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ORIGINAL RESEARCH

Clinical prognostic factors in advanced epithelioid haemangioendothelioma: a retrospective case series analysis within the Italian Rare Cancers Network

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Background: This multicentric, retrospective study conducted within the Italian Rare Cancer Network describes clinical features and explores their possible prognostic relevance in patients with advanced epithelioid haemangioendothelioma (EHE) started on surveillance.

Patients and methods: We collected data on adult patients with molecularly confirmed, advanced EHE consecutively referred at five sarcoma reference centres between January 2010 and June 2018, with no evidence of progressive disease (PD) and started on surveillance. Overall survival (OS) and progression-free survival (PFS) univariable and multivariable Cox analyses were performed. In the latter, due to the low number of cases and events, penalized likelihood was applied, and variable selection was performed using a random forest model.

Results: Sixty-seven patients were included. With a median follow-up of 50.2 months, 51 (76%) patients developed PD and 16 (24%) remained stable. PD at treatment start did not meet RECIST version 1.1 in 15/51 (29%) patients. The 3-year PFS and OS were 25.4% and 71.1%, respectively, in the whole population. Tumour-related pain (TRP) was the most common baseline symptom (32.8%), followed by temperature (20.9%), fatigue (17.9%), and weight loss (16.4%). Baseline TRP ($P = 0.0002$), development of TRP during follow-up ($P = 0.005$), baseline temperature ($P = 0.002$), and development of fatigue during follow-up ($P = 0.007$) were associated with a significantly worst PFS. An association between baseline TRP ($P < 0.0001$), development of TRP during follow-up ($P = 0.0009$), evidence of baseline serosal effusion ($P = 0.121$), and OS was recorded.

Conclusion: Because of the poor outcome observed in EHE patients presenting with serosal effusion, TRP, temperature, or serosal effusion, upfront treatment in this subgroup could be considered.

Key words: epithelioid haemangioendothelioma, prognostic factors, serosal effusion, symptoms, surveillance, outcome

INTRODUCTION

Since epithelioid haemangioendothelioma (EHE) was first described, 40 years ago, significant steps forward have been moved in the comprehension of biology and in the definition of management for this ultra-rare vascular sarcoma.[1] Despite the extreme variability in clinical behaviour and the heterogeneity in morphological appearance, EHE is molecularly well defined by the presence of *WWTR1-CAMTA1* fusion product, detected in ~90% of cases.[2,3] A small subset of EHE can harbour either the *YAP1-TFE3* fusion or the recently described rare *WWTR1* translocations involving gene partners other than *CAMTA1*.[4,5]

EHE clinical features include the tendency towards metastatic spreading, with most of the patients presenting with multifocal/multicentric disease (lungs, liver and bones are the sites predominantly involved); the higher incidence in females and the variability in natural history, with cases being naturally stable over time; cases of slowly progressive disease (PD) which may become symptomatic; and highly aggressive cases, akin to high-grade sarcomas.[6] Consistent

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with this clinical behaviour, patients' outcome is variable, with a 5-year survival ranging between 20% and 70% in aggressive and indolent EHE, respectively.[7-9] Clinical and biological factors to predict this clinical heterogeneity are not available and the best treatment approach in each variant is undefined.

Although some clinical features (pleural invasion/effusion, disease burden, bone involvement, weight loss, presence of any symptoms at diagnosis[7,8,10-12]) and pathological or molecular characteristics (high mitotic count, grading, and *WWTR1-CAMTA1* fusion[9,11,13]) have been reported as adverse prognostic factors, the prediction of the outcome in EHE at the time of presentation remains a major challenge. We observed in clinical practice the presence of a small subset of EHE patients reporting inflammatory systemic symptoms [mild fever, weight loss, fatigue, severe tumour-related pain (TRP)], often associated with serosal effusions (SEs), which tend to have a poorer outcome. This clinical picture is peculiar of EHE, while it is conversely rather uncommon in other types of soft tissue sarcomas. The biological bases behind this presentation, as well as its potential prognostic value, are unknown.

Given the unpredictability of EHE evolution, surveillance is often offered upfront in patients with naturally stable or asymptomatic disease, reserving medical treatment to symptomatic or progressive cases.[14-16] However, the definition of radiological progression in this disease is an issue. The possible occurrence of SE and the limited increase in size observed over a short period in slow-growing variants might not meet promptly the Response Assessment Criteria in Solid Tumor (RECIST) definition of progression, making its use often unsatisfactory in the identification of those patients who might benefit from an active treatment.[17]

On this basis, we conducted a multicentric, collaborative, retrospective study within the Italian Rare Cancer Network aiming at providing a clearer description of clinical features and exploring their possible prognostic relevance in adult patients with molecularly confirmed, advanced EHE started on an active surveillance program at the time of presentation.

PATIENTS AND METHODS

All adult patients with a molecularly confirmed, advanced EHE consecutively referred at the below-mentioned sarcoma reference centres between January 2010 and June 2018 were retrospectively reviewed. All patients had no evidence of PD in 6 months prior to the referral and were started on surveillance. EHE patients with localized disease and those started on active treatment at baseline were excluded. Five sarcoma reference centres belonging to the Italian Rare Cancer Network contributed cases to this series: Fondazione IRCCS — Istituto Nazionale Tumori (Milan), University Campus Bio-Medico (Rome), Candiolo Cancer Institute, FPO-IRCCS (Candiolo), Policlinico Paolo Giaccone (Palermo), and Istituto Oncologico Veneto IRCCS (Padua). For patients included, the diagnosis was reviewed and confirmed by an expert sarcoma pathologist. The presence of the disease-specific *WWTR1* or *TFE3* rearrangement was determined by FISH, and only cases carrying one of the two were entered.

In the everyday clinical practice, the contributing centres follow a common approach in the management of advanced EHE referred to the centre: at the baseline, all patients undergo at least a total body computed tomography (CT), a bone scan or positron emission tomography (PET)-CT, and, if bone disease is detected, magnetic resonance imaging (MRI) of the involved sites. In newly diagnosed patients, a first radiological reassessment is done 3-4 months after diagnosis to assess the tendency towards disease progression. Only progressive patients are considered for an active treatment, whereas patients with stable disease are followed through active surveillance.

As per common policy across contributing institutions, the surveillance programme consists of a clinical assessment, a thorax/abdomen/pelvis CT, a CT/MRI of the other involved tumour sites as applicable, and the best radiological study for bone disease (if bone disease is detected at baseline) every 3-4 months for the first 2 years and every 6 months thereafter. In patients with no evidence of baseline bone disease, bone scan or PET-CT is repeated at least in case of disease progression.

In this series, baseline was defined as the first consultation at the sarcoma reference centre. Scans taken during the prior 6 months were reviewed to assess the presence of any sign of PD. PD was defined as the appearance of new lesions and/or any radiological increase in size of known tumour lesions (both as per RECIST version 1.1 or not) and/or the appearance or worsening of SE. For the purposes of this study, CT scans were locally retrospectively reviewed according to RECIST version 1.1 and checked for the presence of SE at the baseline and during surveillance.[17]

Data on patient's demographic (sex and age at baseline), baseline tumour-related symptoms (TRP, temperature $>37.5^{\circ}$C, fatigue, weight loss $>5\%$), type of EHE gene rearrangement (*WWTR1* or *TFE3*), disease baseline extension (baseline presence of metastases, metastatic sites, presence of SE), evidence and date of radiological progression (defined as any radiological increase in size of tumour lesions, both as per RECIST version 1.1 or not, and/or the appearance or worsening of SE), sites of radiological progression, development of tumour-related symptoms during follow-up (new TRP, temperature $>37.5^{\circ}$C, fatigue, weight loss), and patient outcome were collected. The Institutional Review Board of each participant institution approved the study.

Statistical methods

Descriptive statistics were used to summarize patient and tumour characteristics. Contingency tables were used to

describe the associations between pairs of categorical variables. Multivariate association between dichotomic variables (i.e. symptoms at baseline and new symptoms during follow-up), baseline metastatic sites, and sites of PD was studied by applying cluster analysis, the results of which were represented using heat map plots.

Overall survival (OS) and progression-free survival (PFS) curves were estimated with the Kaplan—Meier method and compared with the log-rank test. PFS was calculated from the date of the baseline to the date of first documented evidence of progression (as defined earlier), of death owing to any cause, or of last follow-up. OS was calculated from the date of the baseline to the date of death from any cause or of last follow-up. For those patients with progression and receiving active treatments, postprogression OS (ppOS) analysis was performed; ppOS was calculated from the date of first evidence of progression to the date of death from any cause or of last follow-up. For patients alive and with no evidence of progression at the time t1, the conditional probability of developing a progression at a subsequent time t2 was estimated as the ratio between the corresponding PFS estimates at t1 and at t2; the 95% confidence interval (CI) of this ratio is calculated on a variation of the log—log transformation.[18]

Multivariable prognostic analyses were performed using Cox models; due to the low number of cases and events, which prevent obtaining reliable estimates, the analyses were performed by applying Firth's penalized likelihood, the effect of which is to reduce the hazard ratio (HR) estimates as compared with nonpenalized models.[19] We investigated symptoms and metastatic sites (included serosae), together with patients' age and sex, and molecular data (rearrangement of *WWTR1* versus *TFE3*) as putative prognostic variables. The small size of the series, and the consequent low number of events, prevented us from obtaining reliable results from the Cox models including all the prognostic variables. Thus, we performed a beforehand variable selection by applying a random forest procedure for survival data for inclusion in a subsequent multivariable Cox model for OS and PFS. The variables were selected according to their minimal depth (the lowest the best) and variable importance (the highest the best) criteria. New symptoms and sites of PD during follow-up should have been modelled as time-dependent variables; however, given that the present analyses were explorative, and considering also the aforementioned limitations (low number of patients and events), we have treated them as fixed baseline variables. Because of the low number of cases and events, which prevent us from obtaining reliable estimates, in the multivariable analysis of association between ppOS and SE, the adjustment for sex, age, type of progression (RECIST versus non-RECIST), presence of symptoms at baseline or during follow-up was operated by means of a score beforehand estimated as the linear predictor from a Cox model.

Table 1. Population characteristics

Variable	Statistic/Levels	Value, *n* (%)
Age	Mean (SD)	43.8 (12.8)
	Median (interquartile range)	45 (14.5)
	Min-max	18-72
Sex	Male	23 (34.3)
	Female	44 (65.7)
Gene rearrangement	*WWTR1*	62 (92.5)
	TFE3	5 (7.5)
Baseline tumour extent	Lung	41 (61.2)
	Single site	7 (10.4)
	Soft tissues	13 (19.4)
	Single site	2 (3.0)
	Liver	36 (53.7)
	Single site	9 (13.4)
	Bone	22 (32.8)
	Single site	4 (6.0)
	Lymphonodes	14 (20.9)
	Single site	1 (1.5)
Baseline serosal effusion	Present	4 (6.0)
	Absent	63 (94.0)
Baseline symptoms	Present	40 (59.7)
	Tumour-related pain	22 (32.8)
	Temperature	14 (20.9)
	Fatigue	12 (17.9)
	Weight loss	11 (16.4)
	Absent	27 (40.3)

The analyses were carried out using the SAS (version 14) and R software (version 15). We considered a statistical test as significant when the corresponding *P* value was <0.05.

RESULTS

Patient population

Between January 2010 and June 2018, 67 consecutive advanced EHE patients with no evidence of PD at baseline were started on surveillance.

Population characteristics are summarized in Table 1. The median age at diagnosis was 45 years (range 18-72 years), and there was a predominance in female (male: 23, 34.3%; female: 44, 65.7%).

Outcome and treatment

With a median follow-up of 50.2 months (interquartile range 33.4-80.3), 51 (76%) patients developed PD and 16 (24%) remained stable over time. No spontaneous regressions were observed. The type of radiological progression observed is described in Table 2.

All 51 progressive patients were considered for medical therapy: 49 (97%) received an active treatment (sirolimus: 29, 57%; interferon-α: 10, 20%; gemcitabine: 6, 12%; doxorubicin: 3, 6%; cyclophosphamide: 1, 2%), 1 refused treatment, and 1 was started on palliative care.

At the time of the last data cut-off (March 2020), 23 patients (34%) died (all with previous PD), 8 (12%) were lost at follow-up, and 36 (54%) were alive with disease.

Table 2. Type of radiological progression observed

	Patients
Radiological disease progression[a], *n*	51
Disease progression by RECIST version 1.1, *n* (%)	36 (71)
Concomitant with worsening of existing serosal effusion, *n*	2
Concomitant with occurrence of new serosal effusion, *n*	5
Increase in size of tumour lesions <20%, no new lesions, *n* (%)	14 (27)
Concomitant with worsening of existing serosal effusion, *n*	0
Concomitant with occurrence of new serosal effusion, *n*	4
Isolated progression of serosal effusion, *n* (%)	1 (2%)
Isolated worsening of existing serosal effusion, *n*	0
Isolated occurrence of new serosal effusion, *n*	1

[a] Any radiological increase in size of tumour lesions (both as per RECIST version 1.1 and not) and/or appearance or worsening of serosal effusion.

Association between symptoms (baseline and new symptoms during follow-up), metastatic sites, and sites of progressive disease

The association is represented in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100083, where cluster membership and overlapping red areas identify associated variables. The more strongly associated variables were lung and liver metastases and progression at the same sites (cluster 1); the most frequent combinations were lung metastases and lung progression (10 patients), liver metastases and liver progression (5 patients), lung and liver metastases and liver progression (6 patients), and lung and liver metastases and lung and liver progression (7 patients). The second cluster of associated variables was characterized by TRP and fatigue at baseline, node and bone metastases, and serosal progression; TRP was more closely associated with serosal progression, and node metastasis with fatigue at baseline. All the other variables were grouped together in the third cluster where the data are sparse (not overlapping red areas), and no clear association emerged.

Among 51 progressive patients, 36 (71%) progressed in the metastatic site present at baseline only (yellow areas in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100083), 6 (12%) in new sites only, and 9 (17%) to both (overlapping yellow areas). No substantial association between the different progression sites was identified. Slightly more than half of the progressive patients (29, 57%) presented with progression in a single site (12 liver, 9 lung, 4 soft tissue, 3 serosal, and 1 bone); among the remaining 22 (43%) patients, five developed concomitant lung and liver progression and seven concomitant lung and serosal progression (one with concomitant liver, one with concomitant bone, and one with concomitant soft tissue); the remaining 10 cases presented with other combinations of sites.

Twenty-one (41%) progressive patients developed new symptoms (13, 25%, already symptomatic at baseline and 8, 16%, previously asymptomatic), with TRP being the most common new symptom (11, 22%), followed by weight loss (7, 14%), temperature (6, 11%), and fatigue (6, 11%). Five patients (10%) developed more than one new symptom.

No patients with stable disease overtime developed new symptoms during surveillance.

Association between TRP (baseline and new pain during follow-up), baseline evidence of SE, and development of SE during follow-up

Supplementary Table S1 (available at https://doi.org/10.1016/j.esmoop.2021.100083) presents the results of this association (as well as the concomitant presence of bone metastases). Among 22 patients with TRP at baseline, 3 (14%) presented with SE, while 7 (32%) subsequently developed serosal progression, as compared with 1 (2%) and 3 (7%), respectively, among the 45 pain-free patients.

Progression-free survival

The median PFS in the whole population was 14.8 months (interquartile range 4.8-38.2), with a 6-, 12-, 24-, and 36-month PFS of 68.7% (95% CI 58.4-80.7), 56.6% (95% CI 45.9-69.8), 37.3% (95% CI 27.2-51.5), and 25.4% (95% CI 16.6-39.0), respectively. The conditional probability for patients alive with no evidence of progression at 2 years of developing a subsequent progression at 5 years was 53.9% (95% CI 27.6-74.4).

Through the application of the random forest model, the following variables were selected as predictor of PFS: age, baseline SE, baseline TRP, baseline temperature, and development of fatigue during follow-up. Sex, type of rearrangement (*WWTR1* versus *TFE3*), baseline fatigue, baseline weight loss, baseline evidence of lung metastases, liver metastases, bone metastases, nodal metastases, development of temperature, or weight loss during follow-up were not selected (see Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2021.100083).

The Cox multivariable model confirmed a significant association between PFS and baseline TRP (HR 3.54; 95% CI 1.83-6.87; $P = 0.0002$; Figure 1A), development of TRP during follow-up (HR 3.66; 95% CI 1.58-8.49; $P = 0.005$), baseline temperature (HR 3.44; 95% CI 1.64-7.19; $P = 0.002$), and development of fatigue during follow-up (HR 5.81; 95% CI 1.80-18.78; $P = 0.007$). Patients' age (HR 3rd versus 1st quartile—50 versus 36 years 0.82; 95% CI 0.58-1.17; $P = 0.486$) and evidence of baseline SE (HR 1.19; 95% CI 0.27-5.13; $P = 0.815$) were not significant predictors at multivariable Cox analysis. Kaplan—Meier curves for PFS are shown in Figure 1.

Overall survival

The median OS in the whole population was unreached, with an OS at 12, 24, and 36 months of 86.3% (95% CI 78.4-95.0), 78.2% (95% CI 68.7-89.0), and 71.1% (95% CI 60.5-83.4).

Through the random forest model, the following variables were selected as predictor of OS: age, baseline SE, baseline TRP, development of TRP during follow-up, and development of fatigue during follow-up. Sex, molecular marker, baseline temperature, baseline fatigue, baseline weight loss, baseline evidence of lung metastases, liver metastases,

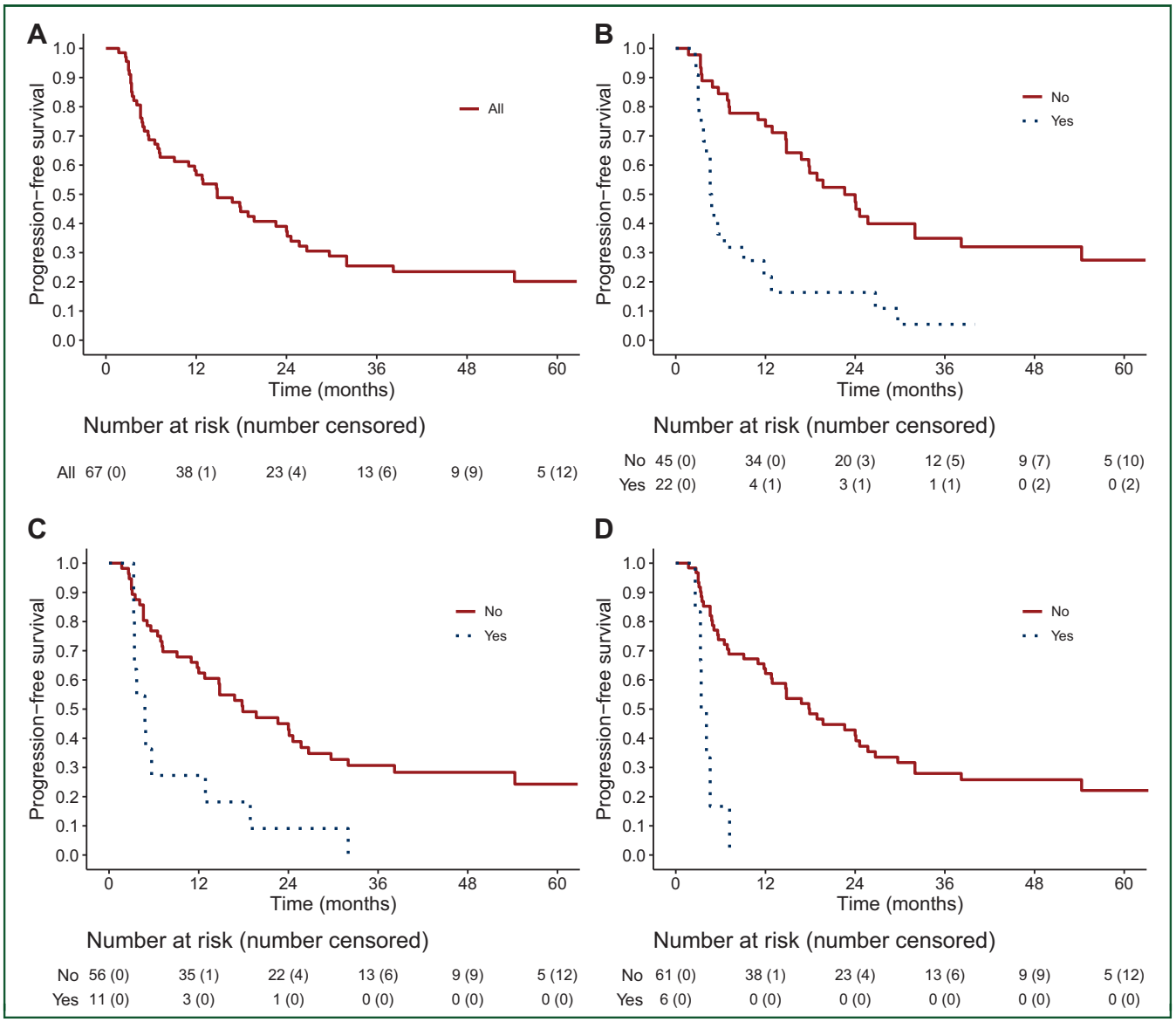

Figure 1. Kaplan−Meier curves for progression-free survival.
(A) Progression-free survival curve in the whole population ($n = 67$), according to the (B) presence of baseline pain, (C) development of pain during follow-up, and (D) development of fatigue during follow-up.

bone metastases, nodal metastases, development of temperature, or weight loss during follow-up were not selected (see Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2021.100083).

The Cox multivariable model confirmed an association between OS and baseline TRP (HR 9.09; 95% CI 2.99-27.63; $P < 0.0001$; Figure 1B), development of TRP during follow-up (HR 6.92; 95% CI 2.17-22.05; $P = 0.0009$), and evidence of baseline SE (HR 4.70; 95% CI 0.62-35.67; $P = 0.121$), whereas the association with development of fatigue during follow-up (HR 1.84; 95% CI 0.48-7.02; $P = 0.386$) and, especially, patients' age (HR 3rd versus 1st quartile: 50 versus 36 years = 1.28; 95% CI 0.79-2.09; $P = 0.254$) was less marked. Kaplan−Meier curves for OS are shown in Figure 2.

None of the non progressive patients died. Among the 49 progressive patients receiving active treatments, the 12-month ppOS was 71.2% (95% CI 59.1-85.8). While in the 35 patients without SE at baseline and during follow-up, the 12-month ppOS was 88.4% (95% CI 78.3-99.8); among the 14 patients with evidence of SE, ppOS drops to 11.7% (95% CI 1.9-71.6, $P < 0.0001$). At multivariable Cox analysis, after adjustment for sex, age, type of radiological progression (RECIST versus non-RECIST), presence of symptoms at baseline or during follow-up, the HR associated with SE was 3.05 (95% CI 0.93-9.97; $P = 0.065$) versus 11.31 (95% CI 3.97-32.23; $P < 0.0001$) in univariable Cox analysis. The 12-month ppOS in the 34 patients progressing according to RECIST version 1.1 was 68.4% (95% CI 54.0-86.8), while in those 14 patients progressing but not meeting RECIST version 1.1 criteria for PD it was 76.9% (95% CI 57.1-100.0; $P = 0.633$). The ppOS at 24 and 36 months was 58.3% and 52.5% and 61.5% and 53.8% in the two groups, respectively. In both groups, the presence of

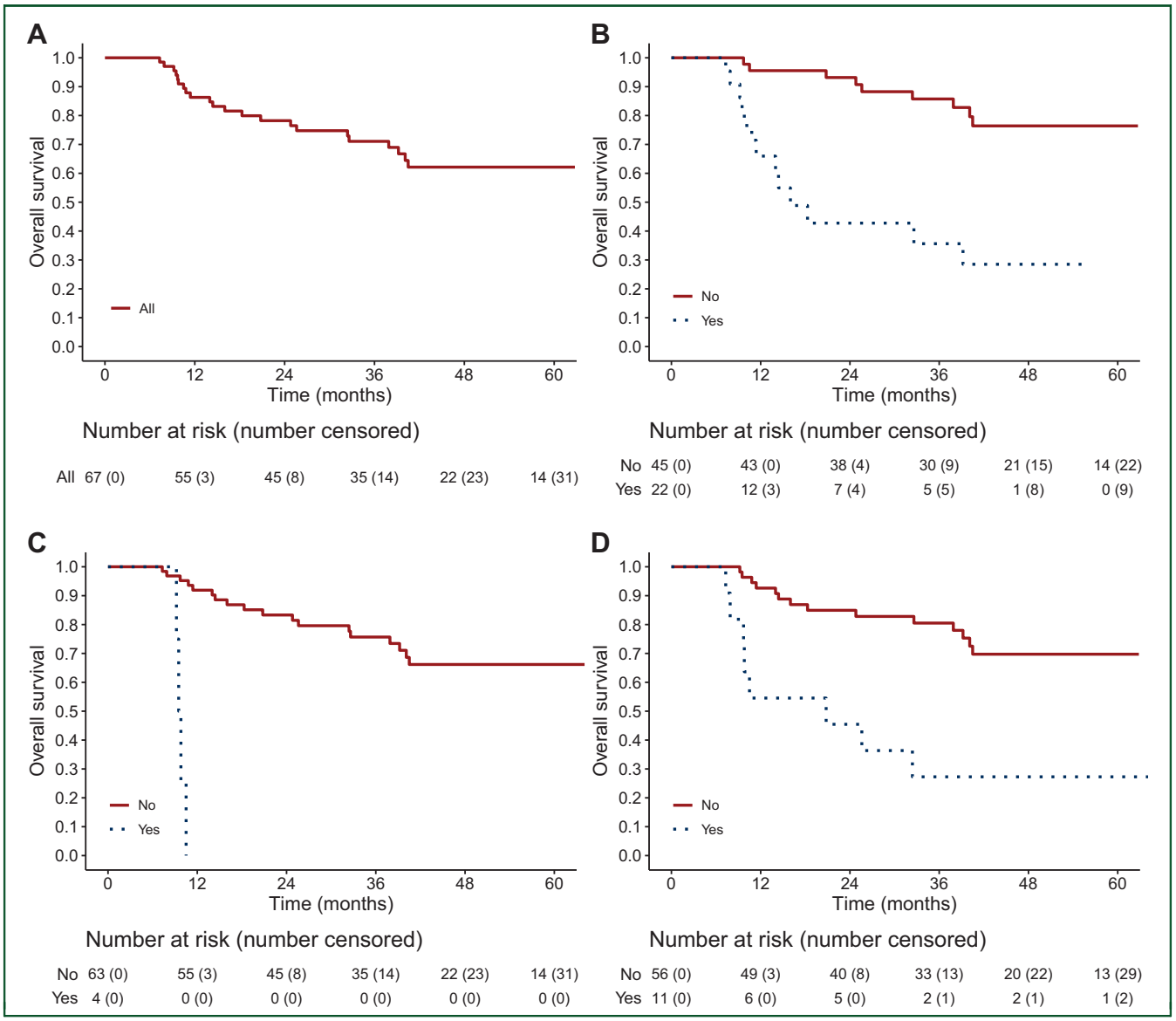

Figure 2. Kaplan–Meier curves for overall survival.
(A) Overall survival curve in the whole population ($n = 67$), according to the presence of (B) baseline pain, (C) baseline serosal effusion, and (D) development of pain during follow-up.

SE at the time of progression (including SE at baseline and during follow-up) was associated with a worst ppOS ($P < 0.0001$ if by RECIST version 1.1, $P = 0.0018$ if not by RECIST version 1.1).

DISCUSSION

In this series of 67 advanced, molecularly confirmed, EHE patients with no evidence of progression in the 6 months prior to baseline and started on a surveillance programme, 76% subsequently developed disease progression, whereas 24% remained stable over time. The median follow-up was 50 months. Although most progressive patients started a systemic treatment, the 3-year PFS and OS were 25% and 71%, respectively. The overall outcome was poorer in patients presenting with baseline TRP, temperature, and SE. Both the development of fatigue and TRP during follow-up were also adverse prognostic factors.

The interpretation of these results is affected by the small sample size, the retrospective nature of data collection and radiologic review, the lack of a control group of untreated patients at the time of disease progression, and the inclusion of patients at different stages of their clinical history, the baseline being set at the time of first consultation at each institution. In addition, this study does not aim to describe the natural history of EHE but focuses on the outcome of a very selected subset of EHE patients, presenting with advanced disease, referred to sarcoma reference centres, and allocated to a surveillance programme due to the absence of progression in the previous 6 months. This series does not include patients with localized EHE, patients referred for PD, those started upfront on

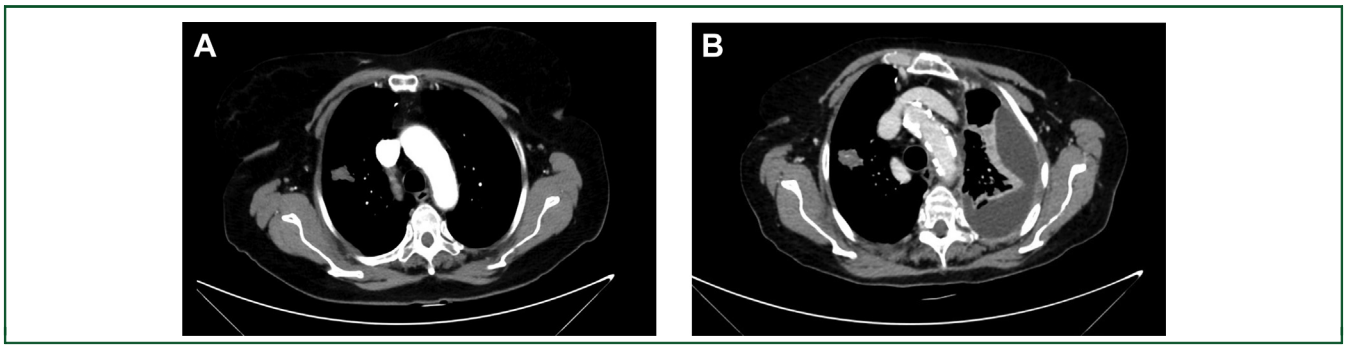

Figure 3. Radiological progression in a patient with pulmonary epithelioid haemangioendothelioma not meeting RECIST criteria for progression.
(A) Baseline chest computed tomography scan with iodine-based contrast media (mediastinal window setting) showing a lesion in the right upper lung lobe (24 mm, maximum diameter); no evidence of pleural effusion. (B) 36 months later, stable disease in the lung, but occurrence of clinically relevant left-sided pleural effusion.

systemic treatments, and, of course, those managed locally and never referred to reference centres. Despite these limitations, this is the first series of molecularly confirmed, advanced EHE patients followed-up through a common surveillance programme within a sarcoma reference network. Besides, it represents the first attempt of shedding light on the symptoms that can occur in this population, at the baseline and during follow-up, and their correlation with outcome.

SE has already been reported as an adverse prognostic factor in patients with advanced EHE, and this is confirmed in our series.[7,9,12,20] In this study, the presence of SE was found to negatively influence both OS (baseline SE: HR 4.70; $P = 0.121$) and ppOS (all SE at the time of progression: HR 3.05; $P = 0.065$). The absence of a statistically significant difference in OS is more likely due to the small sample size (only four patients presenting with SE) than to a true absence of association, whereas in ppOS a clear trend can be observed. We noticed that the development and worsening of SE during follow-up was rarely isolated, being usually associated with a dimensional progression of the disease, though not always matching RECIST version 1.1 criteria for progression (Table 2). In this study, we were not able to explore the prognostic relevance of serosal involvement in absence of effusion, due to the difficulties in accurately assessing the serosal appearance through a retrospective radiological review. In general, serosal radiological appearance in EHE is different from other pleural malignancies, such as mesothelioma, being characterized by modest pleural thickening, evidence of indentations, and rapid changes in the amount of fluid.[7,21] Although proper radiological criteria for evaluation of disease progression taking into account changes in serosal involvement/effusion are lacking for EHE patients, careful assessment of these radiological signs in all patients at baseline and while on surveillance is of major importance, given their impact on prognosis.

The limitations in the use of RECIST for patients with advance EHE are made clear in this series. According to our results, ∼30% of EHE progressive patients show, at the time of treatment start, a progression pattern that cannot be captured by RECIST definition of progression, because those criteria do not consider <20% increase in size of known lesion nor changes in SE.[17] Therefore, sticking to RECIST in EHE might not allow prompt recognition of progression. A paradigmatic case of disease progression in EHE neglected by RECIST version 1.1 is shown in Figure 3.

To our knowledge, for the first time, this study also provides a description of TRP and systemic symptoms in EHE, which were reported at baseline or during follow-up by >50% of advanced EHE patients in this series. The presence of any symptom at diagnosis, weight loss, and haemoptysis have already been suggested as potential prognostic factors in EHE patients.[8,12] Notably, paraneoplastic symptoms, which are well-recognized adverse prognostic factors in several human cancers, are anecdotal in soft tissue sarcoma other than EHE, thus representing a peculiar clinical feature for this subtype. In our series ∼60% of patients were symptomatic at baseline, with TRP being the most common symptom, followed by temperature, fatigue, and weight loss. Approximately 12% of previously asymptomatic patients developed symptoms during the follow-up, and this was always associated with disease progression. The presence of symptoms at baseline, or their development during follow-up, correlated with a worse prognosis. Given these results, in EHE patients on surveillance the presence of symptoms at baseline, as well as their occurrence over time, should be carefully checked and recorded.

The most recorded symptom was TRP, observed in ∼30% of patients at the baseline. Among 30 patients reporting pain, both at baseline and during follow-up, 6 (20%) had concomitant SE only, 7 (23%) had both pleural effusion and bone metastases, and 9 (30%) had bone metastases only. A higher tendency to develop SE during follow-up was observed in patients presenting with baseline pain and no baseline SE (32%), compared with patients with neither baseline pain nor SE (7%). This could suggest that, at least in a proportion of patients, baseline pain could be related to an early serosal tumour infiltration, which can subsequently result in effusion. The association of pain with serosal involvement and bone lesions point to its cause in many cases. Although detailed information about pain type, location, and management is missing, it was possible to observe that in individual cases pain was severe, hard to manage, and associated with sudden and excruciating pain flares that can be described as spontaneous breakthrough pain episodes. In some patients, an elective response was observed to nonsteroidal anti-inflammatory agents, along

with a relatively poor response to opioids. The potential association of significant systemic inflammatory processes and local pronociceptive mechanisms due to the tumour biology and interaction with local tissues is an intriguing hypothesis to explain symptom severity and cluster. Systemic inflammation and chemokine mediators' cascade have been implicated in pain pathophysiology both in cancer patients and in experimental cancer pain models.[22-27] Given the importance of the pain course in this disease we advocate that future prospective series should receive formal pain assessment.

Up today, the mechanisms behind pleural involvement in EHE, the higher frequency of paraneoplastic symptoms and refractory pain as well as the predominance of EHE in females are unknown. A prospective study, supported by EHE Rare Cancer Charity, is ongoing at Fondazione IRCCS — Istituto Nazionale Tumori, Milan, aiming to better understand the biological bases underlying these clinical observations, to prospectively validate the clinical and molecular prognostic factors previously reported, including those from this series, and identify potentially actionable pathways involved in EHE to develop new treatment options.

In conclusion, our study shows that the clinical assessment of EHE patients should include a regular check for the presence of systemic symptoms, pain, and SE, because they have a prognostic meaning. We believe that, given their poor outcome even when radiological disease progression is lacking, in patients presenting with SE it is reasonable to offer upfront treatment, rather starting an active surveillance programme, especially when SE is associated with tumour-related symptoms (TRP and/or temperature and/or SE), which is often the case. Though depending on the case mix, a significant proportion of EHE patients initially allocated to surveillance do ultimately develop PD and require systemic treatments. It is left to assess how high such proportion may be on larger series with a lower potential selection bias.

FUNDING

None declared.

DISCLOSURE

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