

Primary Hepatic Small Cell Carcinoma: Two Case Reports, Molecular Characterization and Pooled Analysis of Known Clinical Data

ADITI SHASTRI^{1*}, PAVLOS MSAOUEL^{2*}, CRISTINA MONTAGNA³,
SHERRY WHITE⁴, MARIA DELIO³, KUNJAN PATEL³, KARENZA ALEXIS⁵,
MARIANNA STRAKHAN⁵, TAREK N. ELRAFEI⁵ and LOUIS JUDEN REED⁵

¹Department of Oncology, Montefiore Medical Center & Albert Einstein College of Medicine, Bronx, NY, U.S.A.;

Departments of ²Internal Medicine, ⁴Pathology, and ⁵Oncology, Jacobi Medical Center, Bronx, NY, U.S.A.;

³Department of Genetics and Pathology, Albert Einstein College of Medicine, Bronx, NY, U.S.A.

Abstract. Primary hepatic small cell carcinoma (HSCC) is a rare malignancy that has previously been described in only few case reports. The clinicopathological course, natural history, molecular markers and ideal treatment strategy for this tumor have not been fully elucidated. Herein, we report on two cases of spontaneously arising, metastatic primary HSCC that were treated at our Institution. Both patients succumbed to their disease within two months of initial presentation. Both cases underwent postmortem examination and no evidence of a pulmonary or other non-hepatic small cell primary was found. Unlike pulmonary small cell tumors, these two hepatic primaries showed only locoregional spread and very few distant metastases. Formalin-fixed samples were obtained at autopsy and sequenced using single-nucleotide polymorphism arrays and whole-genome sequencing. Four mutations in the epidermal growth factor receptor (EGFR) gene known to be associated with response to tyrosine kinase inhibitors (TKIs) were detected in one of the two HSCC samples. A systematic review and pooled analysis of all previously reported cases of primary HSCCs was conducted. The median overall survival was estimated at 4 months. Surgical resection was significantly associated with longer overall survival (hazard ratio =0.13, 95% confidence interval=0.03-0.69). Although several case

reports of primary HSCC have been reported prior to this publication, to our knowledge this is the first time that molecular and systematic analysis has been conducted in order to more fully characterize this rare disease. Our results indicate that surgical resection, when feasible, may be a valid option in primary HSCC, and that some tumors may respond to TKIs against EGFR.

Extrapulmonary small cell carcinoma (EPSCC) originating in the gastrointestinal tract is a very rare tumor, and since its first description in 1952, only a few hundred cases have been reported in the literature (1). The overall understanding of the clinicopathological characteristics of this rare disease is still meager. To our knowledge, no prospective trials exist for this disease and treatment recommendations are extrapolated from studies of small cell lung cancer (SCLC) or derived from single-Institution experiences (1-5).

EPSCC is primarily composed of poorly differentiated, or anaplastic cells, although segments of well-differentiated squamous or glandular tissue may also be present. It usually stains positively for the neuroendocrine markers chromogranin, synaptophysin and CD56 on immunohistochemistry and has a high proliferative index (Ki-67) (6-10). These tumors are usually very aggressive and characterized by poor survival. Outcomes after surgical resection appear to be poor as is the case with other poorly differentiated neuroendocrine tumors, and benefit from chemotherapy or radiation is not well- established (11, 12). No staging system has been specifically established for EPSCC of gastrointestinal origin. Some authors use the TNM system while most others have adopted the Veterans Administration Lung Study group staging that broadly classifies patients as having early-stage vs. extensive-stage disease (13, 14).

Primary hepatic SCC (HSCC) is a very rare clinical entity and to the best of our knowledge, the molecular pathogenesis and optimal clinical management of this disease have yet to

*These Authors contributed equally to this study.

Correspondence to: Aditi Shastri, MD, Attending Physician, Department of Oncology, Montefiore Medical Center & Albert Einstein College of Medicine, 111 East, 210th St, Bronx, New York, NY 10467, U.S.A. Tel: +1 7189204826, e-mail: ashastri@montefiore.org

Key Words: Primary hepatic carcinoma, small cell cancer, neuroendocrine tumor.

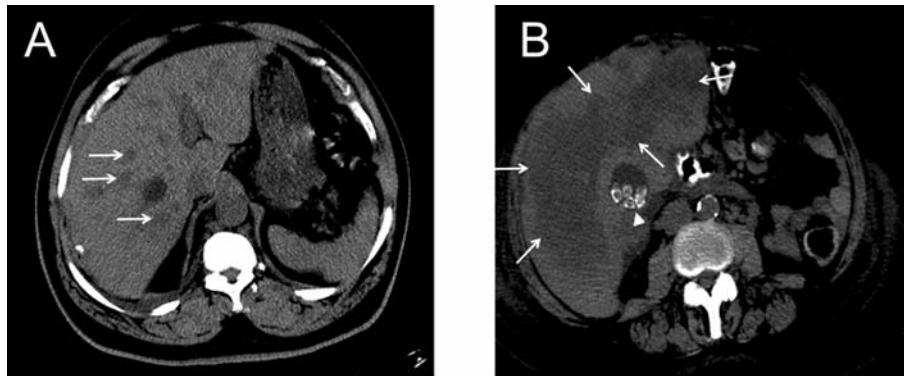


Figure 1. A: Abdominal computed tomography (CT), of patient 1 revealed multiple ill-defined hypodensities (arrows) measuring higher than simple fluid attenuation within both the right and left hepatic lobes. B: Abdominal CT of patient 2 revealed a dominant necrotic liver mass (arrows) that involved the mid-lower right lobe and the quadrate lobe. Cholelithiasis is also noted (arrowhead).

be elucidated. A retrospective cohort study of the Surveillance, Epidemiology and End-Results (SEER) database, which identified patients with primary HSCC revealed the presence of 16 cases reported in adults in the United States from 1973 to 2008 (11). Some of these cases did not have postmortem examinations, leaving a degree of uncertainty as to whether or not they were true primary hepatic small-cell cases. Systematic genomic analysis is difficult to perform as these tumors are rarely treated with surgery and obtaining fresh frozen tumor samples is challenging (15). Only recently have key somatic driver mutations been characterized for SCLC (15, 16). With limited available data, comparison of available molecular analysis in gastrointestinal and pulmonary SCC reveal certain similarities (17).

Overall, there appear to exist several unanswered questions pertaining to the molecular pathogenesis, clinical features, optimal treatment strategies and outcome of primary HSCC, the answers to which are likely to be relevant to EPSCC as a class of tumors. Herein we report clinical data and molecular characterization results of two cases of primary HSCC from our Institution, as well as a systematic review and outcomes analysis of all the cases of primary HSCC reported in the literature.

Case Reports

Case report 1. A 73-year-old Black male, never-smoker, presented to our Institution with sudden-onset acute renal failure and hyperkalemia. His past medical history was significant for hypertension, type II *diabetes mellitus*, and adenocarcinoma of the prostate diagnosed 11 years prior to presentation treated with radical prostatectomy, brachytherapy and intermittent androgen deprivation.

Radiological findings: Computed tomographic (CT) scan with intravenous contrast of the abdomen and pelvis revealed

the presence of an enlarged liver with innumerable poorly defined focal lesions throughout all segments, suspicious for malignancy (Figure 1A). The spleen was not enlarged. The pancreas and adrenal glands were grossly unremarkable. There were multiple enlarged lymph nodes seen predominantly in para-aortic, paracaval and retroaortic regions down to the level of the femoral artery. There was a significant bilateral hydroureteronephrosis as a result of obstruction from lymphadenopathy.

Histopathological findings: A percutaneous biopsy of one of the liver lesions was performed which showed the presence of an infiltrating poorly differentiated malignant tumor. The cells infiltrated the liver in a nesting and clustering pattern (Figure 2A). They exhibited extensive mitosis, single-cell necrosis and nuclear molding, suggestive of a high-grade neuroendocrine carcinoma. The immunohistochemistry profile was positive for chromogranin, synaptophysin (Figure 2B) and CD56. The Ki-67 score was 95%, which confirmed the presence of SCC (Figure 2C).

Clinical course: The patient subsequently had a complicated course in the hospital and was diagnosed with metabolic acidosis and respiratory distress due to worsening renal and liver function despite percutaneous stent placements and initiation of dialysis. He was transferred to the medical Intensive Care Unit, intubated and placed on a mechanical ventilator while inotropic drugs were used to maintain his blood pressure. The patient died of hepatic and renal failure with lactic acidosis and hypotension 30 days from his initial presentation.

Autopsy findings: During the gross examination, the Glisson's capsule was irregular with multiple subcapsular lesions. The cut surface showed extensive parenchymal replacement by grey tan tumor nodules measuring from 1 to 3 cm. The tumor appeared centered in the liver with only locoregional nodal metastases noted. Paraesophageal and

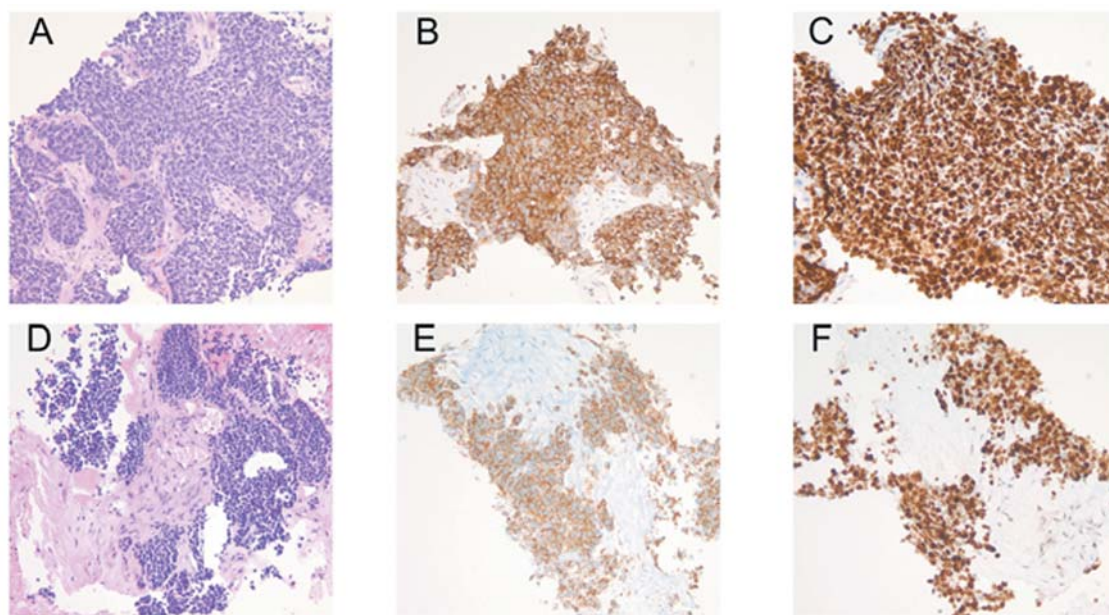


Figure 2. Images A-C are from patient 1, whereas images D-F are from patient 2 (all magnification $\times 20$). A: Liver biopsy, hematoxylin and eosin (H&E) staining. Biopsy shows sheets of cells with scant cytoplasm, nuclear molding, apoptotic cells, and scattered mitotic figures. Rare residual hepatocytes are present. B: Liver biopsy, synaptophysin staining. Strong diffuse positivity. C: Liver biopsy, Ki-67 staining. Strong positivity in 95% of cells. D: Liver biopsy, H&E staining. Biopsy shows cells with scant cytoplasm and nuclear molding in a background of fibrosis. E: Liver biopsy, synaptophysin staining. Strong diffuse positivity. F: Liver biopsy, Ki-67 staining. Strong positivity in 90% of cells.

para-aortic lymph nodes appeared to be enlarged and replaced with tumor. No lesions were noted in the lungs. The pancreas and all other organs appeared unremarkable. These findings were corroborated with microscopy and immunohistochemistry and the tumor was identical in all respects to that originally found on histopathological examination. No intracranial or spinal metastases were detected on neuropathological examination. No evidence of prostate cancer was found at autopsy.

Case report 2. A 64-year-old Hispanic female, former smoker, presented with new-onset icterus and abdominal pain to our Institution. Her past medical history was significant for type II *diabetes mellitus*, hypertension and hyperlipidemia. A follow-up visit and laboratory check performed two months prior to presentation with an outside provider were within normal limits.

Radiological findings: CT scan of the chest, abdomen and pelvis with intravenous contrast showed the presence of a dominant necrotic liver mass that involved the lower right lobe and the quadrate lobe (Figure 1B). It measured 15.4 cm \times 12 cm \times 13 cm in length, anterior–posterior diameter and width, respectively. Enlarged lymph nodes at the *porta hepatis* and portacaval lymph nodes were found to be obstructing the common hepatic duct, causing extrinsic

narrowing of the portal vein and left renal vein. Right pericardiophrenic nodes were also enlarged. The greater omentum and anterior peritoneum were involved by direct tumor extension. Large esophageal varices were noted. No radiographic evidence of a primary esophageal, colonic or lung mass was found.

Histopathological findings: A percutaneous biopsy of the dominant liver lesions was performed. It showed the presence of necrotic tissue, hemorrhage and clusters of small blue round cells (Figure 2D). Immunohistochemistry profile was positive for chromogranin, synaptophysin (Figure 2E) and CD56. The Ki-67 score was 90%, which confirmed the presence of a rapidly proliferating neuroendocrine tumor diagnosed as SCC originating from the liver (Figure 2F).

Clinical course: The patient was admitted for inpatient work-up and treatment. She developed progressive jaundice with severe hyperbilirubinemia (total bilirubin of 21.8 g/dl). She developed altered sensorium and gastrointestinal hemorrhage from esophageal varices. Despite aggressive supportive care, the patient succumbed to liver failure, variceal bleeding and hepatorenal syndrome on the 46th hospital day.

Autopsy findings: At autopsy, the target tumor was centered in the liver with locoregional extension. The liver was found to harbor a 23 cm \times 23 cm \times 17 cm mass protruding through the capsule, involving the gallbladder and head of the pancreas, and

Table I. Baseline characteristics of the 14 patients included in the pooled analysis.

Author and year of publication	Age at diagnosis (years)	Gender	Autopsy	Maximum tumor size (cm)	Presence of lymph node metastasis	Presence of distant metastasis	Chemotherapy	Surgical resection	Overall survival (months)	Outcome
Zanconati <i>et al.</i> (1996) (19)	56	Male	No	5	No	No	No	Yes	5	Death
Zanconati <i>et al.</i> (1996) (19)	69	Male	Yes	10	No	No	No	No	1	Death
Zanconati <i>et al.</i> (1996) (19)	89	Male	Yes	6	No	No	No	No	1	Death
Kim <i>et al.</i> (2004) (21)	53	Male	No	12	No	No	Yes	Yes	4	End of follow-up
Yasuda <i>et al.</i> (2006) (29)	71	Male	Yes	7	Yes	Yes	Yes	No	5	Death
Choi <i>et al.</i> (2007) (25)	82	Female	No	6.7	Yes	No	Yes	Yes	18	End of follow-up
Morikawa <i>et al.</i> (2008) (26)	77	Male	No	10	Yes	No	Yes	No	3	Death
Balta <i>et al.</i> (2008) (30)	71	Female	No	11	No	No	Yes	Yes	18	End of follow up
Huang <i>et al.</i> (2010) (27)	34	Male	No	NR	No	No	No	Yes	98	End of follow-up
Kaman <i>et al.</i> (2010) (28)	40	Female	No	13.5	Yes	No	Yes	Yes	1	End of follow-up
Khaw <i>et al.</i> (2011) (31)	51	Male	Yes	3.5	Yes	No	No	Yes	4	Death
Furqan <i>et al.</i> (2012) (32)	63	Female	No	8.6	Yes	No	Yes	No	1	Death
Present case	73	Male	Yes	3.2	Yes	No	No	No	1	Death
Present case	64	Female	Yes	17	Yes	No	No	No	1.5	Death

NR: Not reported.

extending to the pericolic adipose tissue of the transverse colon. The spleen, kidneys, adrenals, and thoracic organs were uninvolved with malignancy. These findings were corroborated with microscopy and immunohistochemistry and the tumor was identical in all respects to that found on the original histopathological examination. No intracranial or spinal metastases were detected on neuropathological examination.

Molecular analysis. Formalin-fixed tissue was obtained at autopsy from the cut sections of the tumor arising from the liver. DNA was extracted from the tissue using the QIAamp DNA FFPE tissue kit (Qiagen, Valencia, CA, USA). Sequencing of the samples was performed using the OncoScan FFPE assay. (Affymetrix, Santa Clara, CA, USA). Please refer to the supplementary files at <http://cristinam09.wix.com/shastri-supplem-data> in order to review the results of the OncoScan analysis. The OncoScan analysis allows for the screening of single nucleotide variants and small insertions and deletions in nine cancer genes which are V-Raf murine sarcoma viral oncogene homolog 1 (*BRAF*), V-K1-Ras2 kirsten rat sarcoma viral oncogene homolog (*KRAS*), epidermal growth factor receptor (*EGFR*), isocitrate dehydrogenase 1

(*IDH1*), isocitrate dehydrogenase 2 (*IDH2*), phosphatase and tensin homolog (*PTEN*), phosphatidylinositol 3-kinase catalytic alpha (*PIK3CA*), neuroblastoma ras viral oncogene homolog (*NRAS*), tumor protein (*TP53*) covering a total of 65 variants. We were unable to identify any mutation within these regions for patient case 2. On the contrary, the analysis of patient case 1 revealed the presence of several mutations with high confidence in seven genes (Table I). One mutation was a small deletion in *PTEN* resulting in a frameshift (*PTEN*: p.K267fs*9:c.800delA); a small insertion in *EGFR* leading to a frame shift (*EGFR*: p.H773_V774insNPH:c.2319_2320ins9); 27 additional mutations were mapped to *NRAS*, *PIK3CA*, *EGFR*, *BRAF*, *PTEN*, *KRAS* and *TP53*; two non-sense mutations were identified leading to a premature stop of *TP53* and *PTEN*; and an additional complex alteration was found in *EGFR*. We next assessed the potential pathogenicity of these mutations in patient case 1 using ClinVar, (<http://www.ncbi.nlm.nih.gov/clinvar/>) and COSMIC (<http://cancer.sanger.ac.uk/cosmic/>) The majority were predicted to be pathogenic. Four mutations in the *EGFR* gene lacked a clear pathogenicity prediction but were all associated with response to treatment with tyrosine kinase inhibitors.

Literature search strategy and data extraction for systematic review and pooled analysis of published cases. Our systematic review of the literature on HSCC was conducted using the electronic databases PubMed, SciVerse Scopus, Google Scholar (last search, June 2015). The search strategy included the following key words variably combined: “liver cancer”, “small cell cancer”, “extrapulmonary small cell cancer”, “liver neuroendocrine cancers”, “primary small cell cancer of the liver”. We assessed all associated publications to retrieve the most eligible studies. Moreover, their reference lists were searched manually to find other relevant publications. We included the data from the two patients presented in the current report. We did not apply any language restrictions. Two investigators independently searched the literature and independently extracted data from each eligible study.

Statistical analysis. All statistical analyses were performed using R (Foundation for Statistical Computing, Vienna, Austria)(18). We performed an exploratory pooled analysis of all reported HSCC cases (19-32) in order to calculate descriptive statistics and to perform survival analyses. Univariate Cox regression models were constructed to determine the association of age at diagnosis, gender, tumor size in centimeters, presence or absence of lymph node or distant metastases, chemotherapy treatment, and surgical treatment with overall survival. The small sample size of reported cases precluded multivariate analyses. A *p*-value less than 0.05 was considered statistically significant.

Results of pooled analysis. Our search yielded 14 case reports that were reviewed in detail (19-32). Five of these studies did not provide data on overall survival and were thus excluded from the survival analysis (20, 22-24). Thus, a total of 14 patients (including the two cases reported in the present study) were included in our analyses (Table I). The median follow-up period was 3.5 months. The mean patient age was 63.8 years (standard deviation=15.6 years, range=34-89 years). The mean tumor size was 8.7 cm (standard deviation=4.05 cm, range=3.2-17.0 cm). Nine out of 14 patients (64.3%) were male and 8/14 patients (57.1%) had lymph node metastases. Only out of 14 patients (7.1%) was found to have distant metastases. In addition, 7/14 (50%) of patients underwent chemotherapy and 7/14 (50%) underwent surgery. Four out of 14 patients (28.6%) underwent both chemotherapy and surgical resection of their tumor. Autopsy was performed in 6 out of 14 patients (42.9%).

Figure 3 shows the Kaplan–Meier curve for overall survival in patients with primary HSCC. The median overall survival from diagnosis was 4 months. The results of univariate Cox regression analyses are shown in Table II. Although the protective effect of chemotherapy was sizable, it did not reach statistical significance (hazard ratio=0.42,

Table II. Univariate association (Cox regression) of overall survival with patient and tumor parameters.

	HR	95% CI	<i>p</i> -Value
Age at diagnosis (years)	1.03	0.98-1.07	0.314
Gender			
Male	1.00	-	-
Female	1.87	0.39-9.04	0.437
Maximum tumor size(cms)	0.97	0.79-1.18	0.722
Presence of lymph node metastase			
Yes	1.00	-	-
No	1.95	0.48-7.93	0.349
Presence of distant metastasis			
Yes	1.00	-	-
No	0.97	0.12-7.99	0.979
Chemotherapy			
Yes	1.00	-	-
No	0.42	0.1-1.67	0.415
Surgical resection			
Yes	1.00	-	-
No	0.13	0.03-0.69	0.016*

CI: Confidence interval; HR: hazard ratio; *Statistically significant association (*p*<0.05).

95% confidence interval=0.1-1.67; *p*=0.216). On the other hand, surgical resection of HSCC was significantly associated with longer overall survival (hazard ratio=0.13, 95% confidence interval=0.03-0.69; *p*=0.016). The Kaplan–Meier curves of the seven patients who underwent surgery compared with the seven who did not are presented in Figure 4. All patients who did not undergo surgery died within 5 months of diagnosis, whereas five out of seven (71.4%) patients who had surgical resection of their tumor were alive by the end of follow-up.

Discussion

Survival analysis in our series supports the notion that primary HSCC is a rapidly advancing, aggressive, tumor with a median overall survival of 4 months. In a previously reported series, patients with non-metastatic hepatopancreatobiliary primary SCC treated with surgical resection lived longer than those who were treated without resection (11). Our study corroborates this finding, as patients with primary HSCC that underwent surgical resection had longer overall survival than those who did not. These findings, because of selection bias, do not necessarily prove a primary role for surgery in all cases of primary HSCC. However, selected early cases of HSCC may apparently be cured by surgery alone. Chemotherapy did show a trend towards improved survival, which however it was not statistically significant. The two cases reported from our institution had rapidly progressing disease and died within 2 months of initial presentation without receiving any form of therapy. We attribute this to a high burden of disease and late

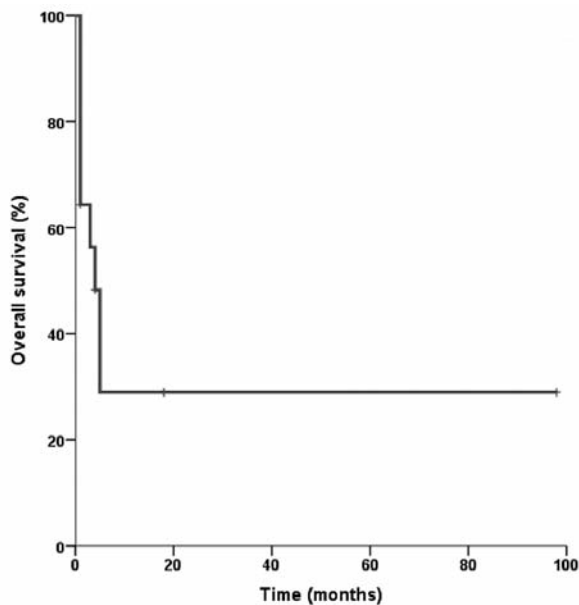


Figure 3. Kaplan-Meier curve for overall survival in small cell liver cancer.

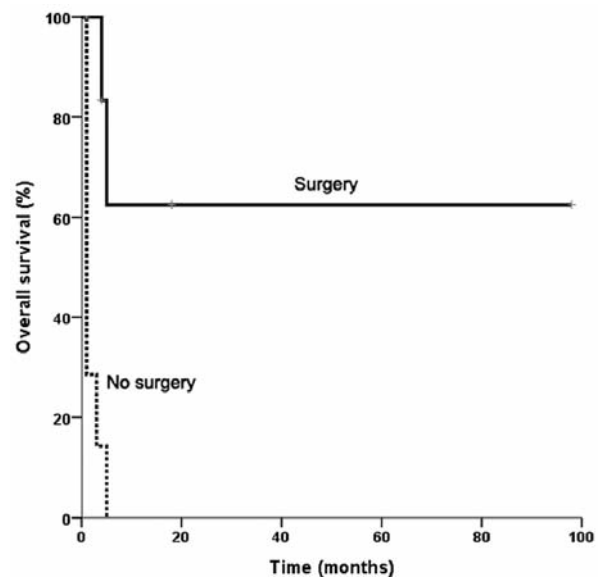


Figure 4. Kaplan-Meier curves demonstrate the significantly better overall survival of the seven patients that underwent surgical resection of small cell liver cancer compared to the seven patients who did not ($p=0.016$).

presentation with metastatic disease. Our current cases correlate with previously reported cases and series from the literature where primary HSCC has been noted to be an aggressive disease, with survival measured in months (Table I).

There are significant similarities and differences between SCLC and primary HSCC. First and foremost, the histology and immunohistochemistry appear identical (Figure 2). One of our two primary HSCC samples harbored mutations in many of the genes known to play a role in SCLC, including *TP53* and *PTEN* (16). Of particular interest are four of the variants identified in *EGFR* suggesting that anti-*EGFR* therapies, including tyrosine kinase inhibitors, may warrant further investigation in at least some patients with primary HSCC. Chemotherapy is likely to be the mainstay of treatment in extensive-stage disease. In the case reports that were analyzed, patients received several different regimens and the sample size of each regimen was too small to make an inference about the best available chemotherapy regimen for primary HSCC. However, some did manifest a transient objective response to the cisplatin/etoposide regimen. Given the rarity of primary HSCC, it will be very challenging to perform randomized prospective studies that would further delineate the best chemotherapy regimen for this tumor. An interesting difference between SCLC and the primary HSCC cases reported herein was the paucity of distant metastases in our two autopsied cases. Not only did the tumor appear to originate in the liver but the tumor spread was locoregional. This pattern was also observed in the majority of the previously reported cases (Table I).

Conversely, SCLC cases nearly always have distant metastases by the time they reach autopsy. The fact that HSCC appears to spread locally from the liver lends support to the observation that a small proportion of cases, if diagnosed early, may be cured by surgery.

Conclusion

In summary, primary HSCC is a rare malignancy with 14 well-reported cases (including the two new cases reported herein) in the world literature (Table I). Clinically, it is a rapidly advancing tumor, with an overall survival estimated to be at 4 months in our case series and analysis. Only surgery was significantly associated with an improvement in overall survival. The two cases reported in our study offer the novel observation that primary HSCC tends to have locoregional spread with a paucity of distant metastases. This correlates with the observation that the few cures previously reported in the literature, presumably early cases, were treated surgically. Molecular analysis of the tumor revealed that commonly mutated tumor-suppressor and oncogenes played a role in one of our two cases of primary hepatic. This tumor harbored mutations that may have conferred sensitivity to anti-*EGFR* tyrosine kinase inhibitors. The genetic analysis of the two cases reported herein and our systematic literature review and pooled analysis indicate that primary HSCC should be considered an entity distinct from other types of SCC.

References

- 1 Cicin I, Karagol H, Uzunoglu S *et al*: Extrapulmonary small-cell carcinoma compared with small-cell lung carcinoma: a retrospective single-center study. *Cancer 110*: 1068-1076, 2007.
- 2 Galanis E, Frytak S, Lloyd RV: Extrapulmonary small cell carcinoma. *Cancer 79*: 1729-1736, 1997.
- 3 Haider K, Shahid RK, Finch D *et al*: Extrapulmonary small cell cancer: a Canadian province's experience. *Cancer 107*: 2262-2269, 2006.
- 4 Lee SS, Lee JL, Ryu MH *et al*: Extrapulmonary small cell carcinoma: single center experience with 61 patients. *Acta Oncol 46*: 846-851, 2007.
- 5 Soto DE and Eisbruch A: Limited-stage extrapulmonary small cell carcinoma: outcomes after modern chemotherapy and radiotherapy. *Cancer J 13*: 243-246, 2007.
- 6 Hosonuma K, Sato K, Honma M *et al*: Small-cell carcinoma of the extrahepatic bile duct: a case report and review of the literature. *Hepatol Int 2*: 129-132, 2008.
- 7 Ibrahim NB, Briggs JC and Corbishley CM: Extrapulmonary oat cell carcinoma. *Cancer 54*: 1645-1661, 1984.
- 8 Quinn AM, Blackhall F, Wilson G *et al*: Extrapulmonary small cell carcinoma: a clinicopathological study with identification of potential diagnostic mimics. *Histopathology 61*: 454-464, 2012.
- 9 Gaffey MJ, Mills SE and Lack EE: Neuroendocrine carcinoma of the colon and rectum. A clinicopathologic, ultrastructural, and immunohistochemical study of 24 cases. *Am J Surg Pathol 14*: 1010-1023, 1990.
- 10 Burke AB, Shekitka KM and Sobin LH: Small cell carcinomas of the large intestine. *Am J Clin Pathol 95*: 315-321, 1991.
- 11 Groeschl RT, Christians KK, Turaga KK and Gamblin TC: Management of primary hepatopancreatobiliary small cell carcinoma. *J Surg Oncol 107*: 692-695, 2013.
- 12 Brennan SM, Gregory DL, Stillie A, Herschtal A, Mac Manus M and Ball DL: Should extrapulmonary small cell cancer be managed like small cell lung cancer? *Cancer 116*: 888-895, 2010.
- 13 Micke P, Faldum A, Metz T *et al*: Staging small cell lung cancer: Veterans Administration Lung Study Group *versus* International Association for the Study of Lung Cancer – what limits limited disease? *Lung Cancer 37*: 271-276, 2002.
- 14 Mitani M, Kuwabara Y, Shinoda N, Sato A and Fujii Y: Long-term survivors after the resection of limited esophageal small cell carcinoma. *Dis Esophagus 13*: 259-261, 2000.
- 15 Peifer M, Fernandez-Cuesta L, Sos ML *et al*: Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet 44*: 1104-1110, 2012.
- 16 Pietanza MC and Ladanyi M: Bringing the genomic landscape of small-cell lung cancer into focus. *Nat Genet 44*: 1074-1075, 2012.
- 17 Brenner B, Tang LH, Klimstra DS and Kelsen DP: Small-cell carcinomas of the gastrointestinal tract: a review. *J Clin Oncol 22*: 2730-2739, 2004.
- 18 R Development Core Team. R: A language and environment for statistical computing. *In*: Vienna, Austria: R Foundation for Statistical Computing, 2012.
- 19 Zanconati F, Falconieri G, Lamovec J and Zidar A: Small cell carcinoma of the liver: a hitherto unreported variant of hepatocellular carcinoma. *Histopathology 29*: 449-453, 1996.
- 20 Sengoz M, Abacioglu U, Salepci T, Eren F, Yumuk F and Turhal S: Extrapulmonary small cell carcinoma: multimodality treatment results. *Tumori 89*: 274-277, 2003.
- 21 Kim YH, Kwon R, Jung GJ *et al*: Extrapulmonary small-cell carcinoma of the liver. *J Hepatobiliary Pancreat Surg 11*: 333-337, 2004.
- 22 Ryu SH, Han SY, Suh SH *et al*: A case of primary small cell carcinoma of the liver. *Korean J Hepatol 11*: 289-292, 2005.
- 23 Kim KJ, Yim HJ, Kim MJ *et al*: A case of primary small cell neuroendocrine carcinoma of the liver. *Korean J Gastroenterol 48*: 37-41, 2006.
- 24 Kim KO, Lee HY, Chun SH *et al*: Clinical overview of extrapulmonary small cell carcinoma. *J Korean Med Sci 21*: 833-837, 2006.
- 25 Choi SJ, Kim JM, Han JY *et al*: Extrapulmonary small cell carcinoma of the liver: clinicopathological and immunohistochemical findings. *Yonsei Med J 48*: 1066-1071, 2007.
- 26 Morikawa H, Nakayama Y, Maeda T *et al*: A case of primary small cell carcinoma of the liver that was treated with chemotherapy. *Hepatol Int 2*: 500-504, 2008.
- 27 Huang YQ, Xu F, Yang JM and Huang B: Primary hepatic neuroendocrine carcinoma: clinical analysis of 11 cases. *Hepatobiliary Pancreat Dis Int 9*: 44-48, 2010.
- 28 Kaman L, Iqbal J, Pall M and Bal A: Primary small cell carcinoma of liver: A rare tumor. *Gastroenterology Research 3*: 180-184, 2010.
- 29 Yasuda E, Takeshita A, Murata S *et al*: Neuroendocrine carcinoma of the liver associated with dermatomyositis: autopsy case and review of the literature. *Pathol Int 56*: 749-754, 2006.
- 30 Balta Z, Sauerbruch T, Hirner A, Büttner R and Fischer HP: Primäre neuroendokrine Karzinome der Leber. *Der Pathologe 29*: 53-60, 2008.
- 31 Khaw YL, Nolan N, Heaslip I, McCormick PA and Sheahan K: Primary intrahepatic small-cell carcinoma arising from combined hepatocellular and cholangiocarcinomas. *J Clin Oncol 29*: e630-633, 2011.
- 32 Furqan S and Zubair H: Primary Small Cell Carcinoma of the Liver: A Rare and Aggressive Tumor. *Kansas Journal of Medicine*: 101-107, 2012.

Received September 23, 2015

Revised November 9, 2015

Accepted November 12, 2015