# Systemic Treatment Options for Epithelioid Haemangioendothelioma: The Royal Marsden Hospital Experience

NADIA YOUSAF[1], MARCO MARUZZO[1], IAN JUDSON[1], OMAR AL-MUDERIS[1], CYRIL FISHER[2] and CHARLOTTE BENSON[1]

[1]*Sarcoma Unit, The Royal Marsden NHS Foundation Trust, London, U.K.;*
[2]*Pathology Department, The Royal Marsden NHS Foundation Trust, London, U.K.*

**Abstract.** *Background: Epithelioid haemangioendothelioma (EHE) is a rare vascular tumour, which can arise at any site. There is little published data about the management of these tumours. Patients and Methods: A retrospective review of patients with histologically-proven EHE presenting to the Royal Marsden Hospital from January 1999 to January 2012. Results: Thirty-two patients (23 females) were identified with a median age of 44 (range=17-78). Twenty patients presented with diffuse disease. Median overall survival (OS) was 9.8 years in 10 patients with operable disease. Amongst those with inoperable disease (n=22), patients with liver disease had the longest median OS (9.8 years), while those with lung and mediastinal disease had the shortest OS (3.6 years). A variety of treatments were used for inoperable disease with infrequent radiological responses. Conclusion: The clinical behaviour can vary depending on the site of disease. Surgery, if feasible, has the best outcome. In those with inoperable disease, a period of observation to assess the tumour behaviour is recommended. The role of medical therapy remains unclear.*

Epithelioid Haemangioendothelioma (EHE) is a rare, often multifocal, intermediate-grade vascular sarcoma (1-2). It originates from endothelial cells and it can arise from any site but most commonly arises in the liver, lung and other soft tissues, although examples involving skin (3) and head and neck (4-5) have been reported. The reported incidence is less than 0.1 per 100,000 population; mean age at diagnosis is 41.7 years with a slight female prevalence (male:female ratio, 2:3) (6). Imaging plays a significant role into the pre-diagnostic assessments for EHE: typically, the tumour appears as solid nodule, which undergoes necrosis, haemorrhage and, occasionally, calcification; a ring-like border shows progressive contrast enhancement on computer tomography or magnetic resonance scans (7). The diagnosis must be confirmed with pathological assessment. Histopathological features of EHE include an infiltrative growth pattern. The tumour is composed of epithelioid, dendritic and intermediate cells in a fibromyxoid stroma (8). Recently, a new hallmark of EHE has been identified: the presence of *WWTR1-CAMTA1* fusion may serve as a useful molecular diagnostic tool in challenging diagnoses (9).

According to the most recent World Health Organisation classification (10), EHE is considered a malignant vascular tumour similar to an angiosarcoma, although with a better prognosis (3). As with all sarcomas, surgery with clear margins is the best treatment for this neoplasm. Most published series are surgical series showing 5-year survival of up to 55% in patients undergoing radical surgery (11). However, many patients have multifocal disease at presentation and surgery is not feasible.

There exists limited clinical information regarding the medical management and clinical behaviour of EHE. In this paper we describe the management and the clinical outcomes of thirty-two consecutive patients with EHE treated at The Royal Marsden Hospital.

## Patients and Methods

We retrospectively reviewed the management and outcome of patients with histologically-proven EHE presenting to the Royal Marsden Hospital between January 1999 and December 2013. Patients were identified from the prospectively maintained Royal Marsden Hospital Sarcoma Unit database and demographics, site, treatment and survival outcomes were collected from the database and patients' electronic case notes. Histological diagnosis of EHE

*Correspondence to:* Dr. Charlotte Benson, The Royal Marsden HNS Foundation Trust Sarcoma Unit, Fulham Road, London SW3 6JJ, U.K. Tel: +44 02078082200, Fax +44 02078082113, e-mail: Charlotte.Benson@rmh.nhs.uk

*Key Words:* Epithelioid haemangioendothelioma, EHE, survival, observation, chemotherapy, surgery, sarcoma.

was reviewed and confirmed in all cases by a designated Sarcoma Unit histopathologist.

Institutional ethical approval was gained for this project before starting data collection.

Overall survival was calculated by the Kaplan-Meier method from the date of diagnosis until death and censored at last follow-up. Statistical analysis was performed using the SPSS version 15 (Softonic Internacional S.A., Barcelona, Spain).

## Results

*Demographics*. Thirty-two patients were seen at the Royal Marsden Hospital between 1999 and 2013. The majority were women (23 patients) with a median age of 44 years (range=17-78). Predominant primary sites of origin were liver, thorax and lungs, abdominal wall. Twenty patients (62%) presented with diffuse disease involving one or more organs. Patients' demographics are summarized in Table I.

Table I. *Demographics*.

| | |
|---|---|
| Age | |
| Median | 44 years |
| (range) | (17-78) |
| Gender | |
| Male | 9 (28%) |
| Female | 23 (72%) |
| Primary location | |
| Liver | 9 (28%) |
| Thoracic/Mediastinum | 6 (19%) |
| Lung | 5 (15%) |
| Abdominal wall | 2 (7%) |
| Head and neck | 2 (7%) |
| Limb | 1 (3%) |
| Other visceral | 2 (6%) |
| Other soft tissue | 5 (15%) |
| Presentation | |
| Operable | 10 (31%) |
| Locally advanced | 2 (7%) |
| Metastatic | 20 (62%) |

*Treatment*. Ten patients (31%) received upfront surgery for their disease; two patients (6%) with locally advanced liver disease received neoadjuvant therapies. The first patient received infusion of 5-fluorouracil (5-FU) and interferon alpha (IFN-α) for five months while waiting for a transplant. After disease stabilization, this patient underwent liver transplant and he is now free of recurrence. The second one received two cycles of weekly paclitaxel for a local advanced disease and, with a best response of stable disease, he underwent definitive surgery.

The majority of patients (62%) had metastatic disease at presentation and received one or more lines of medical treatment with cytotoxic chemotherapy after documented radiological progression. Three patients (9%) progressed after primary surgery and started systemic treatment. For four patients (12%), a watchful waiting policy was adopted at presentation either because of age or physician's decision to observe the natural history of disease before making a treatment decision.

*Medical treatment*. Among the metastatic patients, one was treated with IFN alone because of inoperable disease at presentation and had a reduction in the volume of disease of about 20%; he subsequently underwent surgery and he is now free of recurrence. A second patient received IFN as first-line treatment in a metastatic setting: after six months of therapy, the best response was disease stabilization. Other 3 patients were treated with IFN-α in combination with 5-FU, all of them had stable disease as best response to the treatment.

Other anti-angiogenic drugs (axitinib, semaxinib, pazopanib and sunitinib) have been used in third- or further-line setting without achieving objective response; most of the patients had disease progression at the first assessment. Two patients received axitinib within a clinical trial after disease progression on chemotherapy. The treatment with axitinib resulted in disease stabilisation for a long period of time, 17 and 25 months, respectively. Moreover, both patients experienced significant symptomatic benefit.

Three patients received thalidomide achieving progressive disease as a best response.

The most used chemotherapeutic regimen was paclitaxel (28% of the patients) with a median treatment duration of three months and no objective response achieved. For four of these patients (44%), despite only stable disease on imaging, a symptomatic benefit was detected in terms of reduction of analgesia and improvement of performance status. Eight patients were also treated with anthracyclines, either liposomal pegylated doxorubicin (six patients) or doxorubicin (two patients, of which one in combination with ifosfamide). Other chemotherapeutic regiments have been used in our cohort: three patients received 5-FU in combination with interferon (best response: stable disease) and three patients received cyclophosphamide in combination with vinblastine or etoposide (best response: stable disease). The variety of treatment modalities used for patients with inoperable disease are summarised in Table II.

*Survival*. Median overall survival (OS) for all the patients with EHE is 9.8 years (Figure 1). For patients who had localized operable disease at presentation, median OS is not definable because only 3 out of 10 patients have been censored. Amongst those with inoperable disease (n=22), patients with liver disease had the longest median OS (9.8 years) and those with lung and/or mediastinal disease had the shortest OS (3.6 years) (Figures 2 and 3).

Table II. *Treatments and progression-free survival (PFS).*

| | N (%) | Best response | Median PFS |
|---|---|---|---|
| Upfront surgery | 10 (32) | --- | 2 Recurrences after surgery |
| Observation only | 4 (12) | SD | 61.4 months |
| Neoadjuvant treatment | | | |
| IFN | 1 (3) | PR | Free of recurrence |
| Weekly paclitaxel | 1 (3) | SD | |
| 1st-line treatment (N=19) | | | |
| 5-FU and IFN | 3 (9) | SD | |
| Caelyx | 4 (12) | SD | |
| Celecoxib | 4 (12) | PR | |
| Celecoxib and Lenalidomide | 1 (3) | PD | |
| Doxorubicin | 1 (3) | PD | 6.7 months |
| Imatinib | 1 (3) | SD | |
| IFN | 1 (3) | SD | |
| Paclitaxel | 2 (6) | SD | |
| Carboplatin and Paclitaxel | 1 (3) | SD | |
| Cyclo and Vinblastine | 1 (3) | SD | |
| 2nd-line treatment (N=11) | | | |
| Axitinib | 1 (3) | SD | |
| Caelyx | 1 (3) | PD | |
| Celecoxib | 1 (3) | PD | |
| Cyclo and Etoposide | 1 (3) | PD | 3.3 months |
| Ifosfamide and Doxorubicin | 1 (3) | SD | |
| Paclitaxel | 4 (12) | SD | |
| Thalidomide | 2 (6) | PD | |
| 3rd-line treatment (N=7) | | | |
| Axitinib | 1 (3) | SD | |
| Cyclo and Vinblastine | 1 (3) | PD | |
| Paclitaxel | 1 (3) | SD | |
| Pazopanib | 1 (3) | PD | 1.5 months |
| Semaxinib | 1 (3) | PD | |
| Sunitinib | 1 (3) | PD | |
| Thalidomide | 1 (3) | P | |
| 4th-line treatment (N=3) | | | |
| Caelyx | 1 (3) | PD | |
| Paclitaxel | 1 (3) | PD | 1.4 months |
| Semaxinib | 1 (3) | SD | |

PD: Progressive disease; SD: stable disease; PR: partial response; IFN: interferon.

## Discussion

To our knowledge, this is the largest published single-Institution experience of patients with EHE, a rare endothelial vascular neoplasm among the sarcoma family. As it is such a rare cancer, there is no consensus on the management of the patients with this disease and no commonly accepted treatment strategies, particularly in the metastatic setting. Surgery with clear margins should be considered where technically possible. For hepatic EHE, liver transplant is a management option (12). Our data confirm that surgery, if feasible, has the best outcome. We have demonstrated long-term survival following surgery: with a median follow-up time of 45 months, the median OS for patients with operable disease has not been reached. This confirms the long survival outcome for patients with no evidence of disease after surgery and the low recurrence rate (20% in our series after definitive surgery).

If surgery is not feasible, EHE is challenging to treat and it is unclear if pharmacological options have any real efficacy given the variable natural history of this disease. In fact, cases of durable spontaneous regression of both liver and pulmonary EHE have been reported (13-15). Kitaitchi *et al*. reported partial spontaneous regression of 14% (3 out of 21 patients) in patients with pulmonary EHE (13).

Therefore, without a comparator group it is unclear if 'responses' observed both in our study and those reported in the literature are indeed true responses to treatment or simply reflective of the natural history of the disease and spontaneous regression.

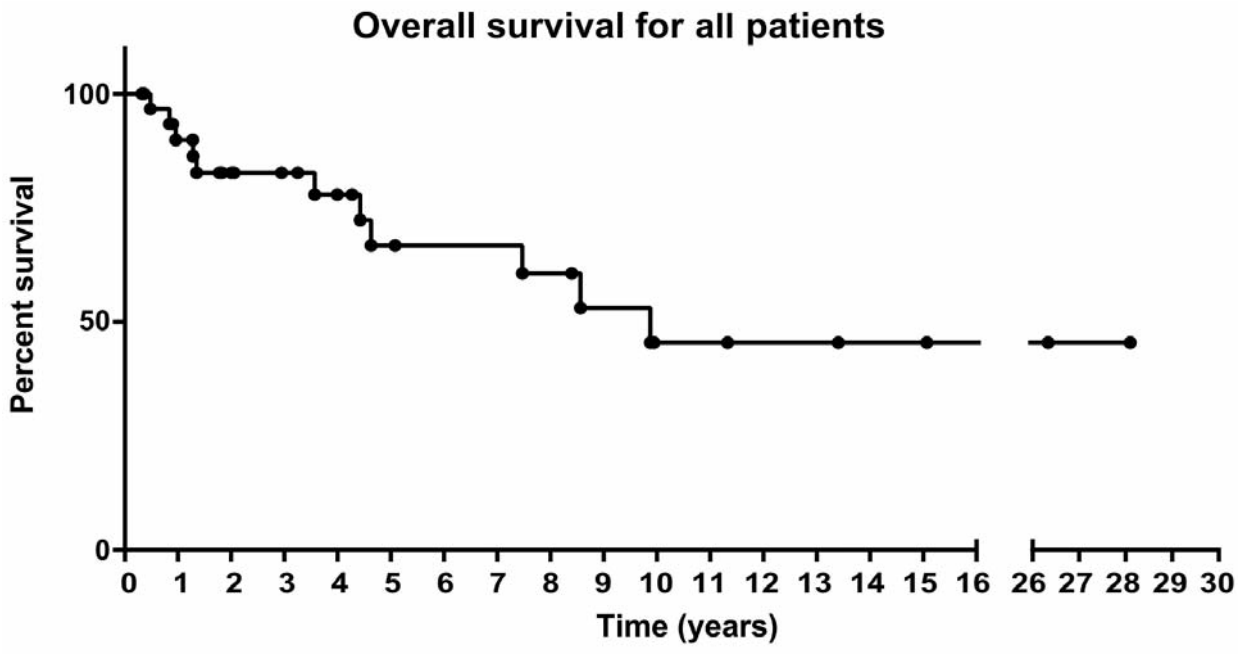


Figure 1. *Overall survival for all EHE patients.*

IFN-α has immunomodulatory effects in the regulation of cell cycle and it also reduces the sensitivity of vascular cells to pro-angiogenic factors and vascularization (16). Other series have also reported responses with IFN in hepatic EHE (17-18), in breast EHE (19) and in primary lung EHE (20). In our cohort of patients, we treated patients either in neoadjuvant and metastatic setting. The best response achieved was partial response for a patients, and disease stabilization for all the others.

Other anti-angiogenic drugs have been used in this patient cohort. There is scientific rational for using vascular endothelial growth factor (VEGF) targeted therapies: expression of VEGF and vascular endothelial growth factor receptor (VEGFR) has been demonstrated in EHE and angiosarcoma (21). However, the literature on treatment with antiangiogenic drugs is limited and consists mostly in retrospective studies, case reports and small series. The largest series has been recently reported by the French Sarcoma Group (22): in this phase II study, 2 out of 15 patients with EHE reported partial responses after receiving treatment with sorafenib. A small cohort of 7 patients treated with bevacizumab has been reported recently (23): among 7 patients with EHE, two had a partial response and four showed stable disease. In our series, anti-angiogenic drugs were used in advanced setting after previous chemotherapy and objective responses were not demonstrated. The best response was stable disease, even if most patients had disease progression at the first assessment. No patients have been treated with sorafenib but we used other tyrosine kinase inhibitor, such as axitinib and semaxinib, in the context of ongoing clinical trials, as well as pazopanib and sunitinib.

Two patients received axitinib with prolonged disease stabilisation and significant clinical benefit. Up to date, no published data to compare with are available. The effect of axitinib in soft tissue sarcomas is under investigation in clinical trials (EudraCT 2008-006007-23). However, angiogenesis is a hallmark of tumour growth (24) and there is evidence that anti-angiogenic drugs can lead to tumour regression in a variety of tumours (25). In our series, durable disease stabilisation was not seen with the other VEGF inhibitors.

Salech *et al.* (26) reported a partial response in a patient with hepatic EHE with thalidomide and a partial response has been reported in pulmonary EHE with bevacizumab and chemotherapy by another group of authors (27).

More recently, an experience with a selective drug targeting the mammalian target of rapamycin (mTOR) pathway has been reported (28). Among 12 patients treated with sirolimus, as a single agent, they reported one response and six stabilisations proving that sirolimus resulted in a high proportion of possibly long-lasting tumour responses.

Other reports describe a variety of differing cytotoxic treatments for metastatic EHE: a long term disease stabilisation has been reported with doxorubicin, vincristine

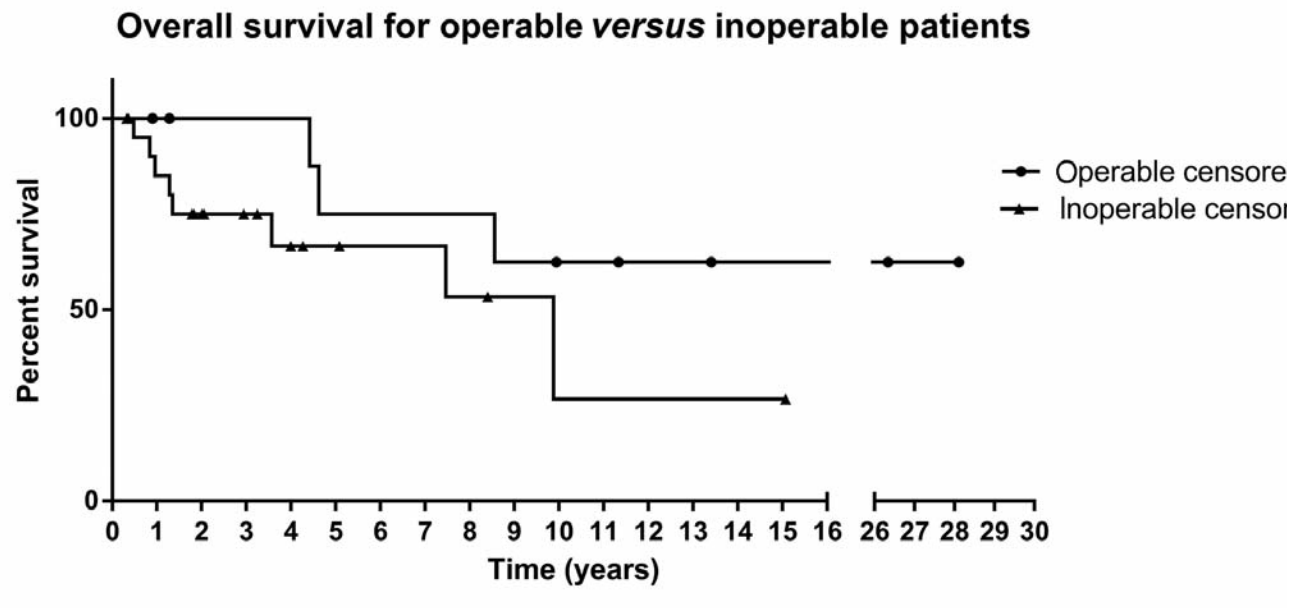


Figure 2. *Overall survival for operable vs. inoperable patients.*

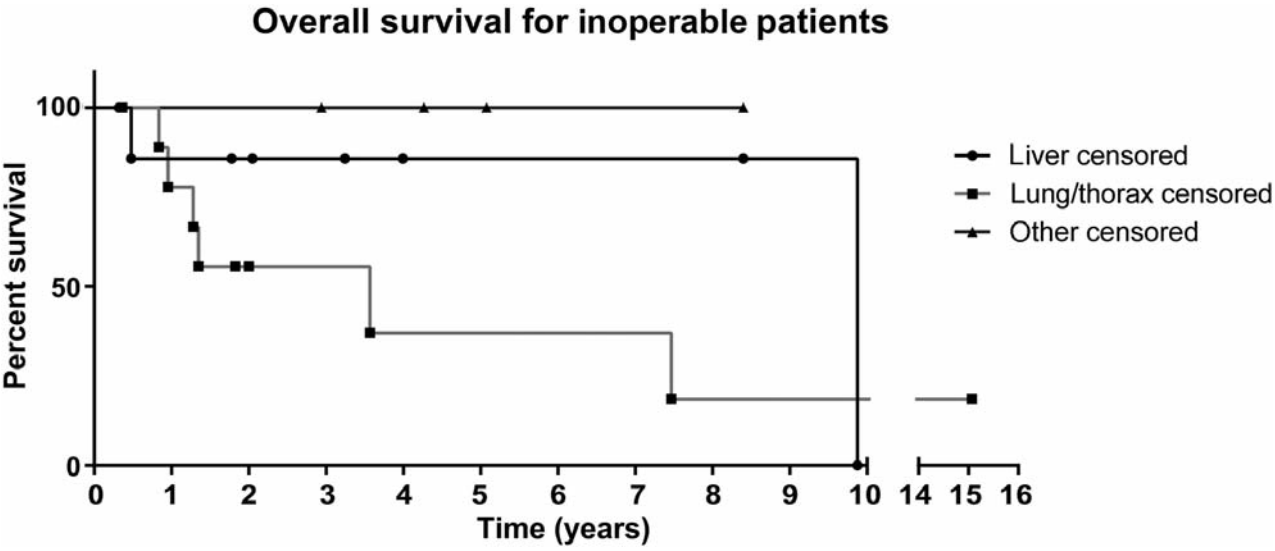


Figure 2. *Overall survival for inoperable patients.*

and 5-FU (29), regression has been observed with doxorubicin alone, while the combination of epirubicin and dacarbazine showed no efficacy on disease control (30). Cioffi *et al*. (31) reported a large retrospective series in which most of the patients were treated with chemotherapy: 16 patients out of 34 received doxorubicin, 6 patients received other chemotherapeutic regimens. In that study, no objective responses have been reported but 14 patients experienced stable disease for more than six months.

From our series, the most used chemotherapeutic regimen was paclitaxel with no, however, objective response achieved, even if with symptomatic benefit for some patients. In keeping with our experience, in the ANGIOTAX study (32) the authors reported a median time to progression of

four months within metastatic angiosarcoma, a disease belonging to the same group of vascular sarcoma. These data have been recently updated at the last ASCO Annual Meeting with the result of ANGIOTAX-Plus study, which showed some small improvement (33). Intriguingly, in our experience, angiosarcoma performs better than EHE, even if they belong to the same group of sarcoma.

Anthracyclines have been the standard first-line treatment for sarcomas since 1976 (34-37) but, in our series of patients with EHE, we did not find any objective responses, with stable disease being the best response. In the majority of our patients, chemotherapy was used in the first-line setting and, therefore, we do not know if this systemic treatment altered the natural history of the disease.

Six patients in our cohort have been treated with celecoxib, a non-steroidal anti-inflammatory (NSAID) drug. It works by inhibiting cyclooxigenase, which is involved in the inflammation process. It has been known, in fact, that inflammation is a critical component of tumour progression (38) and several cases have been reported on the use on NSAIDs in different neoplasms (39-41).

Finally, four patients have undergone surveillance alone. With a median follow-up of 61.4 months, only one patient died more than 10 years after the diagnosis, at the age of 85. Hence, in patients with inoperable disease an initial period of watchful waiting should be recommended to assess the behaviour of the tumour before any consideration is made for systemic therapy.

## Conclusion

The major limitations of the present study are its retrospective and descriptive nature, lack of comparator group; also due to disease rarity the recruitment was over a long period of 14 year period. Based on our experience at the Royal Marsden Hospital, we recommend an initial period of observation with interval CT scan to assess disease behaviour. If slow disease progression is demonstrated, then upfront treatment with celecoxib is reasonable. In those with more aggressive disease, since the disease belongs to the vascular tumour group, an approach similar to angiosarcoma should be considered. The use of paclitaxel is, therefore, reasonable, while we do not think there should be a role for other cytotoxic drugs, which does not seem to offer advantage in terms of survival or clinical benefit.

Anti-angiogenic drugs should be considered, since increasing data are emerging on their possible role, and we hope to receive significant indication from that side.

Moreover, whenever possible, early entry into clinical trials of experimental agents should be considered for such a rare disease in order to give patients the best possible multimodal management.

Additionally, diagnosis of EHE within the spectrum of vascular sarcomas can be difficult and until recently diagnosis has been purely dependent on histological appearances. With advances in molecular diagnostics is now possible to classify EHE more reliably and objectively. Recently, the novel fusion gene *WWTR1-CAMTA1* has been identified as a hallmark of disease (9). It is, therefore, possible that the variable clinical behaviour reported in ours and other series is simply the result of histological misclassification. Identification of a specific fusion gene with oncogene properties is a significant step forward in understanding the behaviour of this rare tumour and may help to direct future therapies.

## Conflicts of Interest

None.

## Acknowledgements

Clinical nurse specialists: Alison Dunlop, Rolyn Alvarado, Cerys Propert Lewis and Sam Hackett.

## References

1 Weiss SW and Enzinger FM: Epithelioid hemangio-endothelioma: a vascular tumor often mistaken for a carcinoma. Cancer *50*: 970-981, 1982.

2 Weiss SW and Enzinger FM: Spindle cell hemangio-endothelioma. A low-grade angiosarcoma resembling a cavernous hemangioma and kaposi's sarcoma. Am J Surg Pathol *10*: 521-530, 1986.

3 Deyrup AT, Tighiouart M, Montag AG and Weiss SW: Epithelioid hemangioendothelioma of soft tissue: a proposal for risk stratification based on 49 cases. Am J Surg Pathol *32*: 924-927, 2008.

4 Marrogi AJ, Boyd D, El-Mofty S and Waldron C: Epithelioid hemangioendothelioma of the oral cavity: report of two cases and review of literature. J Oral Maxillofac Surg *49*: 633-638, 1991.

5 Orsini G, Fioroni M, Rubini C and Piattelli A: Epithelioid hemangioendothelioma of the oral cavity: report of case. J Oral Maxillofac Surg *59*: 334-337, 2001.

6 Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler MW and Schmidt J: Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer *107*: 2108-2121, 2006.

7 Lin J and Ji Y: CT and MRI diagnosis of hepatic epithelioid hemangioendothelioma. Hepatobiliary Pancreat Dis Int *9*: 154-158, 2010.

8 Thin LW, Wong DD, De Boer BW, Ferguson JM, Adams L, Macquillan G, Delriviere L, Mitchell A and Jeffrey GP: Hepatic Epithelioid Haemangioendothelioma: challenges in diagnosis and management. Intern Med J *40*: 710-715, 2010.

9 Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, Healey JH and Antonescu CR: A novel wwtr1-camta1 gene fusion is a consistent abnormality in epithelioid hemangio-endothelioma of different anatomic sites. Genes Chromosomes Cancer *50*: 644-653, 2011.

10 Fletcher CD: The evolving classification of soft tissue tumours - an update based on the new 2013 WHO classification. Histopathology *64*: 2-11, 2014.
11 Läuffer JM, Zimmermann A, Krähenbühl L, Triller J and Baer HU: Epithelioid hemangioendothelioma of the liver. A rare hepatic tumor. Cancer *78*: 2318-2327, 1996.
12 Langrehr JM, Petersen I, Pfitzmann R and Lopez-Hänninen E: Malignant epithelioid hemangioendothelioma of the liver. Results of surgical treatment strategies. Chirurg *76*: 1161-1167, 2005.
13 Kitaichi M, Nagai S, Nishimura K, Itoh H, Asamoto H, Izumi T and Dail DH: Pulmonary epithelioid haemangioendothelioma in 21 patients, including three with partial spontaneous regression. Eur Respir J *12*: 89-96, 1998.
14 Otrock ZK, Al-Kutoubi A, Kattar MM, Zaatari G and Soweid A: Spontaneous complete regression of hepatic epithelioid haemangioendothelioma. Lancet Oncol *7*: 439-441, 2006.
15 Satpathy A, Moss C, Raafat F and Slator R: Spontaneous regression of a rare tumour in a child: angiolymphoid hyperplasia with eosinophilia of the hand: case report and review of the literature. Br J Plast Surg *58*: 865-868, 2005.
16 Dinney CP, Bielenberg DR, Perrotte P, Reich R, Eve BY, Bucana CD and Fidler IJ: Inhibition of basic fibroblast growth factor expression, angiogenesis, and growth of human bladder carcinoma in mice by systemic interferon-alpha administration. Cancer Res *58*: 808-814, 1998.
17 Kayler LK, Merion RM, Arenas JD, Magee JC, Campbell DA, Rudich SM and Punch JD: Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantationand interferon alpha-2b. Transplantation *74*: 128-130, 2002.
18 Calabrò L, Di Giacomo AM, Altomonte M, Fonsatti E, Mazzei MA, Volterrani L, Miracco C and Maio M: Primary hepatic epithelioid hemangioendothelioma progressively responsive to interferon-alpha: is there room for novel anti-angiogenetic treatments? J Exp Clin Cancer Res *26*: 145-150, 2007.
19 Marsh Rde W, Walker MH, Jacob G and Liu C: Breast implants as a possible etiology of epithelioid hemangioendothelioma and successful therapy with interferon-alpha2. Breast J *11*: 257-261, 2005.
20 Radzikowska E, Szczepulska-Wójcik E, Chabowski M, Oniszh K, Langfort R and Roszkowski K: Pulmonary epithelioid haemangioendothelioma – interferon 2-alpha treatment--case report. Pneumonol Alergol Pol *76*: 281-285, 2008.
21 Stacher E, Gruber-Mösenbacher U, Halbwedl I, Dei Tos AP, Cavazza A, Papotti M, Carvalho L, Huber M, Ermert L and Popper HH: The VEGF-system in primary pulmonary angiosarcomas and haemangioendotheliomas: new potential therapeutic targets? Lung Cancer *65*: 49-55, 2009.
22 Chevreau C, Le Cesne A, Ray-Coquard I, Italiano A, Cioffi A, Isambert N, Robin YM, Fournier C, Clisant S, Chaigneau L, Bay Jo, Bompas E, Gauthier E, Blay JY and Penel N: Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the french sarcoma group (GSF/GETO). Cancer *119*: 2639-2644, 2013.
23 Agulnik M, Yarber JL, Okuno SH, Von Mehren M, Jovanovic BD, Brockstein BE, Evens AM and Benjamin RS: An open-label, multicenter, phase ii study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol *24*: 257-263, 2013.
24 Hanahan D and Weinberg RA. The hallmarks of cancer. Cell *100*: 57-70, 2000.
25 Rugo HS, Herbst RS, Liu G, Park JW, Kies MS, Steinfeldt HM, Pithavala YK, Reich SD, Freddo JL and Wilding G: Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. J Clin Oncol *23*: 5474-5483, 2005.
26 Salech F, Valderrama S, Nervi B, Rodriguez JC, Oksenberg D, Koch A, Smok G, Duarte I, Pérez-Ayuso RM, Jarufe N, Martínez J, Soza A, Arrese M and Riquelme A: Thalidomide for the treatment of metastatic hepatic epithelioid hemangioendothelioma: a case report with a long term follow-up. Ann Hepatol *10*: 99-102, 2011.
27 Belmont L, Zemoura L and Couderc LJ: Pulmonary epithelioid haemangioendothelioma and bevacizumab. J Thorac Oncol *3*: 557-558, 2008.
28 Stacchiotti S, Palassini E, Libertini M, Marrari A, Bertulli R, Morosi C, Messina A, Crippa F, Dagrada G, Dei Tos AP, Gronchi A, Pilotti S and Casali PG: Sirolimus in advanced hemangioendothelioma. J Clin Oncol 31 (suppl; abstr 10565), 2013.
29 Idilman R, Dokmeci A, Beyler Ar, Bastemir M, Ormeci N, Aras N, Ekinci C, Uzunalimoglu O, De Maria N and Van Thiel DH: Successful medical treatment of an epithelioid hemangioendothelioma of liver. Oncology *54*: 171-175, 1997.
30 Kelly H and O'Neil BH: Response of epithelioid haemangioendothelioma to liposomal doxorubicin. Lancet Oncol *6*: 813-815, 2005.
31 Cioffi A, Italiano A, Penel N, Berge Y, Toulmonde M, Salas S, Chevreau C, Le Cesne A, Duffaud F, D'adamo DR, Keohan ML, Genebes C, Antonescu C, Coindre J, Bui Nguyen B and Maki RG: Metastatic epitheloid hemangioendothelioma (ehe): role of systemic therapy and survival. J Clin Oncol 29 (suppl; abstr 10079), 2011.
32 Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, Kerbrat P, Fournier C, Taieb S, Jimenez M, Isambert N, Peyrade F, Chevreau C,Bompas E, Brain Eg and Blay JY: Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the angiotax study. J Clin Oncol *26*: 5269-5274, 2008.
33 Penel N, Blay JY, Mir O, Tresch E, Bompas E, Domont J, Cassier Pa, Rolland F, Piperno-Neumann S, Italiano A, Chevreau C, Cupissol D, Bay Jo, Collard O, Saada E, Bertucci F, Isambert N, Delcambre C, Clisant S, Ray-Coquard IL and GSF/GETO. Angiotax-plus trial: a randomized phase ii trial assessing the activity of weekly paclitaxel (WP) plus or minus bevacizumab (B) in advanced angiosarcoma (AS). J Clin Oncol 32 (suppl; abstr 10501), 2014.
34 Santoro A, Tursz T, Mouridsen H, Verweij J, Steward W, Somers R, Buesa J, Casali P, Spooner D and Rankin E: Aldoxorubicin *versus* cyvadic *versus* doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol *13*: 1537-1545, 1995.
35 Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shiraki M, Frytak S and Parkinson DR: Randomized comparison of doxorubicin alone *versus* ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol *11*: 1269-1275, 1993.

36 Chang P and Wiernik PH: Combination chemotherapy with adriamycin and streptozotocin. I. Clinical results in patients with advanced sarcoma. Clin Pharmacol Ther *20*: 605-610, 1976.

37 Antman K, Crowley J, Balcerzak SP, Rivkin SE, Weiss GR, Elias A, Natale RB, Cooper RM, Barlogie B and Trump DL: An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol *11*: 1276-1285, 1993.

38 Coussens LM and Werb Z: Inflammation and cancer. Nature *420*: 860-867, 2002.

39 Ogura K, Shinoda Y, Okuma T, Ushiku T, Motoi T and Kawano H: Recurrent epithelioid hemangioma: therapeutic potential of tranilast and indomethacin. J Orthop Sci *17*: 194-198, 2012

40 Nomura K, Sasaki C, Murai T, Mitsuhashi Y and Sato S: Angiolymphoid hyperplasia with eosinophilia: successful treatment with indomethacin farnesil. Br J Dermatol *134*: 189-190, 1996.

41 Gurpinar E, Grizzle WE and Piazza GA: NSAIDs inhibit tumorigenesis, but how? Clin Cancer Res *20*: 1104-1113, 2014.

*Received August 29, 2014*
*Revised September 25, 2014*
*Accepted September 30, 2014*