the NETSARC+ database, while it is available in the subset of Conticabase. Single site multifocal disease was observed in 12.5% of patients and represented 27.3% of patients with advanced EHE (Supplementary Table 1).

No significant difference in age at diagnosis or tumour size were observed in patients with initially localised versus metastatic stages. Similarly, age and tumour size were not significantly different in female versus male, primary liver sites, lung sites, bone (not shown).

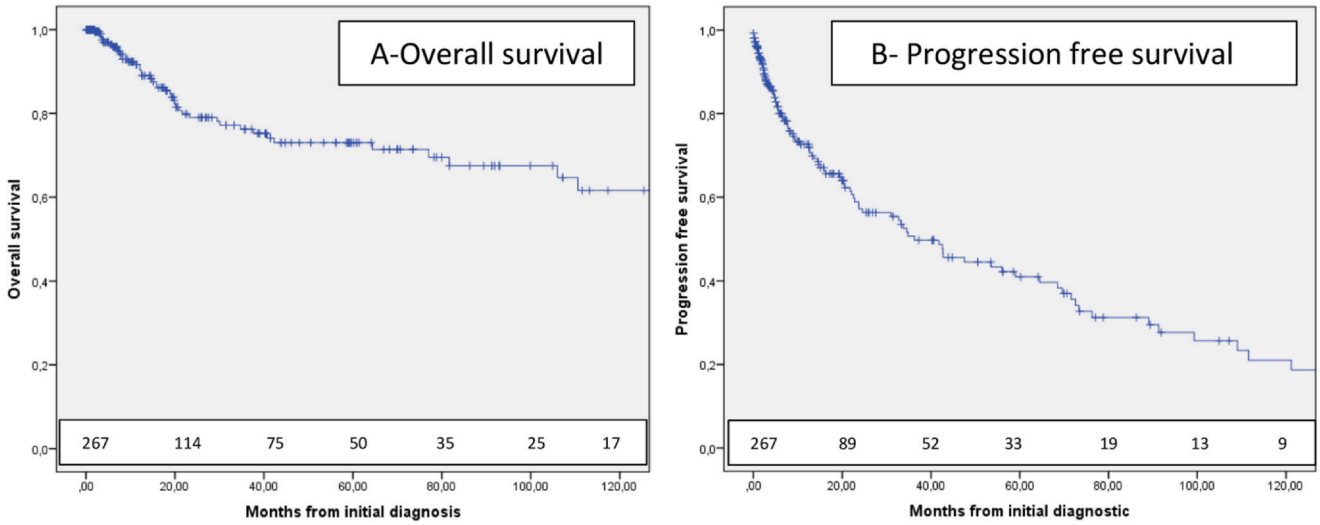

Fig. 1. Overall and progression-free survival of 267 patients with EHE with localised and metastatic disease at diagnosis. (A) Overall survival of the 267 patients; (B) progression-free survival of the 267 patients. EHE, epithelioid hemangioendothelioma.

The characteristics of patients in the different localisations were then compared. Patient with liver and lung tumours had more frequently multifocal or metastatic disease at diagnosis, and soft tissue primaries were more frequently localised (Table 1). Patients with liver primaries had larger tumour size at diagnosis (median 48 versus 33 mm, U-Test p = 0.004), as patients with bone sites (mean 55 versus 36 mm U-test, p = 0.036). Patient with pleural sites were significantly older (median 66 versus 49 years, U-test p < 0.001).

3.2. Survival and progression free survival

With a median follow-up of 20 months for the whole series of 267 patients, OS and PFS rates at 24 months were 82% and 67% respectively. At 10 years, OS and PFS were projected to be 62% and 21% respectively. (Fig. 1A and B).

The median OS of patients with localised disease was superior to that of patients with systemic 'metastatic' disease (log-rank, p = 0.01) with a projected 5-year OS of 82% and 62% for both groups (Fig. 1C). Male sex (Fig. 2A) and pleural sites (not shown) were also associated with a worse OS, both in patients with localised and metastatic tumours. Conversely, bone, visceral, soft tissue, liver, lung sites, age (continuous variable), and largest size (continuous variable) were not significantly correlated to OS. Intriguingly, the OS of female patients and male patients was not influenced similarly by the age: female patients aged 51 and above had a significantly worse OS, while this was not observed for male patients (Fig. 2B). In multivariate analysis, male gender, pleural site, and presence of metastasis at diagnosis were independent poor-prognosis factors for OS (Table 2).

The median PFS of patients with localised disease and metastatic disease were 42 and 34 months (Fig. 1D) respectively, with a projected 5-year PFS of 39.5% and 42.3% for both groups (p = NS). None of the following initial characteristics of the patients were associated with a worse PFS in the whole series: age (continuous variable), sex, size (continuous variable), sites (liver, lung, pleura…), presence of metastasis at initial diagnosis. The PFS of female and male patients was similar, both under and over age 51 (not shown). Only primary bone sites were associated with shorter PFS in univariate analysis in the whole series (log-rank p = 0.037) and was the only prognostic factor in multivariate analysis for the whole series as well as for patients with localised disease. For patients with initially metastatic disease, lung site was the only significant prognostic parameter for PFS, booth in univariate and multivariate analysis (Table 2).

Within the Conticabase, we compared the survival and PFS of patients with localised disease, versus multifocal single organ disease, versus multiorgan dissemination, and both multiorgan and multifocal disease (Supplementary Fig. 1). The survival and progression free survival from of the patients with (1) multifocal disease in one organ, (2) metastatic disease from a single lesion and (3) both at initial diagnosis was found to be similar, and inferior as expected to that of patients with localised disease.

3.3. Management at diagnosis

A total of 109 (40.8%) patients were reported to have had an initial (< 4 months post diagnosis) surgery, 21/107 metastatic patients (19.6%) and 88/160 (55.0%) non-metastatic patients (p = 0.000). Thirty-five (13.1%) were reported to receive an immediate (< 4 months) systemic treatment after diagnosis, including 19/107 (17.8%) metastatic patients, and 16/160 (10%) non-metastatic patients (p = 0.066). 127/267 (47.6%) patients did not

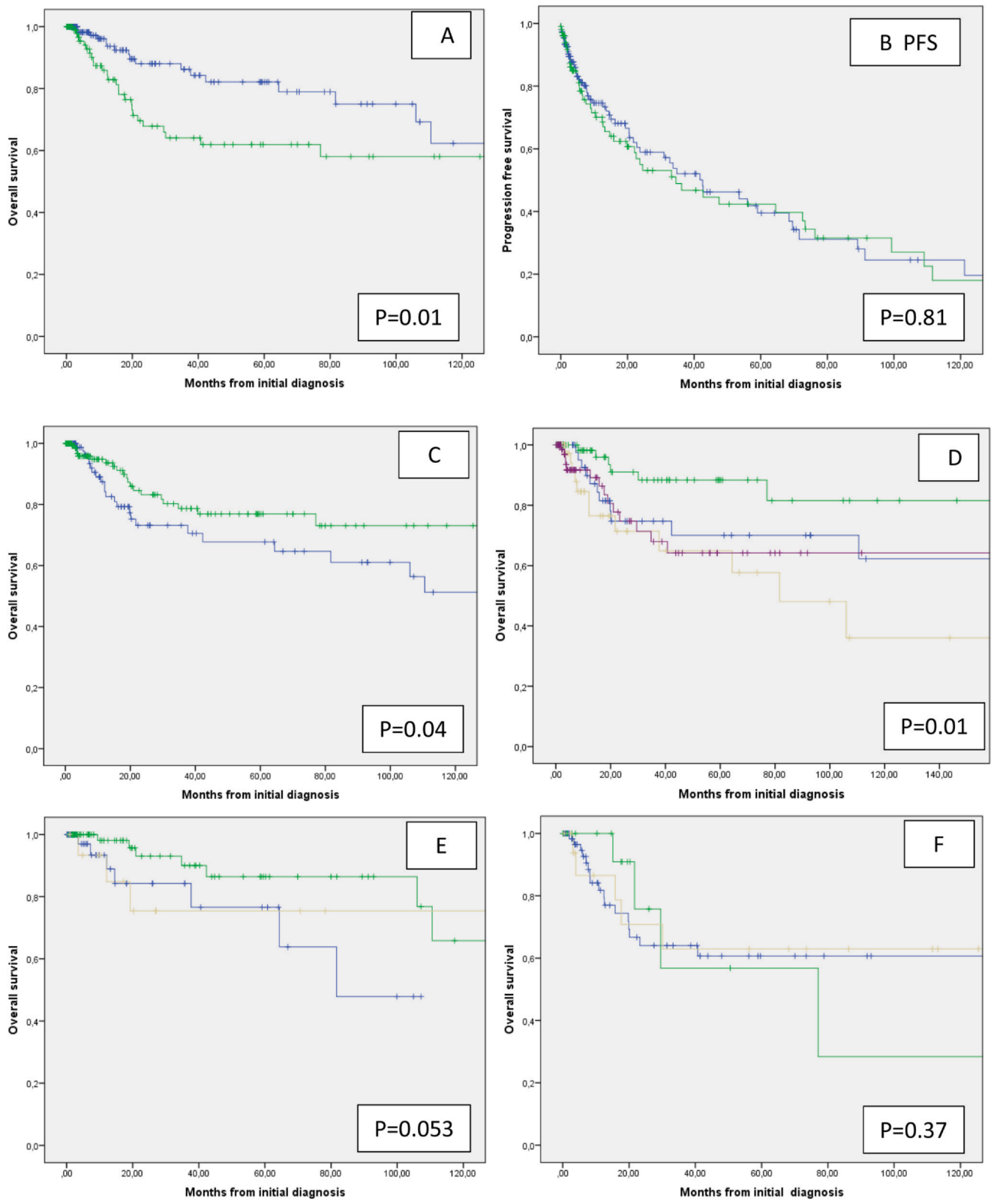

Fig. 2. Overall survival according to M status, gender and presence of metastases at diagnosis. (A) Overall survival of patients with localised (blue) or metastatic disease (green) at diagnosis (Logrank, p = 0.01); (B) progression-free survival of patients with localised (blue)

or metastatic disease (green) at diagnosis (logrank, p = 0.81); (C) overall survival of female (green) and male (blue) patients (logrank, p = 0.04); (D) overall survival of female patients aged under 51 (green), of male patients aged 51 and above (brown), of female patients aged 51 and above (blue), and of male patients aged under 51 (purple) (logrank,p = 0.01); (E) overall survival of patient with localised disease at diagnosis treated with immediate surgery (green), immediate medical treatment (brown), or receiving no immediate (i.e. < 4 months) treatment (blue) (logrank p = .0.53 surgery versus others). (F) Overall survival of patient with metastatic disease at diagnosis treated with immediate surgery (green), immediate medical treatment (brown), or receiving no immediate treatment (blue) (lograk test, p = 0.37).

receive a therapeutic intervention in the first 4 months following diagnosis, including 68/107 (63.6%) of metastatic patients, and 59/160 (36.9%) of non-metastatic patients (p = 0.000). The proportion of patients receiving a first treatment after 4 months increased in the recent years (57/138 [41.3%] before 2016 versus 70/129 [54.3%] after 2016).

We then analysed the impact of immediate surgery on OS.

Immediate surgery was associated with a marginally better OS in the subgroup of non-metastatic patients (Fig. 2C, p = 0.053), and was an independent favourable prognostic factor in multivariate analysis (Table 2).

In metastatic patients, immediate surgery, immediate systemic treatment or no immediate intervention were not associated with a different OS in univariate (Fig. 2D) or multivariate (Table 2) analysis.

We then evaluated the outcome of patients treated with immediate surgery, immediate systemic treatment, or managed with no immediate therapeutic intervention on PFS. The PFS of the three groups was not significantly different, in the whole group of 267 patients, in the group with localised disease at diagnosis, as well as in the group of metastatic patients. In the multivariate analysis on the 107 patients with metastasis at diagnosis, neither initial surgical treatment nor medical treatment were associated with different overall survival (not shown).

Table 2
Multivariate analysis of prognostic factors for PFS or OS.

Whole population	HR (95% CI)	p
Overall survival		
Female sex	0,51 (0.38–0,69)	0.030
Metastasis at diagnosis	2.76 (2.01–3.78)	0.001
Pleural site	4.55 (2.95–7.02)	0.000
Progression free survival		
Bone site	1.83 (1.375–2.449)	0.035
Localized EHE		
Overall survival		
Pleural site	7.28 (4.07–13.0)	0.001
Bone site	4.47 (2.19–9.23)	0.037
With treatment parameters[a]		
Immediate surgery	***0,27 (0.16–0.45)***	***0.019***
Pleural site	7.6 (4.2–14.2)	0.001
Bone site	5.0 (2.4–10.5)	0.028
Progression free survival		
Bone site	2.58 (1.78–3.76)	0.011
Metastatic EHE		
Overall survival		
Female sex	0.45 (0.28–0.68)	0.030
Progression free survival		
Lung	1.99 (1.44–2.73)	0.030

CI, confidence interval; EHE, epithelioid hemangioendothelioma; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a] Therapeutic parameters (immediate surgery yes/no; immediate medical treatment yes/no) were introduced in the model in addition to clinical parameters. Only those retaining significant prognostic value ('immediate surgery' for overall survival in localised EHE) are presented.

3.4. Systemic treatment in EHE

Since the NETSARC database does not include the details of the medical treatments received, the efficacy of systemic treatments on the progression of the EHE was analysed within the group of 72 patients treated in the reference centres since initial diagnosis (the Conticabase registry). Among them, 23 (32%) patients received a systemic treatment. The mean time between diagnosis and medical treatment was 9 months (range 0.6–44 months). Hereunder, we provide a description of the outcome of medical treatments in this retrospective series.

Table 3
Treatment proposed to patients treated in NETSARC centres.

	N (%)	PFS (months) Median (95% CI)
Medications		
Doxorubicin	17 (36.2%)	NR (**55%** at 60 months)
Ifo/Cyclophosphamide	10 (22.2%)	3.2 (0.0–16.0)
Trabectedin	4 (8.5%)	7.0 (0.0–17.1)
Pazopanib	3 (6.4%)	4.6 (0.0–11.2)
Sorafenib	3 (6.4%)	4.2 (3.9–4.4)
Taxane	3 (6.4%)	1.7 (0.6–2.9)
Others	7 (15.8%)	3.7 (0.3–7.1)
Lines of treatment		
1	23 (49.0%)	NR (**50.2%** at 60 months)
2	13 (17.7%)	3.2 (0.3–6.1)
3	5 (10.8%)	4.9 (3.2–6.6)
4	4 (8.5%)	4.0 (2.1–5.9)
5–6	2 (4.2%)	1
Line 1		
Doxorubicin	14 (60.9%)	NR (**61%** at 60 months)
Ifos/cyclophosphamide	3 (13.0%)	25.2 (0% at 60 months)
Pazopanib/Sorafenib	3 (13.0%)	4.6 (0.0–11.2)
Other[a]	3 (13.0%)	NR (67% at 25 months)
Line ≥2		
Ifos/cyclophosphamide	7 (29.2%)	1.2 (0.5–1.9)
Doxorubicin	3 (12.5%)	3.9 (0–8.3)
Trabectedine	3 (12.5%)	7.0 (0.0–12.1)
Pazopanib/Sorafenib	3 (12.5%)	4.1 (3.9–4.4)
Other	8 (33.3%)	2.7 (0.1–5.4)

CI, confidence interval; PFS, progression-free survival.
[a] Others = trabectedine, paclitaxel, inferferon alpha.

Table 3 describes the treatment received and the different lines. As expected, a diversity of regiments was given in first, second and later lines in this retrospective study. Only two objective responses were observed both after first-line doxorubicin regimen (2/14, 14%), with no response for other agents in any line. Median PFS and OS reported after initiation of first-line systemic treatment were not reached with a median follow-up of 60 months. First-line treatments provided the longest PFS, with 13 patients without documented progression. No progression was reported after 25 months and six patients were progression-free thereafter at a median time of 59 months (range 28–156) after first-line treatment. Treatment efficacy was more limited in second line or more (Table 3) though a median PFS > 4 months was observed for most treatment used. The median OS from the date of progression post first-line systemic treatment was 13 months.

4. Discussion

This work reports on a large nationwide series of EHE, collected from the nationwide registry of sarcoma NETSARC+ in place since 2010 taking advantage of the mandatory pathology review for all sarcomas in the country which enables to confirm and collect of diagnosis of sarcoma in the country. In this database, all sarcomas are reviewed centrally by reference pathology centres before integration ensuring a reliable diagnosis. From 2010–2022, 267 patients were included, for an incidence of 0,32/10^6/y, close to that reported in our previous publication on 4 years [1]. The exhaustivity of a registry is always difficult to assess. Because (1) all diagnosis of connective tissue tumours must be confirmed by central pathology review, and (2) cancers are diseases with an obligatory declaration for universal health coverage in France, no diagnosis of sarcoma, in this case EHE, is made without referral to the NETSARC network. While we cannot exclude that some patients may be left aside to the health care system despite universal health coverage, this is unlikely throughout disease course of a malignant disease. EHE are therefore one of the ultrarare sarcomas with the proposed definition of < 10^6/y [34].

The results show that EHE have a unique natural history as compared to other sarcomas, with a large proportion of patients with multifocal, that is, metastatic disease at diagnosis, the lack of significance of classical prognostic factors for survival with the notable exception of female gender, a very large proportion of long-term survivors even in metastatic 'systemic' phase, different prognostic factors for PFS and OS, and a limited impact of therapeutic interventions on survival.

The frequency of metastatic dissemination at diagnosis, 40%, is unusual in sarcoma were 12% are most often reported [20]. The classical definition of metastasis was used there, as opposed to the proposed terminology of 'locoregional metastasis', designing multiple sites on a single organ, proposed recently [2], but which is not consistently documented in the database. In this report we refer to multifocal, systemic or metastatic disease for EHE with more than one tumour site. The localised 'non- multifocal' EHE from soft tissue sites had only a slightly higher proportion of metastasis at diagnosis as other sarcomas (19% versus 12% in the NETSARC series) [1,19,20], in marked contrast with liver and lung sites which were multifocal in > 50% cases in this series.

The results presented here suggest that metastatic EHE may not be a disseminated stage of a previously localised disease, although they present with similar molecular alterations [4–7]. Their primary sites are different. Only a minority of localised primary EHE relapse in distant sites. The median size of the 'primary' tumour is similar in localised and metastatic diseases. Also, the age a diagnosis is similar in localised versus metastatic EHE at diagnosis, while the relatively indolent natural history would have suggested an older age for metastatic EHE. These observations challenge the concept that EHE may follow the classical paradigm of a primary tumour subsequently disseminating. Instead, some EHE may present initially as metastatic, or 'systemic', 'loco-regional metastatic' without a first, even indolent, localised phase. Of note the survival of the patients with more than one site (e.g. liver and lung) and a single organ site (e.g. multiple liver metastases or multiple lung metastasis) was not different in the CONTICABASE group of patients in whom these information were available. The molecular characterisation of these groups of EHE, localised and metastatic, deserve further analysis to better understand the biological basis of tumour progression.

In this series, long-term survival was observed in a large proportion of patients despite a relatively short median PFS in the whole group. The observation that only 21% of the patients are projected to be progression-free at 10 years while 61% are projected alive is unusual for sarcomas. The long-term survival of EHE patients with metastatic disease surviving at 5 or 10 years, may be then 10-fold higher than that of other metastatic sarcomas [35,36]. Interestingly, female patients were found to have a favourable OS, in univariate and multivariate analysis, while PFS is similar in male and female. This more favourable survival of female patient was however age-dependent. The survival of women aged 51 (median age of the series) and above is not different from that of male patients of the same age. The most favourable survival is observed in women aged under 51, whether or not metastatic may point to a potential role of estrogens and progesterone in tumour control in this disease. Of note successful pregnancies without significant impact on progression were reported in metastatic EHE [37]. Hormonal treatments may deserve to be explored in clinical trials for progressive EHE.

An important question is to identify early those metastatic or unresectable patients at risk for progression or death. The multivariate analyses conducted in the entire series, in the group of patients with localised disease and in the subgroup of patients with metastatic disease identified completely different predictors for progression-free and overall survival. This decorrelation strongly suggest that volumetric progression is a poor predictor of survival and that additional modes of evaluation of disease activity are needed for this rare sarcoma. Biological factors such as Comité de Revue des Protocoles, or performance status are not consistently documented in the database. This is one of the challenges of future research on EHE to identify clinical, biological, imaging (FDG-PET) or other parameters associated with worse survival to best guide the treatment proposed to patients with advanced disease [38].

We investigated the impact of initial treatment on patient outcome. For patients with localised disease, while delayed treatment, or medical treatment, was proposed to a fraction of patients, the classical surgical approach used as standard for localised sarcomas [14–20] was associated with better OS in univariate (trend) and multivariate analysis in this series. R0 resection was associated with numerically superior OS, the difference was not statistically significant (not shown). Intriguingly, no improvement for PFS was observed with immediate surgery conversely. Additional series will be needed to confirm these observations. This further points to the specificity of the natural history of EHE versus other sarcoma, and the decorrelation between prognostic factors for PFS and OS in this disease. Nevertheless, the standard treatment paradigms of treatment of sarcomas in localised phase applies for localised EHE.

In advanced stage, immediate medical treatment, immediate surgery or no intervention were associated with similar outcome. The OS and PFS of patients managed with the three options was not found different in multifocal or metastatic EHE at diagnosis. When introduced in the multivariate analysis, the use of initial surgery was not found to be significantly correlated to a better survival or PFS. These results will need to be confirmed in future series and studies.

In desmoid-type fibromatosis, a locally aggressive connective tissue disease with no metastases, watchful surveillance has been proposed as initial approach [39]. In contrast, watchful surveillance is not demonstrated in EHE Using an opposite strategy to the watchful surveillance approach, liver transplantation has been proposed in cases of limited hepatic EHE [40].

This series also provides information on the outcome of patients receiving systemic treatments for EHE. The published literature provides limited information on the value of systemic treatments in these diseases, with only two prospective studies evaluating bevacizumab and sorafenib to our knowledge [22,23]. Consensus reports on medical treatments are therefore based mostly on case reports and retrospective series [41]. These data will contribute to strengthen these recommendations. Only a minority of patients received systemic treatment and most received it more than 6 months after initial diagnosis. The first-line treatment, mostly anthracyclines'-based, resulted in prolonged PFS and OS in most patients. Other cytotoxics and antiangiogenics showed activity in these patients, but results beyond the first line were less favourable, with a median PFS close to 4 months and a median OS of 13 months. Despite the retrospective nature of this analysis, these data add information on a topic where very little is available in the literature. Prospective studies are needed to identify the best systemic treatment option for these patients. In this series, doxorubicin was the most frequently used and the treatment associated with the best PFS and OS in first line. In the present study the decision criteria for starting systemic treatment (response evaluation criteria in solid tumors progression, symptoms…) were not documented and metastatic EHE may be spontaneously stable for years. The criteria to start medical treatments and their efficacy should also be tested in prospective clinical studies and on real life datasets.

This study has several other limitations. The follow-up remains limited, the total number of patients (though an exhaustive nationwide series) is small to characterise the different clinical presentations of the disease, and the details of the systemic treatments for the entire dataset are not available. The presence of a pleural effusion is not consistently reported and systemic symptoms are not collected in this series. The translocation subtype is not documented on the entire series. Biological parameters such as additional mutations have not been tested, clinical characteristics with potential prognostic value are not available. A large retrospective clinical research programme to complete these information is scheduled.

In conclusion, these results show that EHE have a unique natural history, notably different from other sarcomas. Clinical characteristics, survival and PFS of the localised and metastatic presentations are unique. Localised EHE should be treated as a localised sarcoma. Metastatic EHE can be proposed for a watchful surveillance under the careful supervision of a reference centre. In the absence of a clinical trial, anthracyclines remain a reasonable treatment option in first line. Better second line treatments are needed. Overall, though frequently indolent, still a subset of localised and disseminated EHE are life-threatening. Tools to identify these patients are lacking.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113262.

References

[1] de Pinieux, Karanian M, Le Loarer F, Le Guellec S, Chabaud S, Terrier P, et al. NetSarc/RePPS/ResSos and French Sarcoma Group- Groupe d'Etude des Tumeurs Osseuses (GSF-GETO) networks. Nationwide incidence of sarcomas and connective tissue tumours of intermediate malignancy over four years using an expert pathology review network. PLoS One 2021;16(2):e0246958.

[2] Stacchiotti S, Miah AB, Frezza AM, Messiou C, Morosi C, Caraceni A, et al. Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts. ESMO Open 2021;6:100170.

[3] Stacchiotti S, Frezza AM, Blay JY, Baldini EH, Bonvalot S, Bovée JVMG, et al. Ultra-rare sarcomas: a consensus paper from the connective tissue oncology society community of experts on the incidence threshold and the list of entities. Cancer 2021;127:2934–42.

[4] Rosenberg A, Agulnik M. Epithelioid hemangioendothelioma: update on diagnosis and treatment. Curr Treat Options Oncol 2018;19:19.

[5] Errani C, Zhang L, Sung YS, et al. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosomes Cancer 2011;50:644–53.

[6] Antonescu CR, Le Loarer F, Mosquera JM, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. Genes Chromosomes Cancer 2013;52:775–84.

[7] Witte S, Weidema M, Kaal S, Versleijen-Jonkers Y, Flucke U, van der Graaf W, et al. The heterogeneity of epithelioid hemangioendothelioma (EHE): a case series and review of the literature with emphasis on treatment options. Semin Oncol 2021;48:111–8.

[8] Frezza AM, Ravi V, Lo Vullo S, Vincenzi B, Tolomeo F, Chen TW, et al. Systemic therapies in advanced epithelioid haemangioendothelioma: a retrospective international case series from the World Sarcoma Network and a review of literature. Cancer Med 2021;10:2645–59.

[9] Frezza AM, Napolitano A, Miceli R, Badalamenti G, Brunello A, Buonomenna C, et al. Clinical prognostic factors in advanced epithelioid haemangioendothelioma: a retrospective case series analysis within the Italian Rare Cancers Network. ESMO Open 2021;6(2):100083.

[10] Mentzel T, Beham A, Calonje E, et al. Epithelioid hemangioendothelioma of skin and soft tissues: clinicopathologic and immunohistochemical study of 30 cases. Am J Surg Pathol 1997;21:363–74.

[11] Lau K, Massad M, Pollak C, et al. Clinical patterns and outcome in epithelioid ehmangio endothelioma with or without pulmonary involvement: insights from an internet registry in the study of a rare cancer. Chest 2011;140:1312–8.

[12] Ajay PS, Tsagkalidis V, Casabianca A, Burchard PR, Melucci AD, Chacon A, et al. A review of hepatic epithelioid hemangioendothelioma—analyzing patient characteristics and treatment strategies. J Surg Oncol 2022;126:1423–9.

[13] Gusho CA, Tepper SC, Gitelis S, et al. Epithelioid hemangioendothelioma of bone: a survival analysis of 50 cases from the SEER database (1992–2016). Rare Tumours 2021;13:20363613211005593.

[14] Strauss SJ, Frezza AM, Abecassis N, Bajpai J, Bauer S, Biagini R, ESMO Guidelines Committee, EURACAN, GENTURIS, ERNPaedCan, et al. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2021;32:1520–36. Electronic address: clinicalguidelines@esmo.org.

[15] Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. ESMO Guidelines Committee, EURACAN, GENTURIS. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Ann Oncol 2021;32:1348–65.

[16] Blay JY, Palmerini E, Bollard J, Aguiar S, Angel M, Araya B, et al. SELNET clinical practice guidelines for bone sarcoma. Crit Rev Oncol Hematol 2022;174:103685.

[17] Blay JY, Hindi N, Bollard J, Aguiar Jr S, Angel M, Araya B, et al. SELNET clinical practice guidelines for soft tissue sarcoma and GIST. Cancer Treat Rev 2022;102:102312.

[18] von Mehren M, Kane JM, Agulnik M, Bui MM, Carr-Ascher J, Choy E, et al. Soft tissue sarcoma, version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20:815–33.
[19] Blay JY, Honoré C, Stoeckle E, Meeus P, Jafari M, Gouin F, et al. Surgery in reference centers improves survival of sarcoma patients: a nationwide study. Ann Oncol 2019;30:1407.
[20] Blay JY, Soibinet P, Penel N, Bompas E, Duffaud F, Stoeckle E, et al. Improved survival using specialized multidisciplinary board in sarcoma patients. Ann Oncol 2017;28:2852–9.
[21] Soape MP, Verma R, Payne JD, et al. Treatment of hepatic epithelioid hemangioendothelioma: finding uses for thalidomide in a new era of medicine. Case Rep Gastrointest Med 2015;2015:326795.
[22] Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol 2013;24:257–63.
[23] Chevreau C, Le Cesne A, Ray-Coquard I, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group (GSF/GETO). Cancer 2013;119:2639–44.
[24] Saada E, Saint Paul MC, Gugenheim J, et al. Metastatic hepatic epithelioid hemangio-endothelioma: long-term response to sunitinib malate. Oncol Res Treat 2014;37:124–6.
[25] Bally O, Blay JY, Derbel O, et al. Eight years tumour control with pazopanib for a metastatic resistant epithelioid hemangioendothelioma. Clin Sarcoma Res 2015;5:12.
[26] Yousaf N, Maruzzo M, Judson I, et al. Systemic treatment options for epithelioid hemangioendothelioma: the Royal Marsden Hospital experience. Anticancer Res 2015;35:473–80.
[27] Kollár A, Jones RL, Stacchiotti S, et al. Pazopanib in advanced vascular sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. Acta Oncol 2017;56:88–92.
[28] Stacchiotti S, Simeone N, Lo Vullo S, Baldi GG, Brunello A, Vincenzi B, et al. Activity of sirolimus in patients with progressive epithelioid hemangioendothelioma: a case-series analysis within the Italian Rare Cancer Network. Cancer 2021;127:569–76.
[29] Tong D, Miah AB, Zaidi SH, Benson C, Van Der Graaf W, Jones RL, et al. The role of local therapy in multi-focal epithelioid haemangioendothelioma. Anticancer Res 2019;39:4891–6.
[30] Epithelioid hemangioendothelioma. Soft tissue and bone tumours WHO classification of tumours, 5th edition, volume 3, 2020; pp. 172–175.
[31] Cousin S, Le Loarer F, Crombé A, et al. Hémangioendothéliome épithélioïde (Epithelioid hemangioendothelioma). Bull Cancer 2019;106:73–83.
[32] Moreau-Bachelard C, Campion L, Toulmonde M, Le Cesne A, Brahmi M, Italiano A, et al. Patterns of care and outcomes of 417 patients with METAstatic SYNovial sarcoma (METASYN): real-life data from the French Sarcoma Group (FSG). ESMO Open 2022;7(2):100402.
[33] Penel N, Coindre JM, Giraud A, Terrier P, Ranchere-Vince D, Collin F, et al. Presentation and outcome of frequent and rare sarcoma histologic subtypes: a study of 10,262 patients with localized visceral/soft tissue sarcoma managed in reference centers. Cancer 2018;124:1179–87.
[34] Stacchiotti S, Frezza AM, Blay JY, Baldini EH, Bonvalot S, Bovée JVMG, et al. Ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society community of experts on the incidence threshold and the list of entities. Cancer 2021;15(127):2934–42.
[35] Yazigi A, Lecointe-Artzner E, Cesne AL, et al. Pregnancy in women with metastatic sarcomas. Oncologist 2020;25(12):e2010–2.
[36] Blay JY, van Glabbeke M, Verweij J, van Oosterom AT, Le Cesne A, Oosterhuis JW, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. Eur J Cancer 2003;39:64–9.
[37] Carbonnaux M, Brahmi M, Schiffler C, Meeus P, Sunyach MP, Bouhamama A, et al. Very long-term survivors among patients with metastatic soft tissue sarcoma. Cancer Med 2019;8:1368–78.
[38] Frota Lima LM, Packard AT, Broski SM. Epithelioid hemangioendothelioma: evaluation by 18F-FDG PET/CT. Am J Nucl Med Mol Imaging 2021;11:77–86.
[39] Desmoid Tumour Working Group. The management of desmoid tumours: a joint global consensus-based guideline approach for adult and paediatric patients. Eur J Cancer 2020;127:96–107.
[40] Kaltenmeier C, Stacchiotti S, Gronchi A, Sapisochin G, Liu H, Ashwat E, et al. Treatment modalities and long-term outcomes of hepatic hemangioendothelioma in the United States. HPB (Oxford) 2022;24:1688–96.
[41] Stacchiotti S, Maria Frezza A, Demetri GD, Blay JY, Bajpai J, Baldi GG, et al. Retrospective observational studies in ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society (CTOS) community of experts on the minimum requirements for the evaluation of activity of systemic treatments. Cancer Treat Rev 2022;110:102455.