# Treatment and Prognosis of Patients with Fibrolamellar Hepatocellular Carcinoma: A National Perspective

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**BACKGROUND:** Surgery remains the only potentially curative option for patients with hepatocellular carcinoma (HCC) and fibrolamellar carcinoma (FLC). We sought to investigate the differences over time in surgically managed FLC compared with conventional HCC using population-based data.

**STUDY DESIGN:** Using SEER data, we identified 7,225 patients with surgically managed FLC or HCC from 1986 to 2008. We examined differences in clinicopathologic and surgical factors associated with long-term survival.

**RESULTS:** Of the 7,225 patients, the majority had HCC (n = 7,135; 99%) vs FLC (n = 90; 1%). Patients with FLC were younger (25 years vs 59 years) and more often were women (44% vs 27%) than patients with HCC (both $p < 0.001$). Regional disease was more common among patients with FLC (42.2%) vs patients with HCC (22.1%) ($p < 0.001$). More than one-third of patients with FLC (36.9%) were operatively managed with a hemihepatectomy compared with patients with HCC, who were more often managed with a liver transplant ($p < 0.001$). On univariable analysis, there was a marked difference in overall survival, with patients with FLC surviving a median of 75 months vs 43 months for HCC (hazard ratio [HR]: 0.59; $p = 0.001$). There was a marked difference in survival when patients were stratified by localized (FLC, 78 months vs HCC, 49 months; $p = 0.012$) vs regional disease (FLC, 46 months vs HCC, 23 months; $p = 0.002$.

**CONCLUSIONS:** Patients with FLC have many clinicopathologic features that are different from those of patients with HCC, including younger age and female sex. Despite a higher likelihood of advanced disease at the time of diagnosis, surgically treated FLC patients had better long-term outcomes than patients with conventional HCC. (J Am Coll Surg 2014;218: 196–205. © 2014 by the American College of Surgeons)

**CME questions for this article available at http://jacscme.facs.org**

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In 2013, the American Cancer Society estimates there will be 28,720 new cases of primary liver cancer, with 20,550 deaths in the United States.[1] Primary liver cancers include hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and the more uncommon fibrolamellar carcinoma (FLC) variant of HCC. It is estimated that FLC comprises approximately 1% of all HCC based on population data derived from the SEER data maintained by the National Cancer Institute (NCI).[2] Fibrolamellar carcinoma is distinct from HCC in both its clinical and pathologic manifestations, often affecting younger patients and having a higher incidence in women.[2,3] Importantly, FLC has been shown to have a general better prognosis than HCC, leading to significant interest in maximizing the intent for cure in this often young and otherwise healthy patient population.[2-6] In recent years,





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**Abbreviations and Acronyms**
HCC = hepatocellular carcinoma
FLC = fibrolamellar carcinoma
HR = hazard ratio
NCI = National Cancer Institute
OS = overall survival

advances in surgical care and improvements in preoperative imaging and surgical techniques have decreased the morbidity associated with liver resection.[7,8] However, the distinct clinicopathologic features of FLC compared with HCC, including no association with cirrhosis, necessitate a better understanding of factors influencing outcomes in patients with operable FLC vs HCC.

To date, there have been several small institutional series summarizing the surgical management of patients with FLC. Unfortunately, these studies have been limited by small sample sizes due to the rarity of FLC, and therefore they have lacked the statistical power to draw meaningful conclusions.[3,9,10] Population-based data may help better characterize patterns of care among patients with low-incidence cancers such as FLC. Using population-based data, more patients can be included in the study cohort and data on therapeutic management beyond that delivered just at tertiary referral centers can be examined. Although general epidemiologic trends have been examined using national data, FLC has yet to be examined from a surgical perspective using the SEER database.[2] As such, the objective of this study was to characterize the surgical management of patients with FLC, as well as define national trends in the specific use of operative procedures and treatments among patients with FLC. In addition, we sought to examine whether there have been improvements in survival among patients with surgically managed FLC vs HCC on a population basis over time.

## METHODS

### Data source

This study was a retrospective analysis of prospectively collected data from the SEER database maintained by the NCI. The SEER data derive from 20 cancer registries, representing approximately 28% of the United States population.[11] These data include information on patient demographics, tumor and disease characteristics, course of treatment, use of cancer-directed surgery and medical therapy, survival, and cause of death for individuals diagnosed with cancer.

### Study population

Patients with a diagnosis of primary liver cancer from 1986 to 2008 within the SEER database were identified by the International Classification of Diseases for Oncology (ICD-O-3) topography, behavior, and histology codes using SEER*Stat software.[12] Patients with intrahepatic cholangiocarcinoma and other biliary tract cancers were excluded from the cohort. We chose 1986 as the first year of the study because FLC (8171) was not recognized and coded as a distinct entity separate from HCC until that year. To fully capture all of the incident cases of HCC from 1986 to 2008, we included all histology codes relevant to HCC as determined by a gastrointestinal pathologist at the Johns Hopkins Hospital (RAA). Histologies relevant to HCC included hepatocarcinoma (8170), hepatocellular carcinoma—scirrhous (8172), hepatocellular carcinoma—spindle cell (8173), hepatocellular carcinoma—clear (8174), and hepatocellular carcinoma—pleomorphic (8175); collectively, these histologies comprised the HCC population of our study. We excluded other histology codes specific to cholangiocarcinoma from the analysis and included only patients undergoing a cancer-directed operation that was histologically or microscopically confirmed. Finally, we selected only patients with local or regional disease as defined by the SEER historical stage in the study population; patients with metastatic disease were excluded. The SEER historic stage is often used when dealing with datasets that span several revisions of the American Joint Committee on Cancer (AJCC) staging manual in order to ensure some uniformity of staging data over time. The historic stage has been standardized and simplified to ensure consistent definitions over time and is preferred to the AJCC staging system that is more commonly used in the clinical settings. Localized cancer is defined by SEER as cancer that is limited to the organ in which it began, without evidence of spread outside of the primary organ. For hepatic malignancies this is defined as no evidence of spread to regional or distant lymph nodes and no evidence of extrahepatic disease. Regional cancer is cancer that has spread beyond the original (primary) site to nearby lymph nodes or organs and tissues including nodal stations in or along the hepatic pedicle, inferior vena cava, hepatic artery, porta hepatis, and periportal basins. Distant cancer is cancer that has spread from the primary site to distant organs or distant lymph nodes (eg, para-aortic, peripancreatic, and retroperitoneal). For further information regarding staging of hepatic malignancies by SEER, please see Appendix C, available at http://seer.cancer.gov/manuals/2010/appendixc.html.

### Outcomes and predictor variables

Using SEER*Stat data, clinicopathologic information on patient age, sex, race, year of treatment, grade, cancer