A Systematic Review: Treatment and Prognosis of Patients with Fibrolamellar Hepatocellular Carcinoma

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BACKGROUND: Fibrolamellar hepatocellular carcinoma (FLC) is a rare primary liver tumor presenting earlier in life than nonfibrolamellar hepatocellular carcinoma (NFL-HCC), with distinct epidemiologic and clinical characteristics. Although FLC is believed to have a better prognosis than NFL-HCC, data on treatment and prognosis are scarce. We performed a systematic review to investigate treatment options and clinical outcomes of patients with FLC.

STUDY DESIGN: The study is a systematic review of the literature and pooled analysis of individual patient data.

RESULTS: A total of 35 series were analyzed, reporting on 575 patients (52% female, elevated alpha-fetoprotein in 10%, cirrhosis in 3%, hepatitis B in 2%), most of whom were treated with partial hepatectomy (55%) or orthotopic liver transplantation (23%). Nineteen studies provided data on 206 individual patients with a median age of 21 years and tumor size of 12 cm. Median overall survival (OS) was 39 months; 1-year, 3-year, and 5-year OS rates were 85%, 53%, and 44%, respectively. For patients treated with liver resection, median OS was 18.5 years and 1-year, 3-year, and 5-year OS were 93%, 80%, and 70%, respectively. Based on data from 15 studies, FLC appeared to follow a relatively indolent course compared with NFL-HCC.

CONCLUSIONS: Patients with FLC treated with partial hepatectomy have excellent long-term survival, with 5-year overall survival reaching 70%. Patients fared worse with the use of other therapeutic options including chemotherapy, intra-arterial therapy, and transplantation, although data directly comparing resection vs transplantation were limited. (J Am Coll Surg 2012;215: 820–830. © 2012 by the American College of Surgeons)

Fibrolamellar hepatocellular carcinoma (FLC) is a rare primary malignant tumor of the liver, first described in 1956.[1] Unlike conventional nonfibrolamellar hepatocellular carcinoma (NFL-HCC), FLC typically affects younger patients without underlying liver disease (eg, viral hepatitis or cirrhosis), and women are affected as much as men. The age-adjusted incidence rate was estimated at 0.02 per 100,000 in the US (about 100 times less common than NFL-HCC).[2-5] Distinct laboratory characteristics usually include normal or slightly elevated serum levels of aspartate and alanine aminotransferases[3,4,6,7] and alpha-fetoprotein.[2-5,8] In contrast, there is elevated serum unsaturated vitamin B12-binding capacity, which may also be useful in monitoring disease progression.[2,3,9-13] Serum neurotensin has also been noted to be elevated in some patients.[14-16]

Fibrolamellar hepatocellular carcinoma has unique pathologic and radiologic characteristics. In general, it is a vascular tumor with prominent fibrosis. Microscopically, FLC appears as a well-differentiated tumor comprised of large polygonal cells with large nuclei and nucleoli, and abundant eosinophilic cytoplasm, arranged in lamellar bands of collagen fibers.[1-4,6] Evidence suggests that lower mitotic index and normal hepatocyte growth factor receptor levels indicate a relatively indolent course compared with NFL-HCC, and may in part explain the suspected weak response to standard chemotherapeutic agents,[17] although this has been disputed.[18] On CT scan, FLC is often a hypodense, well-demarcated mass with a central scar, and it exhibits marked enhancement after administration of contrast. Calcifications within the lesion may be evident on CT scan or plain abdominal x-ray.[19-21]

Existing evidence regarding the treatment and prognosis of FLC is scarce and is limited mainly to case series and small cohorts. It is generally believed that FLC carries a favorable prognosis compared with NFL-HCC; however, the better prognosis is often attributed to the younger age and

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Abbreviations and Acronyms

FLC = fibrolamellar hepatocellular carcinoma
NFL-HCC = nonfibrolamellar hepatocellular carcinoma
OS = overall survival

lower comorbidity of the affected patients; others propose that FLC has an inherent indolent course compared with NFL-HCC.[2-4] In this context, we sought to systematically review the available evidence on treatment options and prognosis of patients with FLC, as well as the literature comparing the prognosis of patients with FLC vs NFL-HCC. In addition, we performed a pooled analysis of the available data.

METHODS

Literature search

A systematic search of the literature was performed in the Scopus database in February 2012. The Scopus database is the largest abstract and citation database of peer-reviewed literature, offering about 20% wider coverage than the Web of Science and including 100% Medline coverage.[22,23] The applied search pattern was: (fibrolamellar) AND (outcome OR survival OR prognosis OR mortality). References of the relevant articles, including review studies, were also hand-searched in an attempt to identify additional eligible studies. No limitation on the year of publication was set.

Study selection

The literature was searched and we assessed the studies for potential inclusion in this review. Any study reporting on the clinical outcomes of patients with pathologically confirmed FLC was considered eligible for inclusion, regardless of the potential treatment. Studies assessing patients with FLC without reporting their clinical outcomes were excluded, as were small case series reporting on 5 patients or fewer. Only studies published in English were assessed. Unpublished studies reported as abstracts in conferences were not included in this review.[24]

Data extraction

Data were extracted regarding study setting, period, and design, population characteristics (sample size, age, sex, cirrhosis, viral hepatitis B and C seropositivity, serum alpha-fetoprotein, tumor size, presence of extrahepatic metastasis), treatment of primary FLC, clinical outcomes (perioperative mortality, overall survival, disease-free survival, recurrence, time to recurrence), and the prognostic factors of survival or recurrence. Whenever available, individual patient data were extracted regarding the age, tumor size, treatment, follow-up, and clinical outcomes (alive without disease, alive with disease, or dead) of each patient. Patients diagnosed with FLC during autopsy or those who had no follow-up were excluded. For studies comparing the prognosis of patients with FLC vs NFL-HCC, in addition to the above, data were also extracted regarding the variables that were matched between the compared groups.

In the event that multiple studies reported on overlapping patient populations (for example 2 studies from the same institution), only data from the largest study, or (if sample sizes were similar) the one with the longer follow-up were analyzed. Every effort was made to identify overlapping populations by recording each study's investigators as well as their affiliated institutions.

Data synthesis and statistical methods

Data extracted from each study were analyzed and presented in the form of tables. When a study did not report on one of the outcomes we examined but provided individual patient data for all patients, individual analyses were performed to estimate the median follow-up and/or overall survival (1-year OS, 3-year OS, 5-year OS, and median/mean OS) of each study using the survival life tables and the Kaplan-Meier method. In addition, individual patient data were pooled from all applicable studies and combined, comprising a new cohort of patients with FLC. The actuarial OS of this new cohort of patients was also calculated by the survival life tables and Kaplan-Meier method, and survival curves were compared using the log-rank test. Nonparametrically distributed continuous variables (ie, age) were compared among the groups using the Mann-Whitney or Kruskal-Wallis tests, as appropriate. All analyses were performed using the SPSS 17.0 software (SPSS Inc). A $p < 0.05$ was considered statistically significant.

RESULTS

The search process initially generated 453 articles. The full-text manuscript was reviewed for 161 articles, 39 of which were eventually included in this review (Fig. 1).[5-8,10,15,25-57] All but 1 study were retrospective analyses of patient cohorts or case series; the remaining study was a post-hoc analysis of a phase II trial.[45]

Our new historical cohort – synthesis of individual patient data

Nineteen studies reported sufficient individual patient data and 206 patients were included in our new historical cohort.[6,7,10,15,25,26,29,30,32,35,37,39-41,43,45,48,50,51] The median age of the patients was 21 years (range 1 to 62 years) and median tumor size was 12 cm (range 4 to 20 cm). Median follow-up of the patients was 26 months (range 0.4 to 222 months). Overall, about 80% of partial hepatectomies were performed before 1995 (range 1963 to 2008), and

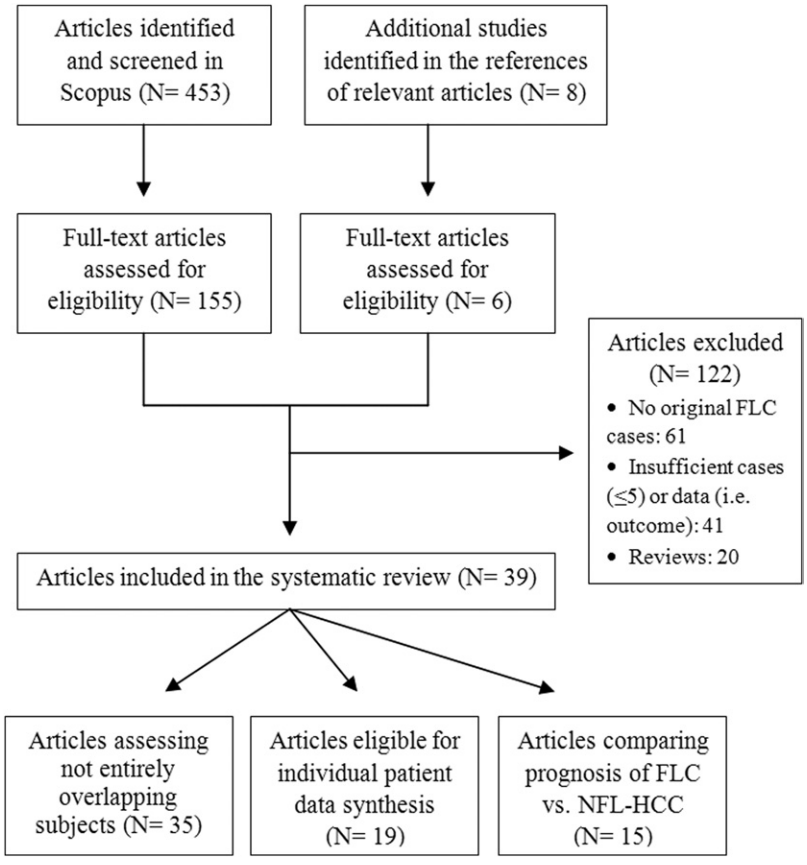

Figure 1. Flow diagram of reviewed studies. FLC, fibrolamellar hepatocellular carcinoma; NFL-HCC, nonfibrolamellar hepatocellular carcinoma.

almost 90% of liver transplantations were performed before 1990 (range 1963 to 1995). There was no difference in the age or tumor size among patients treated with partial hepatectomy or liver transplantation.

Patient prognosis, stratified by treatment, is presented in detail in Table 1. The OS rates after 1, 3, and 5 years were 85%, 53%, and 44%, respectively, with a median OS of 39 months. Patients undergoing surgical treatment had longer OS than those who were not surgical candidates (median OS 74 vs 20 months, $p < 0.001$), and those undergoing a partial hepatectomy (Fig. 2) survived longer than those undergoing liver transplantation (median OS 222 vs 32 months, $p < 0.001$).

Review of published series

Of the 39 included studies, 4 series[26,47,51,57] reported on patients who were also completely assessed in larger or more recent studies.[27,29,33,48] Therefore, these 4 studies were excluded from the analysis. The 35 remaining studies reported on a total of 575 patients. Women comprised ap-

Table 1. Prognosis of the New Historical Cohort, Stratified by Treatment

	Patients		Prognosis			
Variable	**n**	**%**	**1-y OS, %**	**3-y OS, %**	**5-y OS, %**	**Median OS, mo**
Any treatment*	206	61	85	53	44	39
Surgical treatment	125	44	91	69	59	74
Partial hepatectomy	90	17	93	80	70	222
Liver transplantation	35	10	86	42	34	32
Nonsurgical treatment	21	10	81	12	0	20

Median follow-up of the patients was 26 months.
*Specific treatment data were not available for 60 of 206 (29%) patients.
OS, overall survival

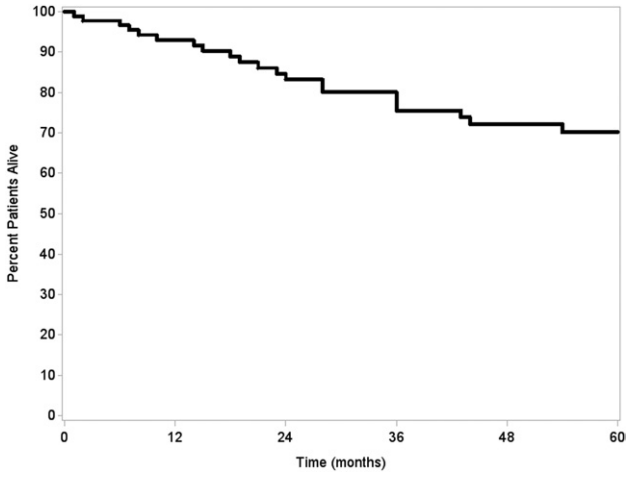

Figure 2. Overall survival of patients with fibrolamellar hepatocellular carcinoma treated with partial hepatectomy (n = 90).

proximately half the group (n = 225 of 431; 52%), the median age of patients ranged from 14 to 33 years, and the alpha-fetoprotein was elevated in 10% (27 of 266) of patients. Eight of 287 (3%) patients had underlying cirrhosis, 2% (5 of 255) were positive for hepatitis B, and 1% (2 of 147) were positive for hepatitis C (Table 2).

Most of the patients were considered to have resectable disease at presentation; 55% (268 of 484) underwent a partial hepatectomy, and 23% (109 of 484) underwent liver transplantation. Chemotherapy was sometimes administered as an adjunct to surgical treatment; it was also administered as palliative treatment in some cases. Radiation, intra-arterial therapy, and ablation were seldom used. One-year OS ranged from 62.5% to 100%, 3-year OS from 14% to 90%, and 5-year OS from 0% to 76%; median OS ranged from 14 to 112 months. Seven studies reported specific survival data on 81 patients managed with partial hepatectomy; 6 studies reported on 79 patients who underwent liver transplantation for management of the FLC. Survival after 1, 3, and 5 years ranged from 82% to 100%, 58% to 100%, and 58% to 82%, respectively, for hepatectomy, and 63% to 100%, 43% to 75%, and 29% to 55%, respectively, for transplantation. Recurrence varied among the studies depending on the length of follow-up (range 33% to 100%) and the type of operation performed.

Eight studies assessed prognostic factors of OS or recurrence-free survival in patients with FLC, although most had a considerably low statistical power due to small sample size. A multivariate analysis was used in only 1 study, and suggested that older age and resectability of tumor were independent predictors of OS.[41] In the remaining studies, univariate analyses indicated that impaired liver function,[28] larger tumor size,[28] multiple tumor foci,[50] presence of comorbidities,[28] and advanced stage of disease (including lymph node or distant metastases and vascular invasion)[7,34,49,50,53] were associated with either worse OS or recurrence-free survival. Of note, 1 study found that administration of chemotherapy was also associated with earlier intrahepatic recurrence of FLC.[49]

Comparative prognosis of patients with FLC vs NFL-HCC

Fifteen articles compared the prognosis of patients with FLC vs NFL-HCC, reporting on a total of 229 patients with FLC and 8,959 patients with NFL-HCC.[5,26,28-30,32-36,38,40,45,54,56] Characteristics and outcomes of the studies are presented in detail in Table 3. It should be noted that most of the studies did not have sufficient statistical power to detect potential differences due to small sample size. In 2 studies, including the largest-to-date, population-based cohort study, patients with FLC and NFL-HCC were matched for several variables, including age, sex, and stage of disease;[5,28] both studies estimated a significantly longer survival of patients with FLC than NFL-HCC. Seven additional studies were matched for liver functional status (absence of cirrhosis) or age and/or stage of disease.[26,29,30,34,35,40,56] The results of those studies were controversial; in general, 4 studies detected a survival benefit in the FLC group, while the remaining 3 did not. One study stratified patients only by treatment modality; a longer OS was reported in patients with FLC vs NFL-HCC undergoing partial hepatectomy, but there was no difference in patients receiving liver transplant.[33] Five studies did not use any matching criteria, with varying results.[32,36,38,45,54]

DISCUSSION

Although FLC is not common, it constitutes one of the major primary liver tumors in younger patients. Clinical data regarding treatment and prognosis of patients with FLC are scarce, probably due to the rarity of this tumor, and are limited to case series and small cohorts. In this study, we pooled individual patient data from previous reports to form the larger cohort of patients with FLC to facilitate identification of trends, possible prognostic factors, and to better understand the prognosis of FLC patients. This study is important because by systematically reviewing and pooling the available data, we amassed roughly twice as many patients compared with any previous report. In doing this, we were able to provide a broad overview of the available literature on FLC and better define the published data on the treatment and prognosis of patients with FLC.

In analyzing individual patient data from the currently available literature, we noted that the 5-year survival of all patients with FLC was 44%. Outcomes after surgical resec-

Table 2. Characteristics of Reviewed Studies, Focusing on Treatment and Prognosis of Patients with Fibrolamellar Hepatocellular Carcinoma

Study, y	Study characteristics			Patient characteristics			Disease characteristics			Treatment	Prognosis				
	Setting, study period	n	F/U, mo	Age,y	Female, %	Cirrhosis, %	Tumor size, cm	Hepatitis	↑ AFP		1-y OS, %	3-y OS, %	5-y OS, %	OS mo	RR
El-Serag 2004	Multicenter (1986–2000)	68	NR	33	51	NR	NR	NR	NR	PHx or OLT 32/68	73	NR	31	NR	NR
Pinna 1997	Denver, CO and Pittsburgh, PA (1968–1995)	41	58 ± 3	25 (9–66)	44	7	13 (3–25)	HBV: 0 HCV: 6	11	PHx 28/41, OLT 13/41, chemo 16/41	~98	~72	66	126.9†	27/41
Stipa 2006	New York, NY (1986–2003)	41	34	27 (14–72)	59	0	9 (3–17)	HBV: 0 HCV: 0	7	PHx 28/41	100 (PHx)	90 (PHx)	76 (PHx)	112 (PHx)	17/28
Ichikawa 2000	Pittsburgh, PA (1989–1997)	40	NR	29† (15–65)	55	NR	13† (3–27)	HBV: 0 HCV: 3	8	PHx 21/40, OLT 4/40	NR	NR	NR	NR	13/17
Penn 1991	Multicenter (1968–1991)	33	NR	NR	NR	NR	NR	NR	NR	OLT 33/33	~85	~60	55	NR	13/33
Craig 1980*	Los Angeles, CA, (1918–1973)	23	20.5 (6–180)	22 (5–69)	48	15	NR	HBV: 25 HCV: NR	0	PHx 11/20, chemo 11/20, rad 1/20	80	26	26	21 (CI: 14.9–27.1)	NR
Iwatsuki 1991	Denver, CO and Pittsburgh, PA (1980–1989)	22	NR	NR	NR	NR	NR	NR	NR	PHx 12/22 OLT 10/22	10080	8350	6538	84.9† ± 15.8 51.4† ± 14.4	NRNR
Ringe 1992*	Hannover, Germany (1974–1988)	20	28 (1–63)	21 (13–38)	45	0	11.5 (4–20)	HBV: 10 HCV: NR	0	PHx 14/20, OLT 6/20	80	51	37	44.5 (1–63)	12/20
El-Gazzaz 2000	Birmingham, UK (1985–1998)	20	NR	27 (12–69)	65	0	13 (2–22)	HBV: 0 HCV: NR	0	PHx 11/20 (2/11 chemo)OLT 9/20 (2/11 chemo)	10090	10075	6550	62	9/20
Kakar 2005	San Francisco, CA, Rochester, MN, and New Haven, CT, (1987–2000)	20	NR	27† (16–47)	45	NR	NR	NR	23	NR	NR	NR	45	NR	NR
Berman 1988*	Pittsburgh, PA (1981–1987)	19	32 (2–120)	25 (14–85)	32	11	13.4† (7–20)	HBV: 0 HCV: 0	27	PHx 12/19 (2 chemo, 1 rad), OLT 5/19 (1 chemo), chemo only 1/19	87	58	58	80† (CI: 52.6–107.4)	NR
Epstein 1998	Baltimore, MD (1985–1990)	17	NR	24 (16–32)	53	0	NR	HBV: 0 HCV: NR	6	Rad 16/17 (10 chemo, 4 chemo + IAT)	~64	~23	NR	25	NA
Nagorney 1985	Rochester, MN (1950–1982)	16	NR	26 (17–75)	44	0	13† (6–22)	HBV: 14 HCV: NR	17	PHx 12/16	~86	~42	~33	~33	9/12

(Continued)

Table 2. Continued

Study, y	Study characteristics			Patient characteristics			Disease characteristics			Treatment	Prognosis				
	Setting, study period	n	F/U, mo	Age,y	Female, %	Cirrhosis, %	Tumor size, cm	Hepatitis	↑ AFP		1-y OS, %	3-y OS, %	5-y OS, %	OS mo	RR
Moreno-Luna 2005*	Mexico City, Mexico (1990–2003)	15	26 (1–67)	23† (17–45) ± 2.6	NR	0	NR	HBV: 0 HCV: 0	NR	PHx 10/15	66	40	26	30 ± 6	NR
Wood 1998	Houston, TX (1960–1983)	15	NR	26† (9–47) ± 10	73	0	10†	HBV: 14 HCV: NR	33	PHx 9/15 (complete in 7), chemo only 5/15, rad 1/15	NR	NR	25	32	NR
Haas 1989*	Multicenter (1973–1984)	14	18 (1–65)	NR	NR	NR	NR	NR	NR	PHx 10/14 (complete 4)	64	41	23	13	NR
Klintmalm 1998	Multicenter (1992–1997)	12	NR	NR	NR	NR	NR	NR	NR	OLT 12/12	100 @2yr	53 @4yr	NR	NR	NR
Katzenstein 2003*	Multicenter (1989–1992)	10	54 (3–151)	14 (1–16)	NR	NR	NR	NR	11	PHx 5/10, chemo 10/10	80	60	50	45	4/10
Stevens 1995	Rochester, MN (1987–1993)	10	NR	22 (16–55)	40	NR	20 (7–22)	NR	NR	PHx 7/10, palliative PHx 2/10	5/10 died after OS of 29 mo† 3/10 alive after f/u of 40 mo†				7/7
Farhi 1983*	Denver, CO (1963–1981)	10	21 (0–96)	20 (9–31)	40	0	10.5 (4–22)	NR	NR	PHx 6/10 (3 chemo, 1 rad), OLT 2/10, chemo only 1/10	79	67	50	14.2† (CI: 30.1–85.6)	NR
Maniaci 2009*	London, UK (1982–2004)	10	78 (23–222)	24 (16–50)	40	0	14.5 (8–20)	HBV: 0 HCV: 0	33‡	PHx 10/10 (chemo 5/10)	100	90	58	111.6 (CI: 36–222)	10/10
Hemming 1997*	Toronto, ON, Canada (1982–1995)	10	101† ± 55	31† (20–56) ± 11	50	0	8† ± 4	HBV: 0 HCV: NR	10	PHx 9/10, chemo 1/10	100	80	70	NR	6/9
Soreide 1986*	London, UK (1980–1985)	9	11 (2–48)	20 (16–31)	67	0	13 (7–18)	HBV: 0 HCV: NR	11	PHx 7/9 (IAT 1/7), chemo only 2/9	86	61	61	35† (CI: 19.8–50.2)	4/7
Patt 2003*	Houston, TX (1997–2000)	9	23 (3–50)	19 (16–33)	67	0	NR	HBV: 0 HCV: 0	NR	Chemo 9/9 (3 PHx)	100	36	NA	23.1 (CI: 10.3–35.9)	NR
Pichlmayr 1997*	Hannover, Germany (1972–1995)	8	NR	NR	NR	NR	NR	NR	NR	OLT 8/8	63	50	38	35.1	NR
Wang 1999	Beijing, China (1987–1998)	8	NR	NR	NR	NR	NR	NR	NR	PHx 7/8 (IAT 4/7), IAT only 1/8	88	50	25	NR	NR
Ng 2009*	Sydney, Australia (1990–2008)	8	37 (1–61)	NR	NR	NR	>10	NR	NR	PHx 8/8 (± ablation)	88	58	58	42.6† (CI: 26–59.1)	NR
Ihde 1985*	Bethesda, MD and Washington DC (1973–1981)	7	24 (14–37)	86 < 25yr	86	0	NR	HBV: 0 HCV: NR	0	Chemo 7/7	100	14	0	24 (14–37)	NA

(Continued)

Table 2. Continued

Study, y	Study characteristics			Patient characteristics			Disease characteristics			Treatment	Prognosis				
	Setting, study period	n	F/U, mo	Age, y	Female, %	Cirrhosis, %	Tumor size, cm	Hepatitis	↑ AFP		1-y OS, %	3-y OS, %	5-y OS, %	OS mo	RR
Marcos-Alvarez 1996	Boston, MA (1988–1995)	7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	27.2	NR
Paradinas 1982*	London, UK (NR)	7	14 (6–50)	20 (15–30)	57	0	NR	NR	0	PHx + chemo 2/7, IAT + chemo 3/7, chemo only 2/7	85	28	28	23.3† (CI: 8.9–37.7)	NR
McPeake 1993 & O'Grady 1988*	London and Cambridge, UK (1968–1990)	7	27 (13–95)	23† (13–33)	83	NR	NR	NR	NR	OLT 7/7 (± chemo)	100	43	29	27 (CI: 24.4–29.6)	5/6
Bhaijee 2009	Cape Town, S Africa (1990–2008)	7	61 (7–69)	21 (19–42)	29	0	12 (4–17)	HBV: 0 HCV: 0	0	PHx 6/7, IAT 1/7	86	71	57	60	6/6
Martinez Isla 1997*	London, UK (1989–1996)	6	18 (6–78)	19.5 (17–24)	83	NR	9† ± 2.6	NR	50‡	PHx 6/6, chemo 1/6, IAT 1/6	82	82	82	11† (CI: 44.5–87.5)	2/6
Vauthey 1995	New York, NY (1970–1992)	6	NR	NR	NR	NR	NR	NR	NR	PHx 6/6	NR	NR	75	NR	NR

For continuous variables (F/U, patient age, tumor size, OS) the median values are reported, unless indicated otherwise; parentheses and the "±" symbol indicate range of values and standard deviation, respectively. Four published series[26,47,51,57] reported on patients who were also completely assessed in more recent studies[5,7,9,33,48], those 4 studies have not been tabulated.

*Individual patient data were available in this study.

†Represent mean values (not median).

‡Mildly elevated AFP values.

AFP, alpha-fetoprotein; chemo, chemotherapy; F/U, follow-up; IAT, intra-arterial therapy; NA, not applicable; NR: not reported; OLT, orthotopic liver transplantation; OS, overall survival; PHx, partial hepatectomy; rad, radiation therapy; RR, recurrence rate.

tion, however, were considerably better (70%). Whether prognosis after surgery is better among FLC vs NFL-HCC patients has been controversial. Our collective analysis of available studies to date did suggest that FLC appears to follow a more indolent course compared with NFL-HCC. Of note, the difference in prognosis did not seem to be attributed solely to the younger age and lower comorbidity of patients with FLC. In the study by El-Serag and Davila,[5] which was one of the largest population-based studies available, the authors concluded that patients with FLC were twice as likely as patients with NFL-HCC to survive to 5 years, even after controlling for factors such as age, sex, race, stage of disease, and curative intent of treatment. In looking more globally at other published data, about one-half of the studies we identified that investigated surgery of FLC controlled for age, the presence of cirrhosis, and other factors.[5,26,28-30,34,35,40,56] Most of those studies were notable for similarly showing a more favorable prognosis for FLC patients. The fact that these studies actually reported a difference in outcomes for FLC vs NFL-HCC was particularly notable because most of these studies contained very small number of patients, making them susceptible to being underpowered to detect a difference. In such circumstances, although negative findings (such as lack of difference in prognosis) are not of particular importance due to high probability of a type II error, positive findings (such as evidence of difference in prognosis) can be more safely regarded.[58,59] Although several studies attempted to identify prognostic factors of recurrence and survival after resection, the low sample size of patients included in individual studies did not allow for synthesis of these data to derive evidenced-based conclusions.

One interesting finding in this study was that compared with patients who underwent hepatic resection, patients who underwent transplantation appeared to fare considerably worse. Data comparing resection vs transplant were limited, so such comparisons need to be interpreted with caution. The observed worse survival among patients who underwent transplantation was probably multifactorial. Patients who underwent transplantation were more likely to have been treated in an earlier time period (eg, before 1990) compared with patients treated with liver resection. Given that the more stringent Milan criteria for liver transplantation were not proposed and subsequently adopted until the late 1990s, it is not surprising that outcomes for patients with advanced FLC transplanted before 1990 were poor.[60] In fact, data from the European Liver Transplant Registry indicated a 5-year survival rate of only 22% for liver transplantations (for any cause) performed before 1985; survival has improved over time due to the adoption of more strict transplantation criteria and improvements in

Table 3. Overview of Studies Comparing Prognosis of Patients with Fibrolamellar Hepatocellular Carcinoma vs Conventional Hepatocellular Carcinoma

Study, y	Study design	FLC vs HCC, n	Groups matched for:	Outcomes
El-Serag 2004	Population-based cohort	68 vs 7,896	Age, sex, race, stage of disease, curative intent, time of diagnosis	1-y OS: HR 0.36 (CI: 0.22 – 0.58) (NFL-HCC reference) 5-y OS: HR 0.54 (CI: 0.39 – 0.74) (NFL-HCC reference)
Epstein 1999	Case-control	17 vs 11	Age, sex, Karnofsky status, tumor size, "good risk group", metastases, AFP	OS, median (mo): 14 vs 7.7 ($p < 0.001$)
Kakar 2005	Retrosp ectivecohort	20 vs 32	Noncirrhotic liver Noncirrhoticliver + stage of disease	5-y OS: 45% vs 56% ($p = 0.4$) 5-y OS: 62% vs 58% (NS)
Wood 1998	Retrospective cohort	15 vs 61	None Noncirrhotic liver Noncirrhotic liver + resectable disease	OS, median (mo): 32 vs 7 ($p < 0.001$) OS, median (mo): 50 vs 9 ($p < 0.001$) OS, median (mo): 50 vs 7 ($p = 0.048$)
McPeake 1993	Retrospective cohort	6 vs 16	Noncirrhotic liver	1-y OS: 100% vs 50% 3-y OS: 50% vs 6.3% 5-y OS: 33% vs 6.3% ($p = 0.004$)
Bhaijee 2011	Retrospective cohort	6 vs 16	Noncirrhotic liver	OS, median (mo): 61 (7–69) vs 39 (14–159) 5-y OS: 67% vs 38% ("better prognosis")
Haas 1989	Retrospective cohort	14 vs 14	Stage of disease (in children) Stage of disease	OS, median (mo): 13 vs 7 ($p = 0.51$) OS: HR 1.6 (FLC reference) ($p = 0.34$) 5-y EFS: $p = 0.96$ for stage I, $p = 0.31$ for stage III, and $p = 0.10$ for stage IV
Katzenstein 2003	Retrospective cohort	10 vs 36	None (in children and adolescents)	OS, median (mo): 13.6 vs 3.3 ($p = 0.16$) 5-yr OS, mean ± SD (mo): 30% ±15% vs 18% ±7% ($p = 0.18$) 5-yr EFS, mean ± SD (mo): 30% ±15% vs 14% ±6% ($p = 0.18$)
Farhi 1983	Retrospective cohort	10 vs 13	None (in "young people")	DFS at last f/u: 5/10 vs 0/13 ($p < 0.01$)
Iwatsuki 1991	Retrospective cohort	22 vs 159	Partial hepatectomy Liver transplantation	OS, mean ± SD (mo): 84.9 ± 15.8 vs 42.9 ± 6.5 ($p = 0.028$) OS, mean ± SD (mo): 51.4 ± 14.4 vs 47.5 ± 5.5 ($p = 0.7$)
Patt 2003	Trial; post-hoc analysis	9 vs 34	None	OS, median (mo): 23.1 (CI: 10.3–35.9) vs 15.5 (CI: 8.5–22.5) (NS)
Klintmalm 1998	Retrospective cohort	12 vs 410	None	4-y OS: 53% vs 47% ($p = 0.07$)
Marcos-Alvarez 1996	Retrospective cohort	7 vs 132	None	OS, median (mo): 27.2 vs 11.1
Vauthey 1995	Retrospective cohort	6 vs 99	None	5-y OS: 75% vs 41% (NS) HR 0.55 (CI: 0.14–2.23) (NFL-HCC reference)
Ihde 1985	Retrospective cohort	7 vs 30	None	OS, median (mo): 24 vs 3 ($p = 0.002$)

AFP, serum alpha-fetoprotein; CI, 95% confidence intervals; DFS, disease-free survival; EFS, event-free survival; FLC, fibrolamellar hepatocellular carcinoma; f/u, follow-up; HCC, hepatocellular carcinoma; HR, hazard ratio; NS, not statistically significant; OS, overall survival.

immunosuppression, as reflected in data from the registry (5-year survival: 1985 to 1989, 53% vs 1990 to 1994, 65% vs 1995 to 2000, 72%).[61] The role of transplantation for FLC, however, remains ill defined. Unlike many patients with NFL-HCC who also have underlying cirrhosis, for whom a transplant will have a "dual effect" of treating both the tumor and the cirrhosis, most FLC patients do not have underlying hepatic parenchymal damage and therefore lack the competing risks of cancer vs cirrhosis. So it has been suggested that although patients with FLC have better outcomes than patients NFL-HCC after liver resection, such difference may not be evident among FLC vs NFL-HCC patients undergoing transplantation.[33] Other studies, however, have suggested that transplantation may indeed have a role in treating FLC and lead to better outcomes.[36,40]

This study had a number of limitations. Available study data on FLC were retrospective in nature and most studies included a very small sample size of patients. Due to this limitation, we were unable to analyze and report specific factors associated with prognosis. One such factor was the impact of systemic therapy. We sought to provide specific data whenever possible, but in many cases the original papers or data were not specific regarding this matter. The purpose of this study, however, was to synthesize the data from each of these small individual studies into a new larger "cohort." In doing this, we were able to provide a global overview of the available data on the epidemiology, treatment, overall relative prognosis, and recurrence patterns of patients with FLC. Although the impact of publication bias was not formally assessed, such bias seems unlikely given that all "positive" or "negative" reports on FLC are likely to have been published, as indicated by the high number of published case series and case reports.

CONCLUSIONS

In conclusion, patients with FLC treated with surgical resection had favorable outcomes, with a reported 5-year survival ranging from 58% to 82%. Prognosis after surgical resection was better for patients with FLC vs NFL-HCC, even after controlling for several potential confounders. Despite the durable long-term survival associated with hepatic resection, recurrence was common. Several studies noted that surgical treatment of recurrence may result in prolonged survival.[7,37,62]Although liver transplantation may be another therapeutic option, data on transplantation for FLC are largely from the 1980s and early 1990s, and reported results have been poor. Given the rarity of FLC, future efforts should be aimed at building prospectively collected multi-institutional registries so that more robust clinical and translational data can be collected to better define treatment and prognosis of patients with FLC.

Author Contributions

Study conception and design: Mavros, Mayo, Hyder, Pawlik

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Analysis and interpretation of data: Mavros, Mayo, Hyder, Pawlik

Drafting of manuscript: Mavros, Mayo, Hyder, Pawlik

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