Ann Surg Oncol (2019) 26:576–582
https://doi.org/10.1245/s10434-018-7062-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Hepatic Angiosarcoma: A Multi-institutional, International Experience with 44 Cases

Gregory C. Wilson, MD[1], Nuria Lluis, MD[2,4], Michael A. Nalesnik, MD[3], Aziza Nassar, MD[2], Teresa Serrano, MD[4], Emilio Ramos, MD[4], Michael Torbenson, MD[5], Horacio J. Asbun, MD[2,6], and David A. Geller, MD[1]

[1]Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA; [2]Departments of Surgery and Pathology, Mayo Clinic Florida, Jacksonville, FL; [3]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA; [4]Department of Surgery, Hospital Universitario de Bellvitge, Barcelona, Spain; [5]Department of Pathology, Mayo Clinic Rochester, Rochester, MN; [6]Department of Surgical Oncology, Miami Cancer Institute, Miami, FL

ABSTRACT

Background. Hepatic angiosarcoma is a rare primary liver tumor. The aim of this current study was to evaluate the presentation and treatment outcomes in a modern cohort.

Methods. This was a retrospective, multi-institutional, observational study of patients with histopathologic diagnoses of primary hepatic angiosarcoma from four institutions. Clinicopathologic characteristics, treatments, and patient outcomes were examined.

Results. Forty-four patients with hepatic angiosarcoma were identified. Patients were predominantly Caucasian and presented at a median age of 63.7 years; 81.4% of patients had bilobar disease and 37.2% had metastatic disease at the time of presentation. Only 10 patients underwent surgical resection. Median overall survival for the entire cohort was 5.8 months (interquartile range 1.9–16.4), and 1-, 3-, and 5-year actual survival was 30.0%, 8.1%, and 5.6%, respectively. There were only two 5-year survivors, both of whom presented with localized disease and underwent curative resection.

Conclusion. The prognosis for hepatic angiosarcoma remains quite poor. Surgical resection for localized disease results in the best outcomes. Unfortunately, current imaging modalities are often non- diagnostic, and most patients are unresectable at the time of presentation.

First Received: 9 September 2018;
Published Online: 19 November 2018

D. A. Geller, MD
e-mail: gellerda@upmc.edu

Hepatic angiosarcoma is a rare and aggressive malignant vascular tumor. These tumors are typically hemorrhagic, multinodular tumors consisting of malignant endothelial cells that grow into the lumen of liver sinusoids and veins.[1] Several inciting agents have been linked, including Thorotrast, arsenic, and vinyl chloride exposure, as well as anabolic steroid use.[2] However, the majority of patients lack any known exposure and their tumors are idiopathic in nature.[2,3] Extensive liver involvement and distant metastatic disease are common and survival is typically only a few months.

A recent review of the Surveillance, Epidemiology, and End Results (SEER) database identified only 207 patients with primary hepatic angiosarcoma over a period of 30+ years.[4] In that report, median overall patient survival was 1 month for these patients, which improved to only 6 months for those undergoing surgical resection.[4] That study provided an overview of outcomes related to hepatic angiosarcoma from a national database, lacking patient-specific data on presentation, exposure to causative agents, and therapies outside of surgical resection. The remainder of the available literature consists of retrospective, single-institution case series.[5–9]

Hepatic angiosarcoma remains a rare disease of the liver with a grim prognosis. The rarity of this diagnosis remains a significant obstacle in identifying new, effective treatment protocols. The aim of this current study was to evaluate the presentation and treatment outcomes in a modern cohort of patients with hepatic angiosarcoma treated at high-volume liver cancer centers.

METHODS

This retrospective, observational, multi-institutional study included all patients undergoing treatment for biopsy-proven hepatic angiosarcoma from 1999 to 2017 at one of four institutions: University of Pittsburgh Medical Center (Pittsburgh, PA, USA), Mayo Clinic Florida (Jacksonville, FL, USA), Mayo Clinic (Rochester, MN, USA), and Bellvitge University Hospital (L'Hospitalet de Llobregat, Barcelona, Spain). Clinical staging included contrast computed tomography/magnetic resonance imaging (CT/MRI) of the abdomen/pelvis and CT of the chest. The diagnosis of hepatic angiosarcoma was based on pathologic evaluation, which included standard microscopic analysis in conjunction with immunohistochemistry (IHC). IHC staining included vascular/endothelial markers (CD34, CD31, Factor VIII, Fli1, and ERG) and epithelial markers (Cam5.2 and CK7).[1,10] Patients were identified for study inclusion based on diagnosis and query of pathology records. Retrospective chart review was performed to obtain patient demographics and symptoms at the time of diagnosis, diagnostic imaging, pathologic characteristics, treatment details, and patient follow-up. This study was conducted in accordance with and under the approval of each institution's Institutional Review Board.

Statistical analysis was performed using commercially available software (SigmaPlot, version 11.0; Systat Software, Inc., San Jose, CA, USA). Descriptive statistics were calculated and reported as median with interquartile range (IQR). Survival analysis was performed using Kaplan–Meier methods and survival curves between subgroups were compared using log-rank analysis. Survival was defined as time from initial presentation to date of the patient's death or last known follow-up. Statistical significance was determined by a p value of ≤ 0.05.

RESULTS

Over the study period from 1999 through 2017, a total of 44 patients with biopsy-proven hepatic angiosarcoma were managed at the participating institutions. These patients were predominantly Caucasian (95.5%), with slightly more males (52.3%). Full patient characteristics and presenting signs/symptoms are listed in Table 1. Only one patient had a family history of previous vascular malignancy of the liver, and two patients in this cohort had documented exposure linked to angiosarcoma. No patients had a documented Thorotrast exposure. One patient had documented vinyl chloride exposure, while the other patient was exposed to arsenic. Abdominal pain or fullness was the most common symptom, present in 70.5% of patients. Five patients (11.4%) presented with hemodynamic compromise from intra-abdominal hemorrhage. The remaining signs/symptoms at presentation are listed in Table 1.

TABLE 1 Patient demographics and presentation

Characteristics	Median (IQR) or % (n)
Age, years	63.7 (54.0–70.8)
BMI, kg/m^2	29.3 (23.8–35.6)
Sex	
Male	52.3 (23)
Female	47.7 (21)
Race	
Caucasian	95.5 (42)
Asian	2.3 (1)
Unknown	2.3 (1)
Tobacco abuse	38.6 (17)
Cirrhotic	25.0 (11)
Presenting signs/symptoms	
Abdominal pain/fullness	70.5 (31)
Weight loss	22.7 (10)
Fatigue	38.6 (17)
Ascites	31.8 (14)
Jaundice	15.9 (7)
Splenomegaly	20.5 (9)
Liver failure	25.0 (11)
Intra-abdominal hemorrhage	11.4 (5)
Incidental finding	22.7 (10)
Elevated liver enzymes	25.0 (11)
Nausea and vomiting	4.5 (2)

IQR interquartile range, *BMI* body mass index

Initial diagnostic imaging was CT in 63.6% ($n = 28$) of patients, while the remaining patients underwent ultrasound or MRI. Median size of the largest lesion was 5.4 cm (IQR 3.5–10.9). Morphology and extent of disease at presentation are listed in Table 2. On imaging, these lesions were hypervascular, heterogeneously enhancing masses. Representative images are depicted in Fig. 1. Radiographic diagnosis was inconclusive, with a broad differential diagnosis of liver masses reported, including metastatic disease (36.4%, $n = 16$), hepatocellular carcinoma (31.8%, $n = 14$), hemangioma (20.5%, $n = 9$), cholangiocarcinoma (9.1%, $n = 4$), hepatic cyst (6.8%, $n = 3$), and hepatic adenoma (4.5%, $n = 2$). Overall, 44% ($n = 11$) of patients had a hemorrhagic component on imaging. Pathologic diagnosis was obtained by image-guided percutaneous biopsy in 68.2% ($n = 30$) of patients, surgical biopsy/resection in 20.5% ($n = 9$), transjugular biopsy in 4.5% ($n = 2$), and was not reported in the remaining patients. Pathologic details and reported staining patterns are listed

TABLE 2 Tumor characteristics

Characteristic	Median (IQR) or % (*n*)
Radiographic size at diagnosis, cm	5.4 (3.5–10.9)
Morphology on imaging	
Solitary	18.2 (8)
Dominant mass with satellite nodules	18.2 (8)
Multiple evident nodules	38.6 (17)
Diffusely infiltrating	20.5 (9)
Bilobar disease[a]	81.4 (35/43)
Extrahepatic disease[a]	37.2 (16/43)
Lung	6
Spleen	6
Bone	6
Adrenal	2
Retroperitoneum/distant lymphadenopathy	2
Pathologic grade[a]	
Low	16.7 (4/24)
High	83.8 (20/24)
IHC staining[a]	
Factor VIII	81.3 (13/16)
CD34	76.9 (20/26)
CD31	100 (32/32)
Vimentin	100 (12/12)
Fli1	100 (8/8)
Cam5.2	33.3 (2/6)
ERG	87.5 (7/8)

IQR interquartile range, *IHC* immunohistochemical

[a]Some data points were not available for each patient and therefore *n* is reported as *n*/total reported *n* for that specific data point

in Table 2. Representative preoperative CT imaging, pathology staining, and gross resected hepatic angiosarcoma are depicted in Fig. 2.

Overall treatments for hepatic angiosarcoma are listed in Table 3. Unfortunately, only 22.7% of patients presented with resectable disease (extent of resection is listed in Table 3). R0 resection was achieved in 60% ($n = 6$) of patients undergoing surgical resection, while 30% ($n = 3$) underwent R1 resection and one patient had an R2 resection. Of the five patients who presented with acute intra-abdominal hemorrhage, four required emergent bland embolization. Transarterial chemoembolization with doxorubicin-eluting microspheres was utilized in four patients, with a range of two to six treatments per patient. A total of 40.9% of patients ($n = 18$) received systemic chemotherapy, either in combination with resection/regional therapy or as a stand-alone treatment regimen. Specific chemotherapy regimens are listed in Table 3.

Survival analysis for this cohort is depicted in Fig. 2. Median follow-up was 4.4 months (range 0.1–87.9) for the entire cohort and 15.5 months (range 0.3–87.9) for surviving patients. Median overall survival for the entire cohort was 5.8 months (IQR 1.9–16.4), with a range of 0.1–87.9 months. Actual 1-, 3-, and 5-year survival was 30.0%, 8.1%, and 5.6%, respectively. There were only two 5-year survivors, both of whom presented with localized disease and underwent curative resection. Improved survival was seen in those patients who underwent surgical resection (median overall survival 33.4 months, IQR 10.1–unable to calculate) compared with patients undergoing regional therapy (median OS 9.3 months, IQR 9.1–14.7), systemic chemotherapy (median OS 7.7 months, IQR 4.1–16.7), or no therapy (OS 1.9, IQR 1.1–3.2) by log-rank analysis ($p < 0.001$) (Fig. 2d).

DISCUSSION

In this study, we report on patient characteristics, presentation, treatment, and outcomes of 44 patients with hepatic angiosarcoma. To our knowledge, this series represents the largest multi-institutional case series focused on hepatic angiosarcoma. As a testament to the rarity of this disease, only two larger reports from epidemiologic and administrative datasets (SEER and National Cancer Database) that include outcomes on hepatic angiosarcoma are available.[4,11] In our case series, the study cohort consists predominately of Caucasian patients presenting in their sixth decade of life with a relatively equal sex distribution. Inciting agents in the development of hepatic angiosarcoma have been well-documented, however their importance in the modern era might remain largely of historical interest as only two patients in this series had a documented exposure. This is consistent with recent literature showing very few patients with documented exposure to one of the known inciting agents.[2,3]

Perhaps the most notable finding in this study is the variable nature and extent of disease present at the time of presentation. A wide spectrum of presenting signs/symptoms exist for hepatic angiosarcoma. While a majority of patients presented with poorly characterized abdominal or systemic symptoms, approximately one-quarter of the cohort presented with liver failure and an additional 11% presented with acute life-threatening hemorrhage from tumor rupture. Our experience is similar to available literature in that most patients present with vague symptoms that are not definitive.[9,12] Early diagnosis remains elusive. Imaging was clearly non-diagnostic, with over 30% of patients having a benign liver lesion listed in the differential diagnosis. An important teaching point is to have a high index of suspicion because many of the hepatic

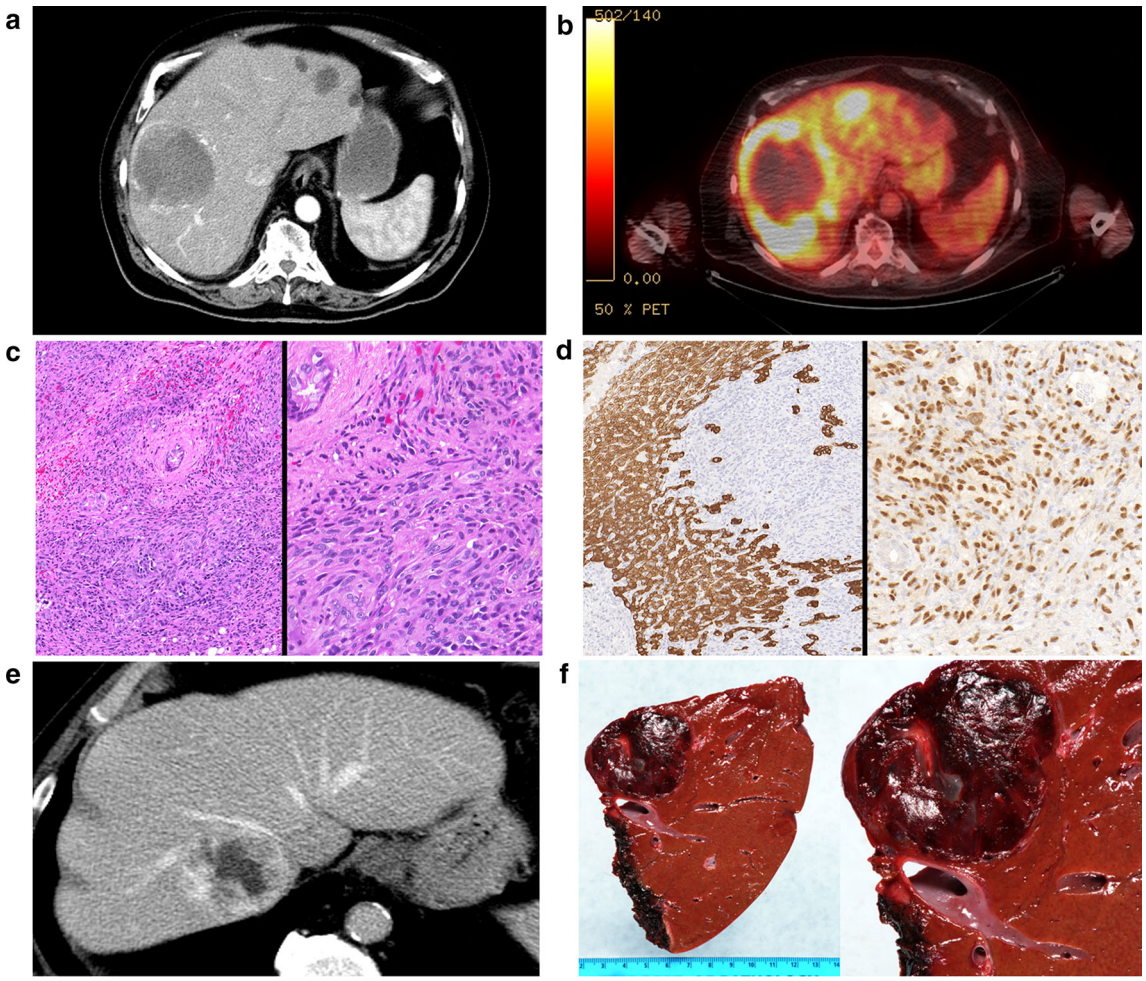

FIG. 1 Radiographic and pathologic characteristics of hepatic angiosarcoma. **a** Representative CT images demonstrate multifocal hepatic lesions that are hypervascular with heterogeneous arterial enhancement and areas of hypoattenuation. **b** Representative PET images demonstrate the hepatic lesion with mixed-intensity of FDG avidity. **c** H&E of representative high-grade angiosarcoma. The left panel shows the diffuse pattern of infiltration with a residual portal tract and bile duct present in the upper mid-portion of the image (H&E × 20), while the right panel shows a higher magnification near the portal tract, highlighting the spindled appearance of tumor cells (H&E × 40). **d** Representative immunohistochemical stains. The left panel shows a pancytokeratin stain demonstrating hepatocyte trabeculae adjacent to the unstained infiltrating tumor. Occasional residual epithelial parenchymal elements are seen within the tumor (Cam5.2, × 20). The right panel shows nuclear uptake of Fli-1 antibody by neoplastic cell nuclei (Fli-1, × 40). **e** Preoperative CT scan; **f** gross images of resected hepatic angiosarcoma. *FDG* 18F-fluorodeoxyglucose, *H&E* hematoxylin and eosin, *CT* computed tomography, *PET* positron emission tomography

angiosarcomas were misdiagnosed as benign lesions on initial radiologic imaging. Unfortunately, the majority of patients present with extensive liver involvement and almost 40% have metastatic disease at the time of diagnosis. These numbers are higher than previous reports[11,12] and may represent the true nature of this disease as previously published reports are case series and datasets of patients who have undergone surgical resection.

Overall survival for hepatic angiosarcoma remains poor, with a median overall survival of 5.8 months for the entire cohort, consistent with previously published reports that have shown survival to range from 1 to 8 months.[4,11–13] Surgical resection remains the only treatment option that provides any chance for long-term survival.[8,11,12,14] In our series, overall survival was 33 months for patients undergoing surgical resection, with two of the patients having a greater than 5-year survival. Acute, intra-abdominal hemorrhage from tumor rupture is not infrequent and patients with hemodynamic instability should undergo transarterial embolization.[12,15] There appeared to be no survival benefit from transplantation, regional liver-directed therapy, or systemic chemotherapy in our patient cohort. Hepatic angiosarcoma is typically viewed as a contraindication for liver transplantation given the early disease recurrence and overall poor results.[16] Regional liver-directed therapy and systemic chemotherapy are additional palliative treatment

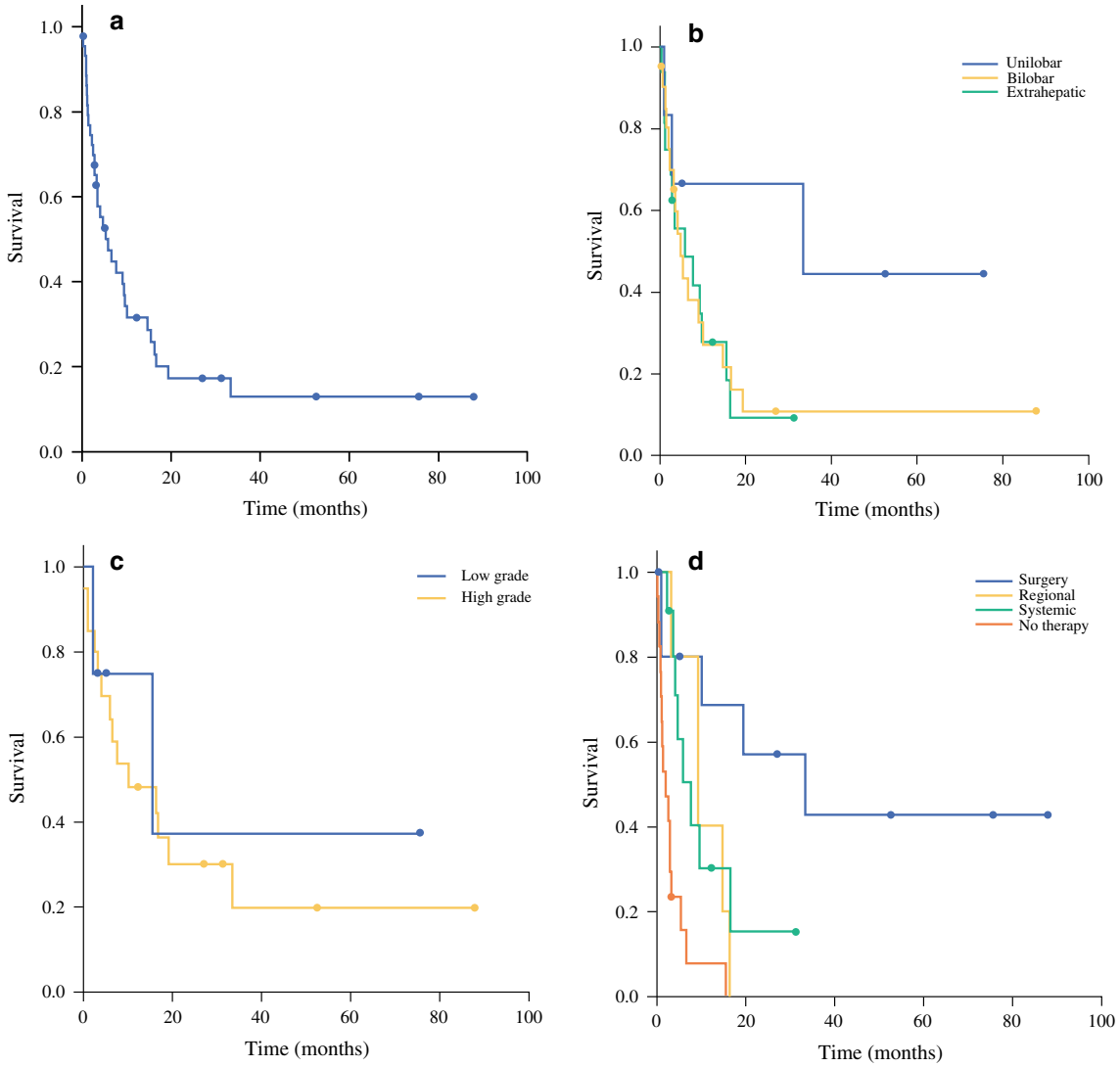

FIG. 2 Overall survival. Kaplan–Meier survival curves for the cohort are depicted. **a** Median overall survival for the entire cohort was 5.8 months (IQR 1.9–16.4). Log-rank analysis was performed based on **b** disease burden at presentation, **c** tumor grade, and **d** treatment. Disease burden at presentation was determined by disease confined to a single hepatic lobe (unilobar), bilobar disease, or metastatic disease (extrahepatic). Tumor grade was stratified as low- or high-grade. Treatment groups were stratified by patients with resectable disease (surgery group), liver disease amenable to regional therapy such as transarterial chemoembolization (regional group), extensive disease for which only systemic therapy was offered (systemic group), and, finally, patients who received no therapy (no-therapy group). There were no differences in survival by disease burden or tumor grade by log-rank analysis; however, there was improved survival in the surgery group ($p < 0.001$, log rank analysis). *IQR* interquartile range

options for patients who are not surgical candidates, which may provide some survival benefit.[13,17] Transarterial chemoembolization has been successful in patients with liver-only disease;[17] however, long-term results have not been rigorously studied and median overall survival for these patients in our cohort was only 9.3 months. Nonetheless, three patients in this cohort appeared to have stable disease through multiple rounds of transarterial chemoembolization prior to disease progression. Systemic chemotherapy was administered to 40% of the patients in this cohort, with taxol-based regimens being the most frequently used regimen. Unfortunately, disease progression was common and median overall survival was poor.

While this study does provide some useful clinical insight into this rare disease, it is limited by its retrospective nature involving multiple institutions over a 20-year period. Patients were identified for study inclusion by pathologic diagnosis, but unfortunately there is no standardized pathologic assessment for these tumors. Similarly, diagnostic evaluation and treatment pathways for these patients were not standardized and were driven by clinician and institutional preferences. This lack of standardization

TABLE 3 Treatment for hepatic angiosarcoma

Treatment details	% (*n*)
Surgical resection[a]	22.7 (10)
Segmentectomy	2
Hemihepatectomy	4
Trisectionectomy	2
Orthotopic liver transplantation	2
Adjuvant systemic chemotherapy in addition to surgical resection	4
Regional therapy[a]	13.6 (6)
Transcatheter arterial chemoembolization	4
Radioembolization	1
External beam radiation	1
Systemic therapy[a]	40.9 (18)
Taxol-based regimen	15
MAP regimen	2
Gemcitabine-based regimen	3
Pazopanib	6
Bevacizumab	2
No therapy[a]	29.5 (13)

MAP mitomycin, adriamycin, cisplatin

[a]Total number greater than the entire cohort as some patients received multiple modes of treatment

and low statistical power make it difficult to draw meaningful conclusions between subgroups. Despite these limitations, this report provides valuable insight into the modern management of hepatic angiosarcoma with direct clinical applicability.

Unfortunately, given the rare nature of these tumors, there are limited data to drive treatment, and even less information is available on primary hepatic angiosarcoma. The majority of angiosarcomas are sporadic, however there may be an association with several familial syndromes, including neurofibromatosis, Maffucci syndrome, and Klippel–Trenaunay syndrome.[18] The limited molecular sequencing data on these tumors have demonstrated KDR-specific mutations,[19] MYC/FLT4 amplifications,[20] and overexpression of vascular endothelial growth factor and its receptors.[21,22] These findings have been the focus of recent ongoing clinical trials using tyrosine kinase inhibitors as the primary treatment of metastatic angiosarcoma.[23] Hopefully, data from the Angiosarcoma project,[24] an ongoing collaboration between the National Institutes for Health and the Broad Institute, will provide further insight into the development of new and effective treatment strategies for this rare tumor.

CONCLUSIONS

This study adds important information to the literature regarding the presentation, treatment, and outcomes of primary hepatic angiosarcoma. The typical patient is a Caucasian male or female in their sixth decade of life. Presentation ranges from asymptomatic or generalized symptoms to life-threatening, acute intra-abdominal hemorrhage. A high index of suspicion by the clinician is of utmost importance to ensure timely diagnosis and initiation of treatment. Surgical resection remains the best treatment option for long-term survival. Regional therapies and systemic chemotherapy are additional palliative treatment options; however, their efficacy requires further investigation before making any definitive conclusions.

DISCLOSURE Gregory C. Wilson, Nuria Lluis, Michael A. Nalesnik, Aziza Nassar, Teresa Serrano, Emilio Ramos, Michael Torbenson, Horacio J. Asbun, and David A. Geller have no conflicts of interest to declare.

REFERENCES

1. Hamilton SRA, Lauri A. World Health Organization classification of tumours. Pathology and genetics of tumours of the digestive system. Lyon: IARC Press; 2000.
2. Falk H, Herbert J, Crowley S, et al. Epidemiology of hepatic angiosarcoma in the United States: 1964–1974. *Environ Health Perspect.* 1981;41:107–13.
3. Chaudhary P, Bhadana U, Singh RA, Ahuja A. Primary hepatic angiosarcoma. *Eur J Surg Oncol.* 2015;41(9):1137–43.
4. Groeschl RT, Miura JT, Oshima K, Gamblin TC, Turaga KK. Does histology predict outcome for malignant vascular tumors of the liver? *J Surg Oncol.* 2014;109(5):483–6.
5. Almogy G, Lieberman S, Gips M, et al. Clinical outcomes of surgical resections for primary liver sarcoma in adults: results from a single centre. *Eur J Surg Oncol.* 2004;30(4):421–7.
6. Duan XF, Li Q. Primary hepatic angiosarcoma: a retrospective analysis of 6 cases. *J Dig Dis.* 2012;13(7):381–5.
7. Zhu YP, Chen YM, Matro E, et al. Primary hepatic angiosarcoma: a report of two cases and literature review. *World J Gastroenterol.* 2015;21(19):6088–96.
8. Matthaei H, Krieg A, Schmelzle M, et al. Long-term survival after surgery for primary hepatic sarcoma in adults. *Arch Surg.* 2009;144(4):339–44 **(discussion 344)**.
9. Molina E, Hernandez A. Clinical manifestations of primary hepatic angiosarcoma. *Dig Dis Sci.* 2003;48(4):677–82.
10. Antonescu C. Malignant vascular tumors: an update. *Mod Pathol.* 2014;27 Suppl 1:S30–8.
11. Konstantinidis IT, Nota C, Jutric Z, et al. Primary liver sarcomas in the modern era: resection or transplantation? *J Surg Oncol.* 2018;117(5):886–91.
12. Li DB, Si XY, Wan T, Zhou YM. A pooled analysis of treatment and prognosis of hepatic angiosarcoma in adults. *Hepatobiliary Pancreat Dis Int.* 2018;17(3):198–203.
13. Kim HR, Rha SY, Cheon SH, Roh JK, Park YN, Yoo NC. Clinical features and treatment outcomes of advanced stage primary hepatic angiosarcoma. *Ann Oncol.* 2009;20(4):780–7.
14. Timaran CH, Grandas OH, Bell JL. Hepatic angiosarcoma: long-term survival after complete surgical removal. *Am surg.* 2000;66(12):1153–7.

15. Rosales A, Que FG. Spontaneous hepatic hemorrhage: a single institution's 16-year experience. *Am Surg.* 2016;82(11):1117–20.
16. Orlando G, Adam R, Mirza D, et al. Hepatic hemangiosarcoma: an absolute contraindication to liver transplantation—the European Liver Transplant Registry experience. *Transplantation.* 2013;95(6):872–7.
17. Park YS, Kim JH, Kim KW, et al. Primary hepatic angiosarcoma: imaging findings and palliative treatment with transcatheter arterial chemoembolization or embolization. *Clin Radiol.* 2009;64(8):779–85.
18. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. *Lancet Oncol.* 2010;11(10):983–91.
19. Antonescu CR, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. *Cancer Res.* 2009;69(18):7175–9.
20. Guo T, Zhang L, Chang NE, Singer S, Maki RG, Antonescu CR. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. *Genes Chromosomes Cancer.* 2011;50(1):25–33.
21. Itakura E, Yamamoto H, Oda Y, Tsuneyoshi M. Detection and characterization of vascular endothelial growth factors and their receptors in a series of angiosarcomas. *J Surg Oncol.* 2008;97(1):74–81.
22. Zietz C, Rossle M, Haas C, et al. MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. *Am J Pathol.* 1998;153(5):1425–33.
23. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet (London, England).* 2012;379(9829):1879–86.
24. Painter C, Dunphy M, Anastasio E, et al. The Angiosarcoma Project: generating the genomic landscape of a rare cancer through a direct-to-patient initiative. *J Clin Oncol.* 2017;35(15 Suppl):1519.