



Published in final edited form as:

J Surg Oncol. 2022 December ; 126(8): 1423–1429. doi:10.1002/jso.27066.

A review of hepatic epithelioid hemangioendothelioma— Analyzing patient characteristics and treatment strategies

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Abstract

Background: Hepatic epithelioid hemangioendothelioma (HEH) is a rare vascular tumor of unknown etiology and unpredictable natural history. To date, no large-scale studies have been published evaluating this disease due to its rare occurrence.

Methods: The National Cancer Database was reviewed between 2004 and 2016 to identify patients with HEH. Univariate analysis with overall survival (OS) was performed by Cox proportional hazards model. Kaplan–Meier method was used to create OS curves and compared using the log-rank test.

Results: We identified 229 patients with HEH. The majority of patients were female (61.1%), white (84.3%), and had a Charlson–Deyo score of 0 (75%). Chemotherapeutic intervention was seen in 26% of the patients while 33% received surgical intervention in the form of wedge/segmental liver resection ($n = 27$), hepatectomy lobectomy/extended lobectomy ($n = 18$), and liver transplant ($n = 22$). Five-year survival in surgical patients was 90.5%, 66.5% and 81%, respectively ($p = 0.485$). Age greater than 55 years (hazard ratio [HR], 2.78; $p < 0.001$), Asian

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ethnicity compared to white (HR, 2.84; $p = 0.012$), and a higher Charlson–Deyo score (score 1: HR, 2.28; $p < 0.001$ and score 2: HR, 2.76; $p = 0.011$) were associated with worse OS.

Conclusion: Treatment for HEH remains variable with only a third of the patients undergoing surgery. International collaboration is necessary to determine the optimal treatment for this rare disease.

Keywords

epithelioid hemangioendothelioma; HEH; HEHE

1 | INTRODUCTION

Epithelioid hemangioendothelioma is a rare tumor of vascular origin characterized by epithelioid and histiocytoid vascular endothelial cells, known to occur in the liver and other parts of the body such as spleen, heart, head and neck, bone, and lungs.^{1–4} The term epithelioid hemangioendothelioma was first proposed by Weiss and Enzinger in 1982,⁵ and is used to name those vascular neoplasms that show a borderline biological behavior, between benign hemangiomas and highly malignant sarcomas.⁶ It has an estimated incidence of 1–2 cases in every 1 million people and occurs more frequently in women with a male to female ratio of 2:3.^{7,8}

The most common clinical manifestations of hepatic epithelioid hemangioendothelioma (HEH) are right upper quadrant pain, followed by hepatomegaly and weight loss.⁸ HEH lesions are hypodense on computed tomography, and on magnetic resonance imaging showed low signal intensity on T1 and high heterogeneous signal intensity on T2,⁹ with some cases showing the characteristic “lollipop sign” on imaging.¹⁰ Diagnosis is aided by the presence of at least one endothelial marker including CD31, CD34, or factor VIII-related antigen.¹¹

The differential diagnosis includes hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma, and metastatic carcinoma among others.¹¹ The treatment options are broad and inconsistent due to lack of sufficient data promulgating one type of treatment over another, mostly due to the paucity of this disease.

With multiple management strategies and treatment options ranging from drugs to liver transplant, added to the lack of established guidelines, there emerges a dire need for an improved understanding of this disease. The purpose of this study is to review the National Cancer Database (NCDB) experience with HEH and identify all treatment approaches and outcomes to consider optimal management for this rare disease.

2 | MATERIALS AND METHODS

2.1 | Data source

The NCDB was queried from 2004 to 2016 to conduct a retrospective study in patients diagnosed with HEH. NCDB is jointly sponsored by the American College of Surgeons and the American Cancer Society. It is a clinical oncology database sourced from hospital

registry data that are collected in more than 1500 Commission on Cancer (CoC) accredited facilities across the United States and Puerto Rico, representing more than 70% of newly diagnosed cancer cases nationwide. It is used to explore trends in cancer care and to serve as a basis for quality improvement.¹²

2.2 | Patient selection

Following exemption from Institutional Review Board review, all patients with liver cancer were identified from 2004 to 2016. Only patients with a diagnosis of HEH (specified histology code: 9133)— according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), were included in this set. Subjects who received treatment with radiofrequency ablation and palliative care patients were further excluded.

2.3 | Demographics and treatment variables

Data of interest included patient characteristics (age, sex, ethnicity, and Charlson–Deyo score), facility location (Northeast, Midwest, West, and South), and type (Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program, and Integrated Network Cancer Program), oncological variables (tumor size, metastasis, lymph node involvement, lymphovascular invasion, and margin status), treatment types (surgery, chemotherapy, and radiation), and sequence of treatment. Surgery of the primary site (liver) was categorized into wedge/segmental resection, lobectomy/extended lobectomy, and transplantation.

2.4 | Statistics

Descriptive statistics were used to summarize patient characteristics. The Kaplan–Meier method was used to estimate overall survival (OS) and survival curves were compared between three surgical intervention groups using the log-rank test. Univariate analysis was performed to assess factors associated with OS using Cox proportional hazards model. Firth’s penalized likelihood bias-reduction approach was used to account for small sample and low event rates. A p value of <0.05 was considered statistically significant for all analyses. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc.).

3 | RESULTS

3.1 | Demographics

Among 192,418 patients with liver cancer between 2004 and 2016, 229 patients met inclusion criteria (Figure 1). The majority of patients were young (median age = 55), female (61.1%), with a male-to-female ratio of 2:3 (Table 1). Univariate association with OS for patients above median age (≥ 55 , $n = 102$) was independently associated with worse OS (hazard ratio [HR], 2.78; $p < 0.001$) compared to patients below median (< 55 years; Table 2). The majority of the cases were seen in white population (84.3%). The Asian population (3.75%) was associated with worse OS (HR, 2.84; $p = 0.012$) compared to the white population. Patients with a Charlson–Deyo score of 2+ predicted a worse OS (HR, 2.76; $p = 0.011$), followed by a score of 1+ (HR, 2.28; $p < 0.001$) when compared to a Charlson–Deyo score of 0.

3.2 | Facility providing care and type of intervention

Patients treated at Academic/Research Programs predicted an improved OS (HR, 0.39; $p = 0.008$) followed by Comprehensive Community Cancer Programs (HR, 0.45; $p = 0.037$), and Community Cancer Programs (HR, 0.48; $p = 0.164$) compared to Integrated Network Cancer Program. Surgery of the primary site was performed in 67 out of 201 patients, of which 25 patients underwent wedge/segmental resection (HR, 0.91; $p = 0.893$), 15 received lobectomy/extended lobectomy (HR, 1.96; $p = 0.345$) compared to 21 patients who received a liver transplant. There was no difference in OS between types of surgical resection ($p = 0.485$). Of these 67 patients, 63 were alive 30 and 90 days after surgery, 2 patients died in less than 30 days and 2 were lost to follow-up. A moderately differentiated grade of tumor was noted in 10 patients (HR, 1.30; $p = 0.758$), while 3 patients had poorly differentiated/undifferentiated tumors (HR, 2.44; $p = 0.368$) when compared to 7 patients with well-differentiated tumors. Regional lymph nodes were positive in 17 patients (HR, 1.61; $p = 0.497$) and negative in 12.

The majority of patients (196 out of 210) did not receive radiation therapy. Among the 14 patients with radiation therapy, 9 had beam radiation (HR, 1.01; $p = 0.99$) and 4 had radioactive implants (HR, 0.84; $p = 0.914$) compared to 1 patient with radiation therapy not otherwise specified. Radiation therapy was administered before surgery in one patient and as adjuvant therapy in two patients, with no difference in survival between the groups ($p = 0.670$). The majority of patients did not receive chemotherapy (145 out of 206). Single-agent chemotherapy was documented in 33 patients and multiagent therapy in 16 patients. Chemotherapy was administered before surgery in three patients, and eight patients received adjuvant chemotherapy. No noticeable survival benefit was noted with respect to the type and sequence of chemotherapy in any group ($p = 0.298$ and $p = 0.383$, respectively).

3.3 | Kaplan–Meier survival analysis of surgical patients

Patients who underwent wedge/segmental resections had the highest 5-year OS of 90.5% (95% CI: 67%–97.5%). This dropped down to 74.6% (95% CI: 44%–90.1%) for the 10-year OS rate. For lobectomy/extended lobectomy, the 5- and 10-year OS rates were the same at 66.5% (95% CI: 31.8%–86.4%) and for liver transplant recipients, the rates were same at 81.0% (95% CI: 56.9%–92.4%). While transplant patients demonstrated an improved 10-year OS, the results did not prove to be statistically significant ($p = 0.4851$; Figure 2).

4 | DISCUSSION

The purpose of this study was to examine the NCDB for all cases of HEH to describe patient characteristics and current management trends in the United States and analyze outcomes in a large cohort of patients with this rare disease. Through our analysis, we found that HEH occurred more commonly in women than men, with a male to female ratio of 2:3, consistent with existing data.⁸ Patients above the age of 55 and Asian ethnicity had an association with worse OS. None of the treatment results elucidated a strategic method to improve survival in these patients.

In our analysis, surgery of the primary site was the most common form of treatment seen in 33% of patients in this study. Wedge or segmental resection was seen in 40% of this population, followed by transplant (33%) and lobectomy/extended lobectomy (27%). There was no significant difference in OS between these cohorts. A literature review by Mehrabi et al.,⁸ between 1984 and 2005, revealed liver transplantation to be the most common surgical treatment modality (83%) followed by liver resection (17%). This demonstrates a substantial change in trend with current strategies favoring wedge or segmental resection, compared to transplantation. This may reflect the negative impact of prolonged immuno-suppressive therapy following transplantation or scarce availability of donors. However, multifocal presentation seen in the majority of patients with HEH may be a limiting factor for liver resection, and in such situations transplantation has proven to have favorable long-term outcomes,^{13–15} despite extrahepatic disease as well as lymph node involvement.¹⁴ Both wedge/segmental resection and liver transplantation had acceptable 5-year survival rates (90% and 81%, respectively) in our study.

Nonsurgical treatment options like chemotherapy were administered in 26% of patients in our analysis. Single and multiagent chemotherapeutic strategies were tried but no significant difference in survival was noted between the groups. Two case reports by Lakkis et al.,¹⁶ showed the benefits of cyclophosphamide-based metronomic chemotherapy, reporting a partial radiological response. Multifactorial modes of action, including immunological and antiangiogenic functions, were attributed to this response. HEH is a vascular tumor and antiangiogenic agents like thalidomide have been tested to show mixed results.^{17–20} A phase 2 study by Chevreau et al.²¹ on sorafenib, showed a 9-month progression-free rate of only 30.7%. A study on immunotherapy, highlighting the use of interferon-alpha 2b (IFN- α 2b) on 42 patients, showed a partial and complete response in 47.6% and 4.8% of the patients, respectively with encouraging 1-, 3-, and 5-year progression-free survival rates of 81.0%, 69.2%, and 62.3%, respectively.²² The use of mammalian target of rapamycin inhibitor, sirolimus, proved to be beneficial in the treatment of HEH in children and adults.^{23,24} Drugs such as propranolol/prednisolone have been tried in infantile HEH with 56% of the patients doing well while 44% needing salvage therapy.²⁵ Only 7% of the patients in this NCDB review received radiation therapy with no significant impact on OS. A case report of palliative radiation therapy in a patient with multiple HEH lesions resulted in complete metabolic response of treated nodules.²⁶ The limited literature restricts our understanding of the impact of radiation in the management of these tumors. While radiofrequency ablation has shown promise,²⁷ the lack of proper management guidelines has made surgery a more viable option along with liver transplantation for multilobar and metastatic disease.²⁸

Our study has several limitations. First, the retrospective nature of this study can lead to a selection bias. Additionally, the NCDB is limited in longitudinal data like disease-free survival. Clinically relevant information regarding patient comorbidities, exact tumor location, details of systemic therapy (name, dose, frequency, and duration), drug toxicity, complications during treatment, and cause of death is not captured in the NCDB. Missing data is another drawback of the NCDB. Despite these limitations, our study is the first large descriptive analysis of HEH patients, analyzing patient characteristics, available treatment strategies, and outcomes.

5 | CONCLUSION

HEH has a better prognosis compared to other hepatic malignancies. Our descriptive analysis identifies patient characteristics and treatment strategies that may help improve understanding of this rare disease, and potentially lead to collaboration between institutions. Both wedge/segmental resection and liver transplantation have shown reasonable 5-year survival rates. New treatment strategies with antiangiogenic agents and immunotherapy have demonstrated promise but require more clinical investigation.

ACKNOWLEDGMENTS

Research reported in this publication was supported in part by the Biostatistics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. This study was supported in part by the Contardi Research Fellowship.

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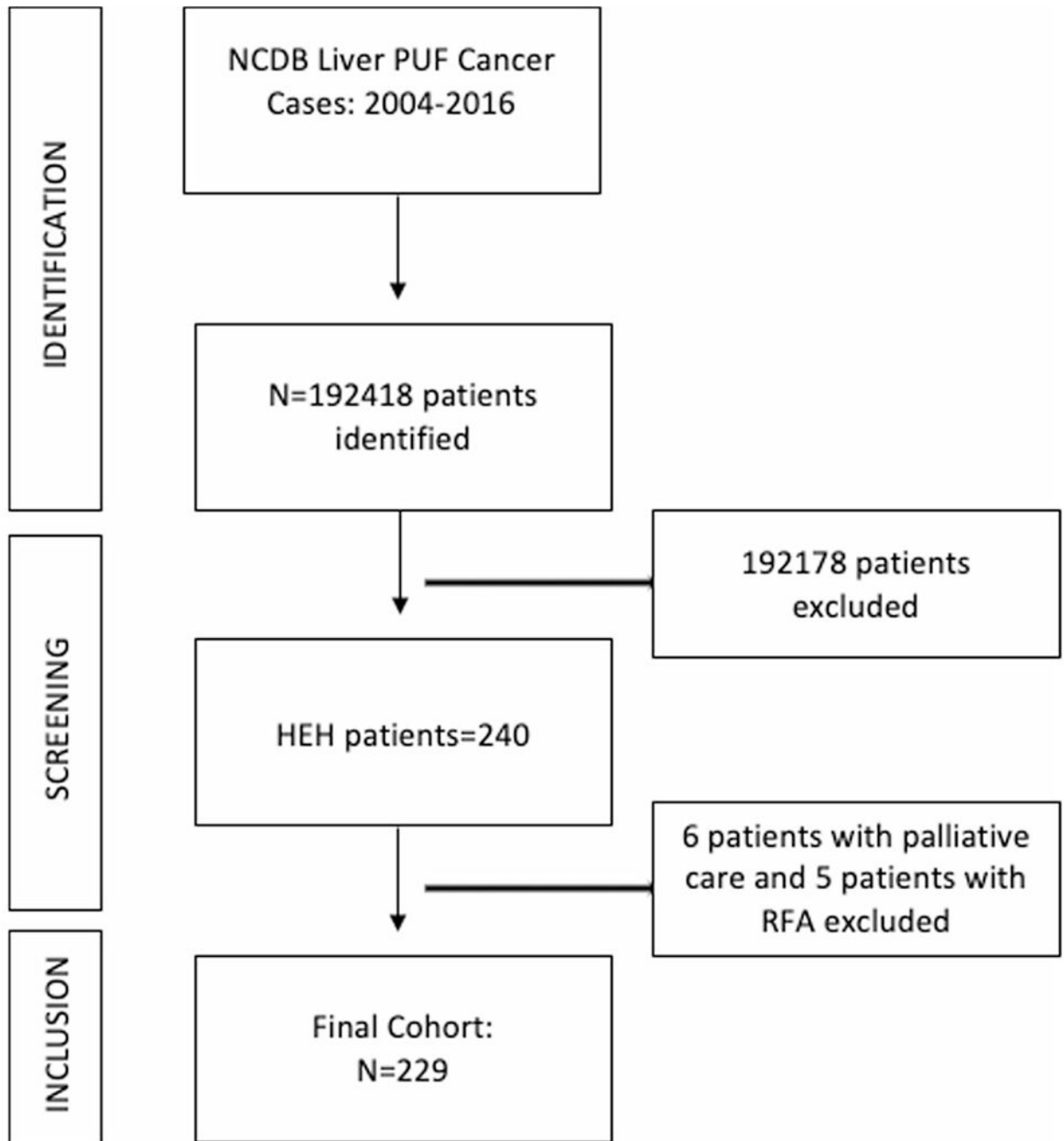
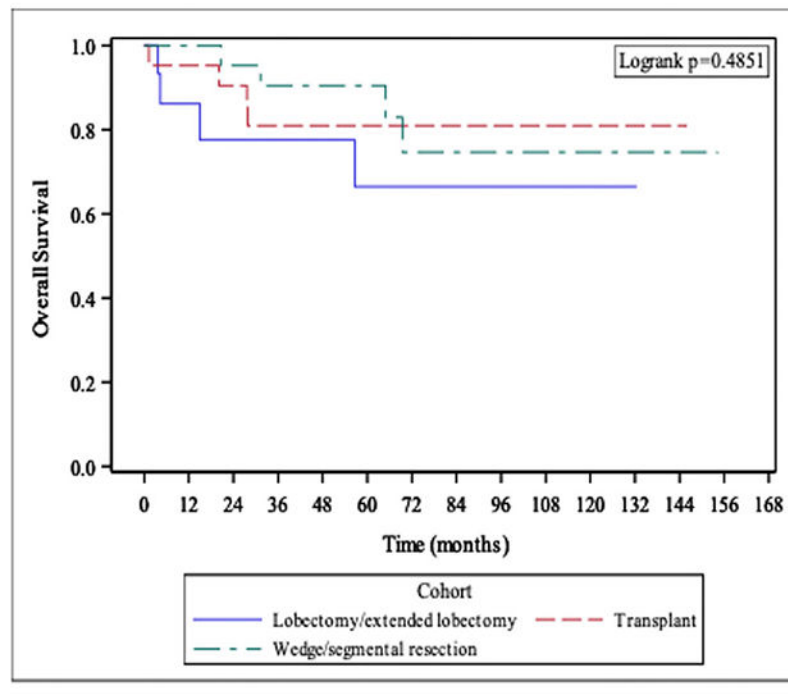


FIGURE 1. Schematic depicting patients inclusion and exclusion criteria. HEH, hepatic epithelioid hemangioendothelioma; N, number; NCDB, National Cancer Database; PUF, participant user data file; RFA, radiofrequency ablation



Cohort	OS	
	(months)	Survival Rate(95% CI)
Lobectomy/extended lobectomy	60	66.5% (31.8%, 86.4%)
	120	66.5% (31.8%, 86.4%)
Transplant	60	81.0% (56.9%, 92.4%)
	120	81.0% (56.9%, 92.4%)
Wedge/segmental resection	60	90.5% (67.0%, 97.5%)
	120	74.6% (44.0%, 90.1%)

FIGURE 2.

Kaplan–Meier plots demonstrating survival curves by type of surgical resection of primary site (liver)—wedge/segmental resection, hepatectomy lobectomy/extended lobectomy, and liver transplantation. Five- and 10-year overall survival statistics included. CI, confidence interval; OS, overall survival.

TABLE 1

Descriptive statistics including demographics, tumor characteristics, and surgical treatment methods used for intervention in patients with hepatic epithelioid hemangioendothelioma

Variable	Level	N (%) = 229
Cohort	Wedge/segmental resection	27 (40.3)
	Lobectomy/extended lobectomy	18 (26.9)
	Transplant	22 (32.8)
	Missing	162
Facility location	Northeast	35 (20.5)
	Midwest	56 (32.7)
	West	29 (17.0)
	South	51 (29.8)
	Missing	58
Age (categorical)	Below median (< 55)	118 (51.5)
	Above median (≥ 55)	111 (48.5)
Sex	Male	89 (38.9)
	Female	140 (61.1)
Race	White	193 (84.3)
	Black	20 (8.7)
	Other	8 (3.5)
	Asian	8 (3.5)
Charlson–Deyo score	0	172 (75.1)
	1	44 (19.2)
	2+	13 (5.7)
Primary Payor	Medicaid/other government/not insured/unknown	30 (13.1)
	Private	131 (57.2)
	Medicare	68 (29.7)
Grade	Well differentiated	8 (36.4)
	Moderately differentiated	11 (50.0)
	Poorly differentiated/undifferentiated	3 (13.6)
	Missing	207
Lymph Vascular Invasion, 2010	Not present	17 (63.0)
	Present	10 (37.0)
	Missing	202
Surgical margins status	Negative	52 (82.5)
	Positive	11 (17.5)
	Missing	166

Univariate association with overall survival analyzing demographics, treatment modalities, and tumor-related characteristics in patients with hepatic epithelioid hemangioendothelioma

TABLE 2

Covariate	Level	N	OS		
			Hazard ratio (95% CI)	HR p value	Log-rank p value
Cohort	Wedge/segmental resection	25	0.91 (0.23–3.52)	0.893	0.485
	Lobectomy/extended lobectomy	15	1.96 (0.50–7.61)	0.345	
	Transplant	21	–	–	
Facility type	Community Cancer Program	11	0.48 (0.16–1.29)	0.164	0.074
	Comprehensive Community Cancer Program	45	0.45 (0.22–0.98)	0.037	
	Academic/Research Program	91	0.39 (0.21–0.81)	0.008	
	Integrated Network Cancer Program	12	–	–	
Age (category)	Above median	102	2.78 (1.77–4.48)	<0.001	<0.001
	Below median	111	–	–	
Race	Black	19	1.01 (0.43–2.01)	0.983	0.127
	Other	7	1.28 (0.35–3.25)	0.661	
	Asian	8	2.84 (1.14–5.89)	0.012	
	White	179	–	–	
Charlson–Deyo score	1	41	2.28 (1.39–3.66)	<0.001	<0.001
	2+	11	2.76 (1.17–5.59)	0.011	
	0	161	–	–	
Primary Payor	Medicaid/other government/not insured/unknown	27	0.36 (0.16–0.72)	0.007	<0.001
	Private	124	0.34 (0.21–0.53)	<0.001	
	Medicare	62	–	–	
Grade	Moderately differentiated	10	1.30 (0.30–7.33)	0.758	0.676
	Poorly differentiated/undifferentiated	3	2.44 (0.36–16.26)	0.368	
	Well differentiated	7	–	–	
Lymph Vascular Invasion, 2010	Not present	16	1.67 (0.52–6.72)	0.435	0.355

Covariate	Level	OS		
		N	Hazard ratio (95% CI)	HR <i>p</i> value Log-rank <i>p</i> value
	Present	8	–	–
Surgical margins status	Positive	9	1.51 (0.29–5.26)	0.575
	Negative	49	–	–
Radiation therapy	None	196	0.53 (0.08–66.93)	0.661
	Beam radiation	9	1.01 (0.11–132.46)	0.996
	Radioactive implants	4	0.84 (0.07–116.39)	0.914
	Radiation therapy, NOS	1	–	–
Metastatic Lung Involvement, 2010–2015	None	73	1.30 (0.62–3.02)	0.509
	Yes	31	–	–
Chemotherapy	None	117	1.07 (0.36–5.18)	0.923
	Chemotherapy administered, type and number of agents not documented	5	1.65 (0.32–9.96)	0.557
	Single-agent chemotherapy	33	1.63 (0.51–8.20)	0.483
	Multiagent chemotherapy	16	1.19 (0.30–6.47)	0.822
	Chemotherapy recommended, unknown if administered	7	–	–

Firth's penalized maximum likelihood estimation was used.

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified; OS, overall survival.