Journal of Pediatric Surgery 50 (2015) 153–156

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Prognostic factors in fibrolamellar hepatocellular carcinoma in young people

David G. Darcy [a], Marcus M. Malek [a], Rachel Kobos [b], David S. Klimstra [c], Ronald DeMatteo [d], Michael P. La Quaglia [a,*]

[a] Pediatric Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY
[b] Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY
[c] Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
[d] Hepatopancreatobiliary Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

ARTICLE INFO

Article history:
Received 4 October 2014
Accepted 6 October 2014

Key words:
Fibrolamellar
Hepatocellular carcinoma
Pediatric
Adolescent
Prognostic

ABSTRACT

Background/purpose: Fibrolamellar hepatocellular carcinoma (FL-HCC) arises in pediatric/adolescent patients without cirrhosis. We retrospectively evaluated the impact of resection, nodal status, metastasis, and PRETEXT stage on overall survival (OS).

Methods: With IRB approval, we reviewed records of 25 consecutive pediatric patients with FL-HCC treated at our institution from 1981 to 2011. We evaluated associations between OS and PRETEXT stage, nodal involvement, metastasis, and complete resection.

Results: Median age at diagnosis was 17.1 years (range, 11.6–20.5). Median follow-up was 2.74 years (range, 5–9.5). Five (28%) patients had PRETEXT stage 1 disease, 10 (56%) had stage 2, 2 (11%) had stage 3, and 2 (11%) had stage 4 disease. On presentation, 17 (68%) patients had N1 disease, and 7 (28%) had parenchymal metastases. Complete resection was achieved in 17 (80.9%) of 21 patients who underwent resection. Five-year OS was 42.6%. Survival was positively associated with complete resection ($P = 0.003$), negative regional lymph nodes ($P = 0.044$), and lower PRETEXT stage ($P < 0.001$), with a trend for metastatic disease ($P = 0.05$).

Conclusions: In young patients with FL-HCC, lower PRETEXT stage and complete resection correlated with prolonged survival, while metastatic disease and positive lymph node status were associated with poor prognosis. Thus, we recommend complete resection and regional lymphadenectomy whenever possible.

Fibrolamellar hepatocellular carcinoma (FL-HCC) is a rare liver malignancy that arises in young people without a history of cirrhosis or viral hepatitis. It often presents with nonspecific symptoms and at an advanced stage. Currently, there are no effective treatments for metastatic disease. For regional disease, surgical resection remains the cornerstone of therapy. Some progress has been made by cooperative group studies (e.g. SIOPEL), which have gathered sufficiently large cohorts for appropriate analysis of prognostic factors [1]. However, analyses regarding patient prognoses and survival for this variant of traditional hepatocellular carcinoma have been inconclusive. To identify the most relevant prognostic factors for overall survival, we conducted a retrospective review of our institution's experience with fibrolamellar hepatocellular carcinoma in patients younger than 22 years.

1. Patients and methods

With institutional review board approval, we identified patients with FL-HCC who received care at Memorial Sloan Kettering Cancer Center (MSKCC) between December 1981 and June 2011. Patient records were reviewed for demographic data, disease characteristics, surgical outcomes and follow-up. Pathology specimens were reviewed to confirm the diagnosis of FL-HCC. Attending radiologist assessments of presurgical radiology were used to determine Pretreatment Extent of Disease (PRETEXT) staging and tumor dimensions [2,3]. Elevated alpha-fetoprotein was defined as >20 ng/mL.

The log-rank test was used to determine significant associations between PRETEXT stage, nodal involvement, and complete (R0) resection status. A P value of <0.05 was considered significant. Survival curves were generated using the Kaplan–Meier method in SPSS statistical software (version 20.0; IBM Inc., Armonk, NY).

2. Results

2.1. Patient characteristics

We identified 25 consecutive patients with FL-HCC, with a median age at diagnosis of 17.1 years (range, 11.6–20.5 years). Fourteen females and 11 males were identified, a ratio of approximately 1.3 to 1. The most common presenting symptom was pain (n = 18; 72%), followed by abdominal distention/mass (n = 11; 44%), anorexia/nausea (n = 8; 32%),

* Corresponding author at: Department of Surgery, Pediatric Surgical Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Suite H-1315, New York, NY 10065. Tel.: +1 212 639 7002; fax: +1 212 717 3373.
E-mail address: laquaglm@mskcc.org (M.P. La Quaglia).

http://dx.doi.org/10.1016/j.jpedsurg.2014.10.039
0022-3468/

and fever and jaundice (n = 5; 20%). One patient with jaundice presented with acute cholangitis, and one patient required percutaneous transhepatic cholecystostomy prior to chemotherapy. Two patients presented with amenorrhea, and none of the patients presented with precocious puberty. One patient's mother had undergone *in vitro* fertilization using exogenous estrogen. None of the patients had viral hepatitis, cirrhosis, or a family history of primary hepatobiliary malignancy. An elevated alpha-fetoprotein was present in 2 (2.3%) patients (22 and 33 IU/mL).

Nineteen (76%) patients had sufficient imaging data for PRETEXT staging. PRETEXT stage distribution was as follows: 5 (26%) patients with stage 1, 10 (53%) patients with stage 2, 2 (10.5%) with stage 3, and 2 (10.5%) with stage 4. Based on the American Joint Committee on Cancer (AJCC) 7th edition, there were 5 (20%) patients with AJCC stage I disease, 1 (4%) patient with stage II, 1 (4%) with stage III, and 18 (72%) patients with stage IV (11 IVA and 7 IVB). Tumors arose in the left lobe in 12 (48%), in the right lobe in 7 (28%), and 6 (24%) were central or had bilateral involvement (segments 4&5 or 4&8). The median tumor size on preoperative imaging was 11 cm (range 4.2–13.6). Seventeen patients (68%) had positive regional lymph nodes and 7 (28%) had distant parenchymal metastases at diagnosis.

2.2. Treatment

Thirteen (52%) patients received chemotherapy, 3 as neoadjuvant, 8 as adjuvant, and 2 as their sole treatment. An additional 5 (20%) patients received radiotherapy, administered as neoadjuvant therapy in 1 patient, as adjuvant therapy in 2, as the sole treatment in 1 patient, and as intraoperative therapy in 1. Patients who received adjuvant therapy all had local invasion (vascular or adjacent organs), nodal disease or parenchymal metastases. The patient who received intraoperative radiation therapy had 10 gray of direct therapy to retrocardiac lymph nodes.

Twenty-one (84%) patients underwent resection for cure, while four patients received biopsy and nonsurgical therapy as their primary treatment. Eight (32%) patients underwent a left lobectomy, 4 (16%) had a right lobectomy, 5 (20%) had a left trisegmentectomy, and 4 (16%) had a right trisegmentectomy. There were no intraoperative deaths.

Among the 21 patients who underwent resection for cure, a complete (R0) resection was achieved in 17 (80.9%) patients, R1 in 2 (9.5%), and R2 in 2 (9.5%). Information about vascular invasion was included in 19 pathology reports, and vascular invasion was evident in 12 (63.2%) of those patients. The median largest tumor dimension, as documented on pathology reports, was 10.5 cm (range 3.5–18). There were no patients with cirrhosis or evidence of intrinsic liver disease.

Median length of hospital stay was 8 days (range 5–14). Postoperative complications included four wound infections and one pulmonary embolus. Four patients were given total parenteral nutrition. The median length of follow-up for the entire cohort was 32.9 months (range 5.3–113.5). The median follow-up for surviving patients was 52.9 months (range 5.3–113.5).

2.3. Outcome

The 5-year rate of survival for the entire cohort was 42.6% (95% CI, 20–65.2) (Fig. 1). The 5-year rate of survival for the patients undergoing resection was 51.6% (95% CI, 26–77.2). Twelve patients had local recurrence in the group with R0 and R1 margin status, with a median disease-free survival of 15.6 months (range 4.3–56.6). Treatment of the recurrences consisted of reresection in 4, resection with chemoradiation in 5, chemotherapy only in 2, hepatic artery embolization in 1, and hepatic artery embolization with Sho-saiko-to (an herbal supplement that may reduce fibrosis and hepatocyte proliferation [4]) in 1. At the time of analysis, 8 (66.7%) patients with a local recurrence had died, while four survivors were alive at 2.96, 7.2, 9.3 and 9.5 years after initial resection.

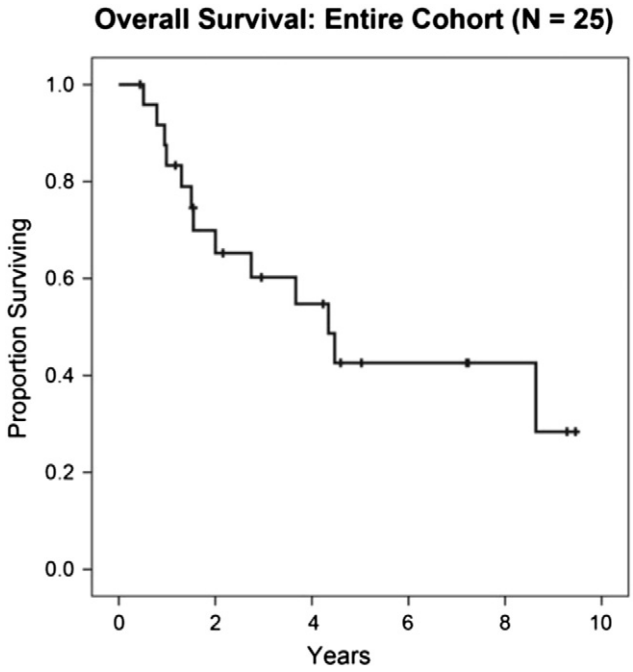

Fig. 1. Kaplan–Meier curve showing the overall survival rate for the entire cohort. Censored data points reflect the time that a patient was last seen; there were no known deaths during the study period.

2.4. Univariate analysis

Prolonged overall survival was found to be positively associated with R0 resection ($P = 0.003$) (Fig. 2), and lower PRETEXT stage ($P < 0.001$) (Fig. 3) and was negatively associated with positive regional lymph nodes ($P = 0.044$) (Fig. 4). There was a trend for decreased survival time with positive distant metastatic disease ($P = 0.05$). See Table 1 for the specific distribution of patients.

3. Discussion

Fibrolamellar hepatocellular carcinoma occurs at a rate of 0.2 per 100,000 population [5]. Despite its low incidence, it is an important primary liver tumor because it arises in young persons without any history of cirrhosis or viral hepatitis. Originally described by Edmondson *et al.* [6] in 1956 as a rare variant of traditional HCC, papers detailing clinical experience were not available until the 1980s. Currently, it is being investigated by multinational cooperative groups, in series of small cohorts, and in population-based reviews. Investigation of prognostic factors and the underlying biology of this rare tumor is hindered by epidemiological databases that lack comorbidities and adjuvant treatments, small series with variable treatment cohorts (especially for chemotherapy), and disparate outcome analyses relative to traditional HCC. Here, we define significant prognostic factors in the largest single-institution cohort of pediatric and adolescent patients with FL-HCC published to date. We focused our analysis on local factors in a cohort treated largely by surgical resection; we identified lower PRETEXT stage and negative resection margins to be positively associated with prolonged overall survival, while regional lymph node involvement and positive distant metastatic disease were negatively associated.

In our cohort, the median age was 17.1 years and the female-to-male ratio was 1.3 to 1. A preponderance of females among patients with FL-HCC has been noted in other studies, which is in contrast to the male predominance in previously published analyses of traditional HCC [5,7–9]. There were no patients with viral hepatitis, similar to other studies of FL-HCC in Western and European countries. In our cohort, 52% of patients received chemotherapy, including various