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Thoracic Epithelioid Malignant Vascular Tumors: A Clinicopathologic Study of 52 Cases with Emphasis on Pathologic Grading and Molecular Studies of *WWTR1-CAMTA1* Fusions

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Abstract

Malignant thoracic epithelioid vascular tumors are an uncommon and heterogenous group of tumors that include low to intermediate grade epithelioid hemangioendothelioma (EHE) and high grade epithelioid angiosarcoma (EAS). We examine the morphologic and immunohistochemical features of 52 malignant epithelioid vascular tumors (10 low-grade EHE, 29 intermediate grade EHE and 13 EAS) involving the thorax (lung, pleura, mediastinum, heart, great vessels) including cases with exclusively thoracic disease (35) and with multiorgan disease including the thorax (17). Intermediate grade EHE differs from low-grade EHE by the presence of necrosis, increased mitotic activity and increased atypia. Morphologic features such as intranuclear inclusions, intracytoplasmic vacuoles, stromal changes (chondroid, myxoid or hyalinized stroma) are seen more frequently in EHE, whereas blood lakes, proliferation of slit-like vessels and prominent nucleoli favor EAS. FISH analysis showed *CAMTA1-WWTR1* fusions in 4/7 low grade and 23/23 intermediate grade EHE ($p<0.001$). In EAS, *CAMTA1* rearrangement was negative in all cases, while a *WWTR1* complex abnormality was found in 1/5 case ($p<0.001$). This offers an objective means of differentiating intermediate grade EHE from EAS, especially on limited biopsies. All cases show expression of at least one vascular marker, which allows differentiation from primary thoracic epithelial malignancies, although keratin expression is a potential pitfall with 29% of EHE and 25% of EAS showing keratin expression. Survival analysis shows that higher tumor grade for all tumors ($p=0.026$) as well as lung and pleural tumors only ($p=0.010$) and the presence of pleural involvement in lung and/or pleural tumors ($p=0.042$) correlate with poor prognosis.

Keywords

epithelioid hemangioendothelioma; angiosarcoma; *WWTR1*; *CAMTA1*; thoracic; prognosis

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Conflict of interest: none

INTRODUCTION

Epithelioid vascular tumors encompass a spectrum of diseases that includes epithelioid hemangioma (EH), a benign neoplasm; epithelioid hemangioendothelioma (EHE), a low to intermediate grade malignancy; and epithelioid angiosarcoma (EAS), a high grade malignancy[1, 2]. Weiss and Enzinger, first described EHE as a vascular tumor with clinical and morphologic features intermediate between hemangioma and angiosarcoma[3]. Due to marked variability in clinical outcome and morphologic features, the WHO of soft tissue tumors proposed the dichotomy of EHE into two histologic grades: classic (low-grade) and malignant (intermediate-grade) EHE[4]. However, this subclassification has not been validated in other anatomic sites. While certain morphologic features allow to distinguish EHE from EH and EAS, the diagnosis can be challenging due to considerable morphologic overlap at both ends of the spectrum, particularly on small biopsies. Recent studies have identified recurrent genetic alterations, such as the *WWTR1-CAMTA1* fusion in EHE, but not in other vascular tumors[5, 6]. In this study we sought to evaluate a large cohort of malignant epithelioid vascular tumors occurring in the thorax for their morphologic features, immunophenotype, clinical course and *WWTR1* and *CAMTA1* gene rearrangements.

MATERIALS AND METHODS

Clinical and Pathologic Features

Fifty-two cases of malignant epithelioid vascular tumors (39 EHE and 13 EAS) with thoracic involvement from our institution and the personal consults of the senior authors (WDT, CRA) were included in our study. The cytologic and architectural features of each case were reviewed and tumors were classified using criteria established in the soft tissue literature and include 10 cases of low-grade EHE (G1); 29 cases of intermediate-grade EHE (G2) and 13 cases of EAS (G3). Cases with either exclusive thoracic disease (35) or multiorgan disease including thoracic involvement (17) were selected in the study. The main sites of involvement for the exclusively thoracic tumors were lung (13), pleura (17) and mediastinum (5). The gross anatomic features, clinical history and clinical outcome were obtained from review of consult letters, pathology reports, clinical notes and public records including the Social Security Death Index and through conversations with pathologists and/or clinicians from the submitting institutions. Statistical analyses with cross tables and chi-square, were performed using SPSS v 22.0. Survival analysis was performed using the Kaplan-Meyer method and log-rank for significance. The time of survival was calculated using Kaplan-Meier estimates from the date of initial diagnosis to the date of death or last clinical followup. The study was approved by the Institutional Review Board 02-060.

Immunohistochemistry

Immunohistochemical stains submitted from outside institutions were reviewed. On in house cases and outside cases where further immunohistochemical workup was needed, we performed immunohistochemistry in our lab for CD31 and ERG (Ventana; pre-diluted) to confirm vascular differentiation and immunohistochemistry for AE1/AE3 (Dako; 1:400), CAM5.2 (Becton Dickinson, 1:50) and CK18 (Dako, 1:1000) as part of an initial workup when vascular differentiation was not evident.

Molecular FISH Studies

FISH on interphase nuclei from paraffin-embedded 4-micron sections was performed applying custom probes using bacterial artificial chromosomes (BAC) for *WWTR1*, *CAMTA1* and *TFE3*. BAC clones were chosen according to USCS genome browser (http://genome.uscs.edu)[5, 7]. The BAC clones were obtained from BACPAC sources of Children's Hospital of Oakland Research Institute (CHORI) (Oakland, CA) (http://bacpac.chori.org). DNA from individual BACs was isolated according to the manufacturer's instructions, labeled with different fluorochromes in a nick translation reaction, denatured, and hybridized to pretreated slides. Slides were then incubated, washed, and mounted with DAPI in an antifade solution, as previously described[8]. The genomic location of each BAC set was verified by hybridizing them to normal metaphase chromosomes. Two hundred successive nuclei were examined using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany), controlled by Isis 5 software (Metasystems). A positive score was interpreted when at least 20% of the nuclei showed a break-apart signal. Nuclei with incomplete set of signals were excluded.

RESULTS

Clinical and Pathologic Features

Demographics—There were 36 males and 16 females included in the study, ranging in age from 22–84 years old (mean 56.4 years) (Table 1). Of note, a female predominance was noted in G1 tumors, while a male predominance was present in G2 and G3 tumors when examining either all thoracic sites ($p < 0.001$) or tumors occurring only in the lung and pleura ($p=0.021$). Patients with EAS were significantly older than those with EHE, regardless if occurring at any thoracic sites ($p=0.008$) or only in the lung and pleura ($p=0.028$).

Gross Features—Because the majority of cases in our study were personal consults and/or small biopsies, the gross extent of disease was assessed by reviewing outside pathology and radiology reports. Also recorded was the multiorgan involvement, the primary site of the tumor, multifocal involvement within the lungs and the degree of pleural involvement (mass, multiple nodules or diffuse thickening). When a dominant mass was present, the size of this mass was noted.

Histologic Features—EHE in the lung typically showed micropolypoid protrusion within alveolar spaces at the periphery of tumor nodules (Fig. 1). Tumors presenting in the pleura showed marked thickening of the pleura by tumor frequently with infiltration of adjacent adipose tissue (Fig. 1B). The EHEs were subdivided into two histologic grades, G1 and G2, using criteria established in the soft tissue EHE on the basis of increased mitotic rate ($p=0.003$, with counts >1 per 2 mm^2), the presence of necrosis ($p<0.001$) and moderate to marked nuclear pleomorphism ($p=0.031$)[4, 9] (Fig. 2). No mitoses were seen in low grade EHE, while the mean was 2 per 2 mm^2 (range 0–9) in intermediate grade EHE and 5 per 2 mm^2 range (1–12) in EAS. The overlap in mitotic counts between intermediate grade EHE and EAS made it difficult to establish a mitotic threshold for separating these tumors. The cytologic features, growth pattern, and the presence/absence of pleural involvement by tumor were assessed. Features suggestive of EHE included intra-cytoplasmic lumens,

nuclear cytoplasmic inclusions and distinctive extracellular stroma, with chondroid, hyalinized or myxoid changes (Table 2 and Fig. 3). Epithelioid angiosarcomas (EAS) were classified by default as G3. Histologic features suggestive of EAS included prominent capillary-like vasoformative elements, blood lakes, papillary growth and prominent nucleoli (Table 2 and Fig.4). The number of mitotic figures increased significantly with tumor grade, with a mean of < 1 mitoses per 2 mm^2 (all had less than 1) for G1 tumors, 2 per 2 mm^2 (range 0–9) for G2 tumors and 5 per 2 mm^2 (range 1–12) for G3 tumors.

Immunohistochemistry

All cases expressed at least one vascular marker (Table 3). We found CD31 and ERG to be the most reliable markers of vascular differentiation, seen in 96% and 100% of cases, respectively. Expression of keratin was seen in a substantial number of cases of both EHE and EA (Table 3). The mesothelial markers WT1 (0/15 cases) and calretinin (0/21 cases) were not expressed in any tumors, while D2-40 expression was seen in over half of tumors (5/9 cases) tested.

FISH Studies for Gene Rearrangements in *WWTR1* and *CAMTA1*

FISH was performed on 35 cases with available material, including 30/39 cases classified morphologically as EHE. Custom break-apart BAC probes for both *WWTR1* and *CAMTA1* genes were tested on all available cases. Gene rearrangements involving both *WWTR1* and *CAMTA1* were seen in 3 of 7 G1 tumors tested and 23 of 23 G2 tumors (Table 4, Fig. 2). No *CAMTA1* gene rearrangement was seen in any of the 5 EAS tumors tested; however, one EAS tumor showed a complex rearrangement involving the *WWTR1* gene (Table 4). These differences were significant for all tumors in the thorax as well as those involving lung and pleura only (Table 4, $p<0.001$). All fusion-negative EHEs and the single EAS case with a *WWTR1* gene rearrangement were re-reviewed and the diagnosis re-confirmed. The *CAMTA1*-*WWTR1* negative EHE were subsequently tested for *TFE3* gene arrangements by FISH, however, no positive case was identified.

Clinical Course and Follow-Up

The most common symptoms at presentation were pleural effusion (39%), chest pain (29%), shortness of breath (16%), hemoptysis (13%) and cough (12%). Two cases were discovered incidentally. Of the 17 cases with multiorgan involvement, 7 had material from multiple sites for histologic examination and 10 had radiologic evidence of multiorgan involvement.

Survival analysis—Survival analysis was performed on 51 cases with followup information available. One patient with a G1 tumor was lost to follow-up. Histologic grade significantly affected prognosis with G2 and G3 having significantly worse prognosis than G1 tumors. This finding was seen either analyzing the entire patient cohort (Fig. 5) or cases involving only the lungs and pleura (Fig. 6). The 4-year survival for G1, G2 and G3 tumors was 75%, 21% and 9%, respectively for all tumors ($p=0.026$) and 83%, 22% and 9% respectively for only lung and pleural tumors ($p=0.010$). There was no statistical difference in survival when the analysis included only primary thoracic tumors. Microscopic evidence of pleural involvement was a poor prognostic indicator for all tumor grades ($p=0.042$, Fig. 7) and in EHE alone ($p=0.049$). For all tumor grades and for EHE alone the 3-year survival rate

was 46% and 52% when lacking pleural involvement compared to 16% and 24%, respectively, when the pleura was involved. A similar trend was seen in EAS; however, it failed to reach significance. Given that higher grade tumors have a higher mitotic rate, it was not surprising to find that increased mitotic activity was a poor prognostic indicator for all tumors (p=0.015) and for those involving only the lung and pleura (p=0.016). The only clinical symptom that was a significantly indicator of poor outcome was hemoptysis (p =0.001). This may be due the fact that hemoptysis was seen in 46% of EAS and only a single case of EHE. There was no difference in survival between those patients with thoracic only versus those with multifocal disease (p>0.05) for all tumors, Grade 1 and Grade 2 EHE. However, for grade 3 EAS, patients with multiorgan disease had a worse 6-month survival (0%) than those with thoracic only involvement (58%, p=0.047).

DISCUSSION

The results of our study show that malignant epithelioid vascular tumors involving the thorax can be classified as low grade EHE, intermediate grade EHE and high grade EAS. This is supported by distinct morphological features between these three entities, our survival data and the demonstration of a *CAMTA1-WWTR1* gene fusion in EHE but not EAS. Our survival data also shows pleural involvement is a poor prognostic indicator. Factors that did not significantly affect prognosis include the presence or absence of extrathoracic disease and tumor size.

In reviewing the histology, features seen significantly more in EHE included intra-cytoplasmic vacuoles, intranuclear inclusions, prominent myxoid, hyalinized or chondroid stroma. In contrast, features associated with the EAS included vasoformative features with capillary-type vascular spaces, blood lakes, papillary growth, marked nuclear atypia, prominent nucleoli and increased mitotic rate. In limited small biopsies, the lack of these histologic features may present a diagnostic challenge in differentiating vascular tumors from carcinoma and malignant mesothelioma, which are more frequently encountered in the thorax and often share similar radiologic[10–12], and pathologic findings[13–15]. Immunohistochemical demonstration of vascular differentiation is crucial in these cases given the similar morphologic features. Keratin expression in epithelioid vascular tumors is a known diagnostic pitfall[16]. Our study showed that 29 % of EHE and 25% of EAS that were tested expressed some degree of keratin expression with either pankeratin, CK7, CAM5.2 or CK18 (Fig. 4). This emphasizes the importance of keeping the differential diagnosis of an epithelioid vascular tumor in mind when diagnosing tumors that in the thorax are often assumed to be carcinomas or mesotheliomas since these tumors are so much more common than EHE or EAS.

Another diagnostic challenge after establishing the vascular differentiation is distinguishing intermediate grade EHE (G2) from EAS (G3) tumors in cases that exhibit increased mitotic activity, necrosis and atypia, but lack overt capillary-like vasoformative elements. Testing for *WWTR1-CAMTA1* gene fusion, a recurrent genetic abnormality seen in EHEs across various anatomic sites, but absent in EAS, offers an objective mean to distinguish EHE from EAS. In fact all G2 tumors tested demonstrated gene rearrangements in both *WWTR1* and *CAMTA1*, whereas none of EAS analyzed demonstrated this gene fusion. The utility of FISH

studies in detecting the *WWTR1-CAMTA1* fusion in a small biopsy is confirmed by the demonstration of *CAMTA1* and *WWTR1* breakapart abnormalities in all 13 EHEs diagnosed on small biopsy material (3 G1 and 10 G2 tumors). Although one case of EAS demonstrated a complex abnormality of *WWTR1*, there was no accompanying *CAMTA1* gene rearrangement to suggest a t(1;3) translocation. While the majority of the G1 tumors showed the *WWTR1-CAMTA1* fusions, 3 cases did not. We considered the possibility of a *YAP1-TFE3* gene fusion, a finding that has been observed in a subset of EHEs that are negative for *WWTR1* and *CAMTA1* abnormalities[7]; however, FISH did not demonstrate a *TFE3* gene rearrangement in any of these cases. Lack of cellularity in the specimens was also considered; however, all 3 had adequate tumor cells for FISH studies.

Our survival data shows that histologic grade significantly affects prognosis within the malignant epithelioid vascular tumor spectrum, with G1 tumors having a relatively favorable prognosis, G2 tumors a poor prognosis and G3 tumors the worst prognosis. This suggests that the reported criteria for classifying and grading malignant vascular tumors within soft tissue might be applicable to tumors in the thoracic cavity. Pleural involvement was another poor prognostic indicator for both EHE and EAS together, and also for EHE alone. Several other studies have highlighted the poor prognosis for vascular tumors of the pleura[17, 18].

Nine cases in our study presented in unusual locations including mediastinum (7 cases), heart (1 case) and superior vena cava (1 case). Due to the small number of cases and relatively short follow-up in survivors, it is difficult to draw any conclusions regarding their outcome. Suster et al.[19] reported a series of 12 cases of anterior mediastinal EHE and found they had an indolent behavior. The only patient with EHE (G1) of the mediastinum in our study died shortly after diagnosis, whereas the one patient with EAS of the mediastinum survived for over 3 years. Two additional patients with intermediate grade EHE (G2) succumbed of their disease after 0.2 and 0.3 years. Three other patients with intermediate grade EHE (G2) are still alive, with follow-up ranging from 0.1–1.1 years. The patient with superior vena cava EHE (G1) was alive at most recent follow-up (0.83 years). Little data exists on the behavior of superior vena cava tumors due to their extreme rarity[20, 21].

In conclusion malignant epithelioid vascular tumors involving the thorax can be classified as low (G1) to intermediate grade (G2) EHE and high grade EAS (G3). We prefer not to use the terms classic and malignant, because all EHE are malignant. This concept is supported by our histologic findings, survival data and demonstration of a *CAMTA1-WWTR1* gene fusion in EHE but not in EAS. The presence of *CAMTA1-WWTR1* gene fusion in EHE but not EAS suggests that EHE and EAS do not form a histologic continuum and it is in keeping with two genetically distinct neoplasms. As the presence of *WWTR1-CAMTA1* fusion is seen in most EHE (both low and intermediate grade tumors), additional genetic abnormalities most likely occur in the G2 subset of tumors to drive their aggressive behavior. FISH analysis for *CAMTA1* and *WWTR1* gene rearrangements offers an objective way to distinguish EHE and EAS in cases with nuclear atypia, necrosis or increased mitotic activity that lack the typical histologic hallmarks of EAS. Expression of keratin is problematic and may lead to a misdiagnosis of carcinoma or mesothelioma, which are encountered more frequently in the thorax and may show clinical, radiologic and morphologic overlap with epithelioid vascular tumors. Careful examination for histologic features suggestive of

vascular differentiation (blister cells, intracytoplasmic lumens, vasoformative elements) and immunohistochemistry with vascular markers are helpful in avoiding this pitfall.

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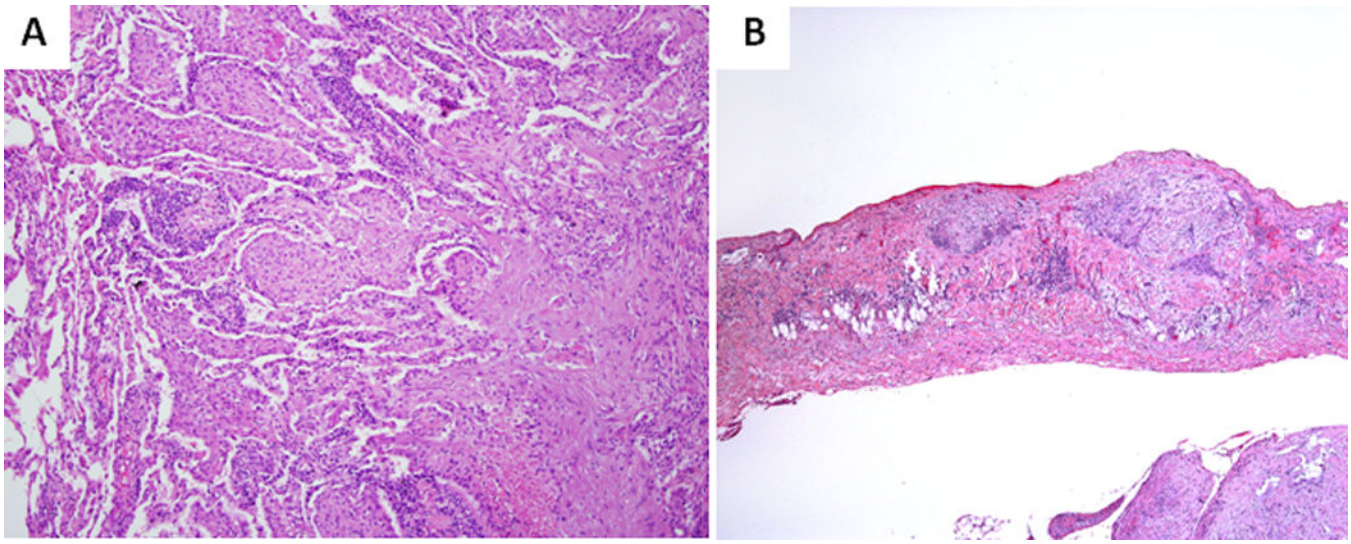

Figure 1.

(A) Representative example of a lung EHE showing micropolypoid growth of tumor cells in alveolar spaces at the edge of a tumor nodule (10×). (B) Representative example of a pleural based EHE showing infiltrative tumor cells in a background of fibrous pleural thickening (4×).

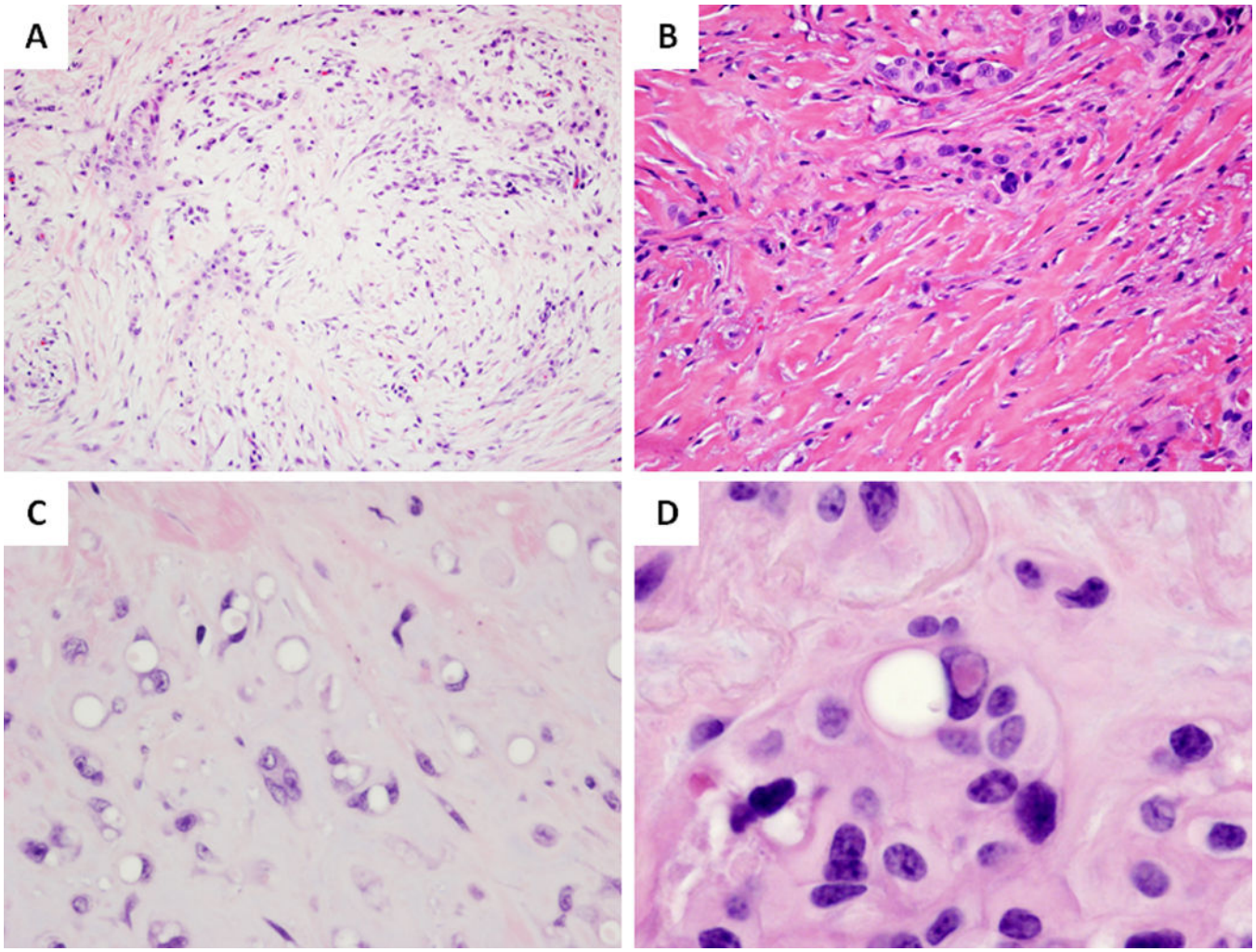

Figure 2.

Histologic features of low grade EHE (A) versus intermediate grade EHE (B, C) and FISH gene rearrangements for *WWTR1* and *CAMTA1* (D,E). Low grade EHE show hypocellular proliferation of cells with mild atypia (A, 20×). No necrosis or increased mitotic activity is seen. Intermediate grade EHE are characterized by the presence of increased nuclear pleomorphism (B, 20×) and/or necrosis (C, 20×). FISH showing break-apart signals (white arrows) for *CAMTA1* (D) and *WWTR1* genes (E) (red, centromeric, green, telomeric)

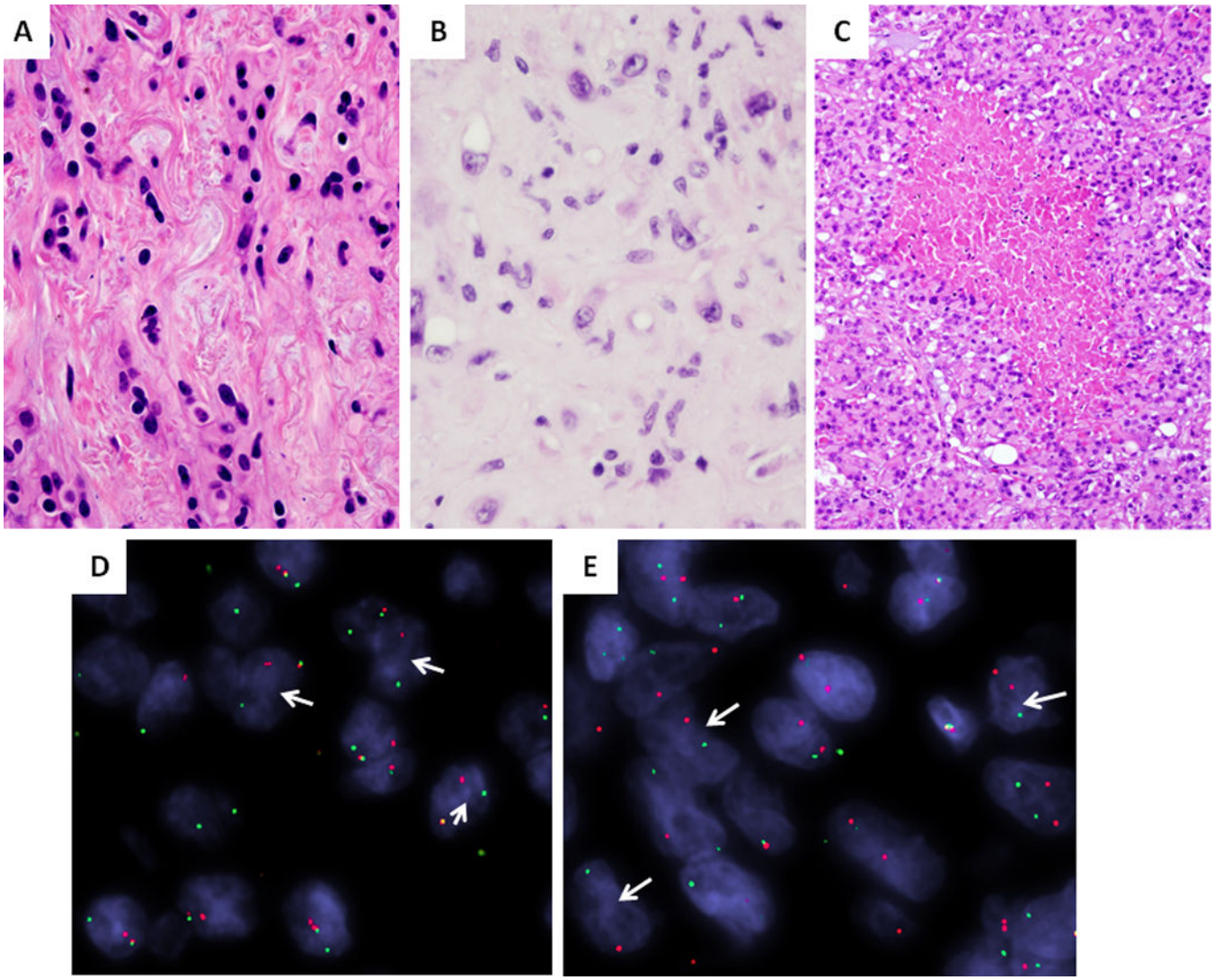

Figure 3.

Histologic feature favoring EHE over EAS include (A) Prominent myxoid stroma (4×), (B) hyalinized stroma (4×), (C) chondromyxoid stroma and intracytoplasmic vacuoles (20×), and (D) intranuclear inclusions (60×)

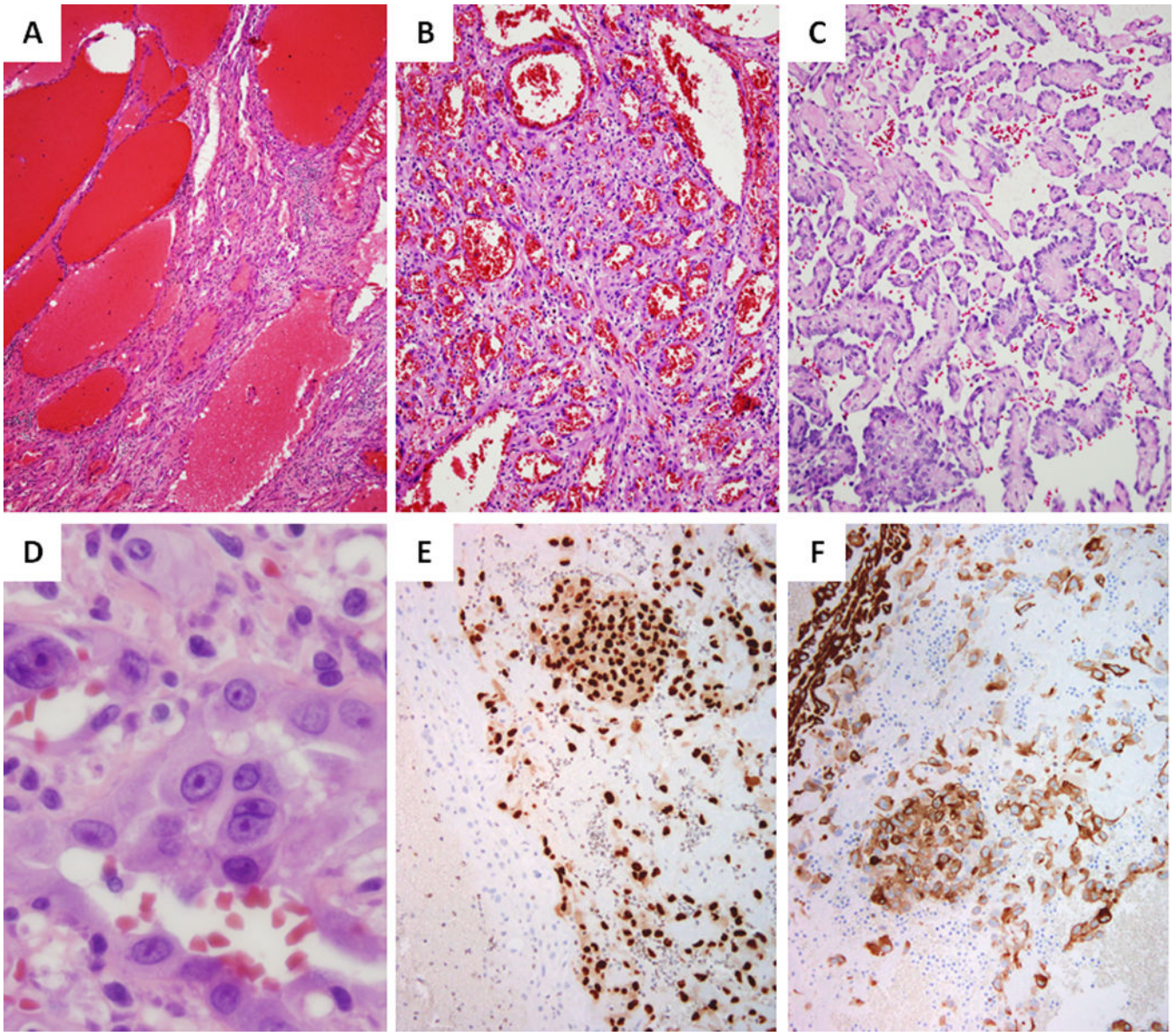

Figure 4.

Histologic features favoring EAS over EHE include (A) blood lakes (2×), (B) proliferation of capillary like vessels (10×), (C) papillary growth (10×) and (D) prominent nucleoli (40×). Immunohistochemistry in an EAS shows strong nuclear staining with (E) ERG and (F) expression of keratin (AE1/AE3)

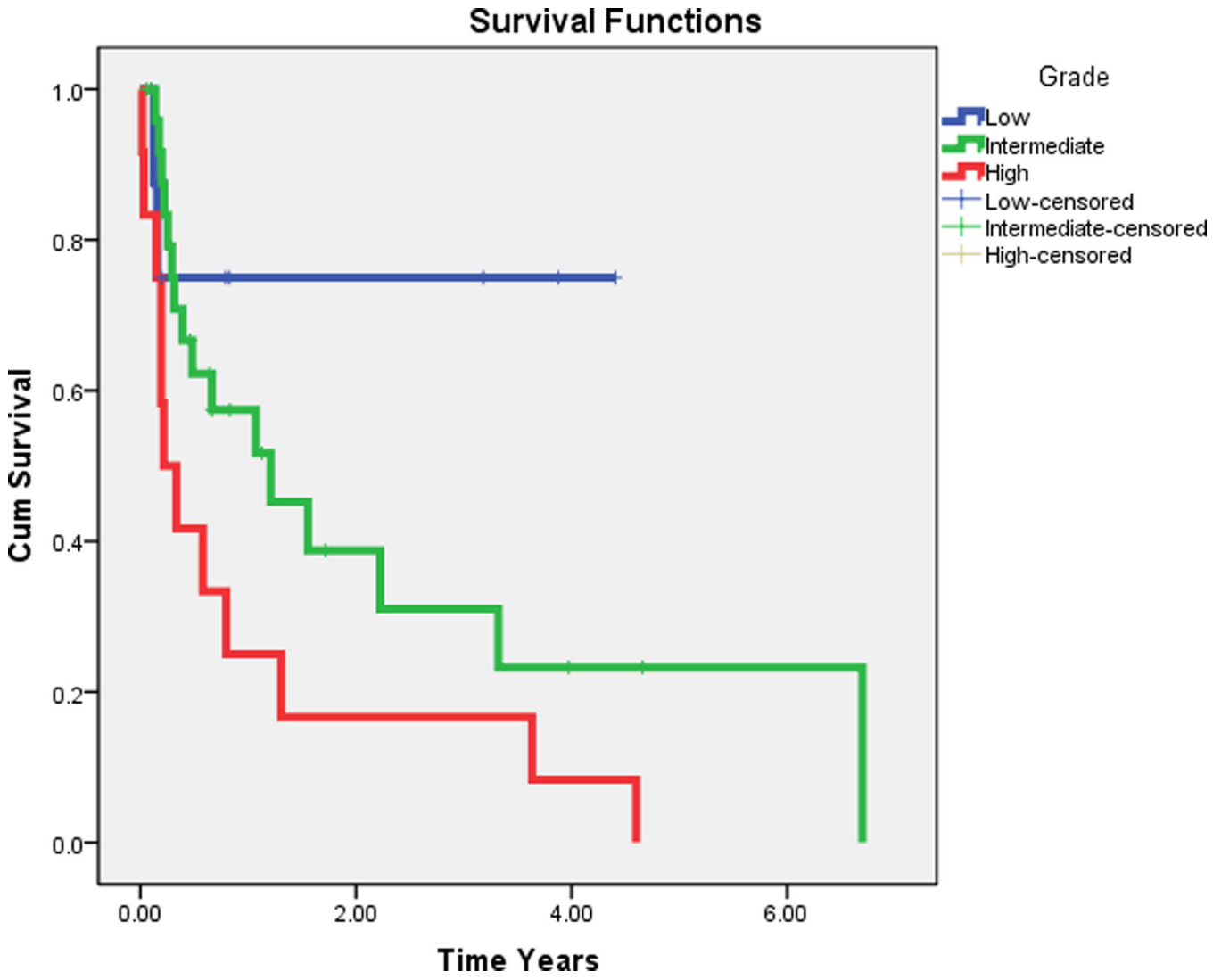

Figure 5.

Comparison of survival by tumor grade for all EHE and EAS cases. Four-year survival for G1, G2 and G3 tumors was 75%, 21% and 9%, respectively Higher grade tumors have a significantly worse prognosis *(p=0.026)*.

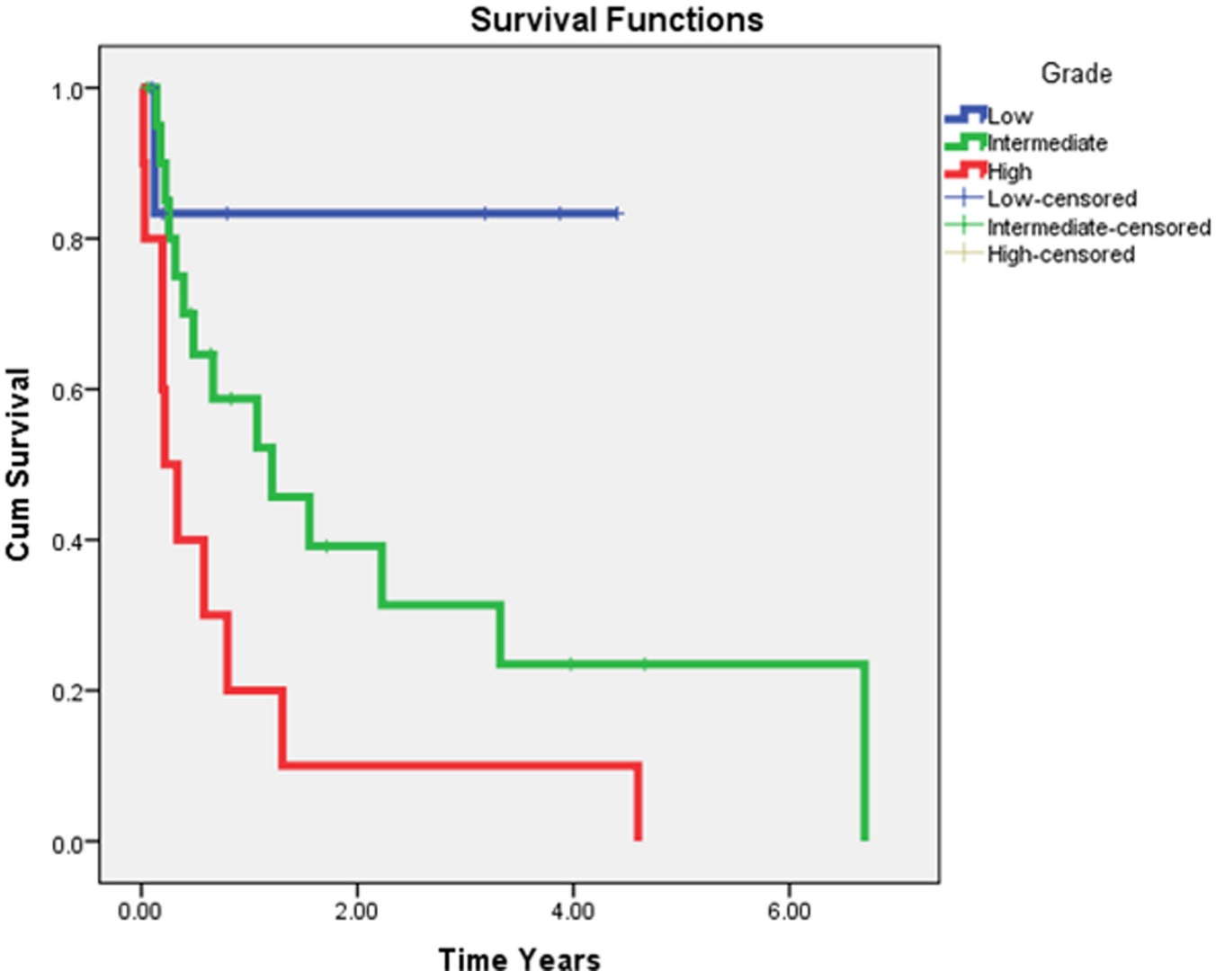

Figure 6.

Survival by tumor grade for lung and pleural cases only. Four-year survival for G1, G2 and G3 tumors was 83%, 22% and 10% respectively. Higher grade tumors have a significantly worse prognosis *(p=0.010)*.

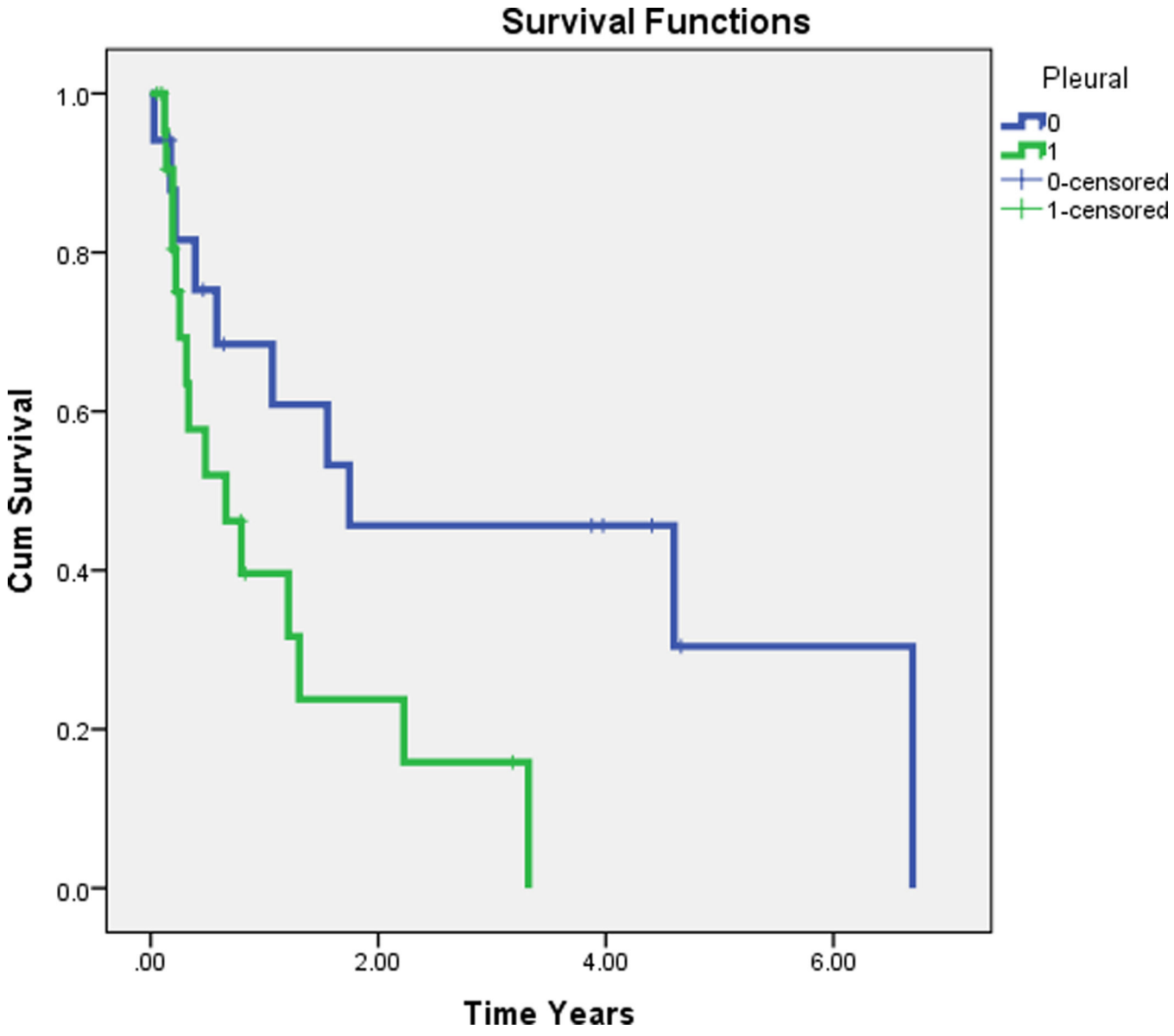

Figure 7.

Comparison of 3-year survival in EHE and EAS patients with tumors involving lung and/or pleura 24% versus those with no pleural involvement 52% *(p=0.042)*.

Table 1

Summary of Clinical Features and Pleural Involvement

	EHE		EAS
	G1 (n=10)	**G2 (n=29)**	**G3 (n=13)**
Median Age (yrs, range)	57.6 (26–83)	51(22–80)	67.5y(28–84y)
Sex (Male/Female)	2/8	24/5	10/3
Site			
Thoracic only	7	20	8
Multiorgan incl. thorax	3	9	5
Site of thoracic involvement			
Lung	5	11	7
Pleura	3	13	4
Mediastinum	1	5	1
Heart	0	0	1
Superior vena cava	1	0	0
Site of extrathoracic involvement			
Bone	0	5	0
Soft Tissue	1	3	5
Liver	1	5	0
Lymph node	0	3	1
Brain	0	1	2
Retroperitoneum	0	0	1
Size of thoracic tumor Mean cm (range)	5 (0.6–14)	2.2 (0.5–15)	5.3 (0.5–8)
Follow-up			
Alive/dead	7/2 *	12/17	1/12
Mean followup time (yrs, range)	1.52y (0.1–4.4)	1.23 (.06–6.7)	0.94 (.02–4.6)
Pleural involvement	6/10 cases	17/29 cases	6/13 cases

* One patient lost to follow-up

G=grade

Table 2

Prevalence of histologic features in EHE and EAS

Histologic Features	EHE	EAS	P-value
Features Suggestive of EHE			
Intracytoplasmic vacuoles	89%	25%	<0.001
Nuclear cytoplasmic inclusions	57%	0%	<0.001
Myxoid Stroma	43%	8%	.037
Hyaline stroma	57%	18%	.039
Chondroid stroma	35%	0%	.021
Features Suggestive of EAS			
Capillary vessels	5%	75%	<.001
Vascular lakes	8%	42%	.015
Papillary growth	0%	33%	.002
Prominent nucleoli	27%	67%	.008
Marked nuclear atypia	8%	50%	.002

EHE=epithelioid hemangioendothelioma; EAS=epithelioid angiosarcoma

Table 3

Expression of vascular markers and cytokeratins.

Immunostain	EHE	EAS
	Vascular Markers	
CD31	35/36 (97%)	12/13 (92%)
CD34	31/38 (82%)	4/12 (33%)
ERG	10/10 (100%)	3/3 (100%)
FLI1	73%	100%
	Cytokeratin	
Pankeratin	7/33 (21%)	3/10 (30%)
CAM5.2	2/13 (15%)	0/4 (0%)
CK7	3/15 (20%)	0/5 (0%)
CK18	5/8 (63%)	0/2 (0%)
Any keratin marker	29%	25%

EHE=epithelioid hemangioendothelioma; EAS=epithelioid angiosarcoma

Table 4

Results of FISH for *CAMTA1* and *WWTR1* gene rearrangements.

Diagnosis	CAMTA1	WWTR1	P-value
All Thoracic Tumors			
EHE (Grade 1)	3/7	3/7	
EHE (Grade 2)	23/23	23/23	p<0.001
EAS	0/5	1/5	
Lung & Pleural Tumors Only			
EHE (Grade 1)	2/5	2/5	
EHE (Grade 2)	19/19	19/19	p<0.001
EAS	0/4	1/4	