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General Surgery

Fibrolamellar hepatocellular carcinoma at a tertiary centre in South Africa

A case series

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Abstract

Background. Fibrolamellar carcinoma (FLC) is an uncommon malignant tumour of hepatocyte origin that differs from hepatocellular carcinoma (HCC) in aetiology, demographics, condition of the affected liver, and tumour markers. Controversy exists whether FLC demonstrates a more favourable prognosis than typical HCC. A review of existing literature reveals a dearth of FLC data from the African continent.

Methods. We utilised the prospective liver resection database at Groote Schuur Hospital to identify all patients who underwent surgery for FLC between 1990 and 2008.

Results. Seven patients (median age 21 years, range 19 - 42, 5 men, 2 women) underwent surgery for FLC. No patient had underlying liver disease or an elevated alpha fetoprotein (AFP) at either initial presentation or recurrence. Six patients had a solitary tumour at diagnosis (mean largest diameter = 12cm), and underwent left hepatectomy (*N*=2), right hepatectomy (*N*=1), extended right hepatectomy (*N*=1), and segmentectomies (*N*=2). Three patients underwent a portal lymphadenectomy for regional lymphatic tumour involvement. One patient with advanced extrahepatic portal nodal metastasis was unresectable. No peri-operative deaths occurred. Recurrence occurred post resection in all 6 patients. Median overall survival was 60 months, and overall 5-year survival was 4 out of 7 (57%). Post-resection survival (*N*=6) was 61 months, with a 5-year survival rate of 4 out of 6 (67%). The patient with unresectable disease survived 38 months after tumour embolisation with Lipiodol.

Conclusion. Our series suggests that despite (i) a high resection rate of solitary lesions with clear tumour resection margins, and (ii) absence of underlying liver disease, FLC has a high recurrence rate with an ultimately poor clinical outcome. These findings concur with recent international experience of FLC.

Fibrolamellar carcinoma (FLC) is an uncommon malignant tumour of hepatocyte origin that differs from hepatocellular carcinoma (HCC) in aetiology, demographics, condition of the affected liver, tumour markers, and prognosis.[1,2] In the past, FLC was termed eosinophilic hepatocellular carcinoma with lamellar fibrosis, hepatocellular carcinoma with polygonal cell type and fibrous stroma, eosinophilic glassy cell hepatoma, and fibrolamellar oncocytic hepatocellular carcinoma.[2] First described by Edmondson in 1956, the distinct clinical and pathological features of FLC were not fully appreciated until 1980.[2,3]

If amenable, FLC, like most localised hepatic malignancies, is best treated by complete surgical resection.[2,4-6] Positive prognostic factors include resectability, absence of lymph node metastases at presentation, normal serum liver enzymes, early clinical stage, and absence of vascular invasion or thrombosis.[7,8] Regional lymphadenopathy and isolated metastases are not an obstacle to resection.[2] A major negative prognostic factor is cirrhosis, which is associated with typical HCC in 90% of patients, but is rarely seen in FLC patients.[1,7] Controversy exists whether, cirrhosis and resectability notwithstanding, FLC demonstrates a more favourable prognosis than typical HCC. In this study, we assessed the clinical outcome of patients with FLC who underwent liver resection at a tertiary centre in South Africa.

Patients and methods

We used the prospective liver resection database at Groote Schuur Hospital to identify patients who underwent surgery for HCC between 1990 and 2008. We collected clinical information from the database, hospital notes, laboratory and pathology reports, and patient interviews. The following data were reviewed: patient demographics, imaging studies including ultrasound and computed tomography (CT), serology, surgical procedures, pathological specimens, evidence of recurrence, and outcome. Follow-up was obtained by personal communication with patients, patients' families, and referring physicians. We used the Couinaud nomenclature to define the extent of the surgical procedures: an extended

right hepatectomy is resection of segments 4 - 8; an extended left hepatectomy is resection of segments 2, 3, 4, 5 and 8; a right hepatectomy is resection of segments 5 - 8; and a left hepatectomy is resection of segments 2 - 4.[9]

Results

Over an 18-year period, 7 patients with FLC were identified. Median age was 21 years; 5 patients were men (Table I). None of the FLC patients had underlying liver disease (cirrhosis/HepB/HepC) or an elevated alpha-fetoprotein (AFP) at either initial presentation or recurrence (Table II). Our patients either presented with nonspecific abdominal pain or discomfort, or the tumours were discovered incidentally during investigation of an unrelated medical condition. The average tumour size was 12 cm (range 4 - 17) (Fig. 1).

TABLE I. PATIENTS AND FIBROLAMELLAR CARCINOMA CHARACTERISTICS

Characteristics	FLC (*N*=7)
Median age, yrs (range)	**21 (19 - 42)**
Male	**5 (71%)**
Underlying liver disease (cirrhosis/hepatitis B/hepatitis C)	**0**
Elevated AFP	**0**
Mean tumour size (cm)	**12**
Number of tumours at presentation	**1**
Lymphatic invasion	**4/7**
Vascular invasion	**2/7**
Recurrence	**6/6 (100%)**
Median overall survival (mo.)	**60**
Overall 5-year survival rate	**4/7 (57%)**
Median post-op survival (mo.)	**61**
Post-resection 5-year survival rate	**4/6 (67%)**

FLC = fibrolamellar carcinoma; AFP = alpha-fetoprotein.

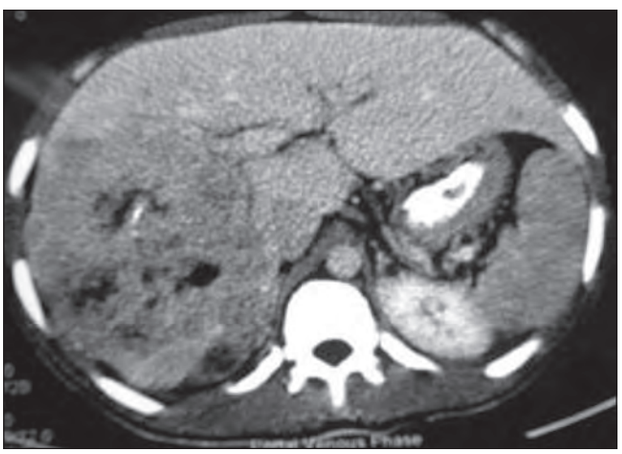

Fig. 1. Portal venous phase CT scan, showing a large, well-circumscribed FLC with internal calcification in the right hepatic lobe.

TABLE II. CLINICAL AND PATHOLOGICAL FEATURES OF PATIENTS WITH FIBROLAMELLAR CARCINOMA

Patient	Age (yrs)	Gender	Serum AFP	Size (cm)	Lymphatic invasion	Vascular invasion	Surgery	No. of segments resected	Recurrence	Post-op survival
1	**21**	**F**	**2.2**	**10**	**Yes**	**No**	**PHx (segs 4, 5, 6), PL**	**3**	**Yes**	**60 months**
2	**21**	**M**	**<8**	**12**	**Yes**	**Yes**	**PHx (segs 2, 3), PL – 1997 PHx (seg. 4), PL – 2001**	**2 1**	**Yes**	**62 months**
3	**42**	**M**	**2.8**	**17**	**No**	**No**	**Extended R hepatectomy**	**5**	**Yes**	**23 months**
4	**21**	**M**	**<1**	**12**	**No**	**Yes**	**L hepatectomy**	**4**	**Yes**	**62 months**
5	**40**	**F**	**3.0**	**4**	**No**	**No**	**L hepatectomy**	**4**	**Yes**	**69 months**
6	**21**	**M**	**1.5**	**14**	**Yes**	**No**	**R hepatectomy, PL**	**4**	**Yes**	**7 months**
7	**19**	**M**	**11.6**	**12**	**Yes**	**No**	**Laparotomy**	**0**	**N/A**	**38 months**

FLC = fibrolamellar carcinoma; F = female; M = male; AFP = alpha-fetoprotein; PHx = partial hepatectomy; R = right, L = left, PL = portal lymphadenectomy.

All 7 patients underwent laparotomy (Fig. 2). Two patients underwent a left hepatectomy, 1 had a right hepatectomy, 1 had an extended right hepatectomy, and 2 patients had segmentectomies which included segments 4, 5, and 6 in one, and segments 2 and 3 in the other (Table II). In addition to the liver resection, 3 patients underwent a portal lymphadenectomy for regional lymphatic tumour involvement (Table II). All patients developed recurrence post resection. One patient (patient 2, Table II) had a repeat liver resection and a retroperitoneal and coeliac axis lymphadenectomy 45 months after the initial resection and lymphadenectomy. There were no peri-operative deaths. One patient who had extensive extraheptic portal nodal metastasis and ascites was irresectable. He underwent selective hepatic artery tumour embolisation with lipiodolised doxorubicin 10 days after laparotomy, and again 3 months later.

FLC was confirmed histologically in all 7 patients. All resection margins were clear. Malignant vascular invasion was documented in 2 cases, and lymphatic involvement in 4 cases (Fig. 3). Histological analysis of all 7 specimens showed the distinctive histopathological features of FLC, which included large, polygonal, well-differentiated, eosinophilic cells with vesicular nuclei, prominent nucleoli and granular cytoplasm. In each specimen, the cells were arranged in sheets, cords, nests or trabeculae, surrounded and separated by distinct parallel lamellae of fibrous tissue (Fig. 4).

Median follow-up from date of operation was 61 months (range 7 - 69). The median overall survival of the 7 patients was 60 months. Following curative resection, median survival was 61 months, with a 5-year survival rate of 67%. The patient with irresectable disease survived 38 months after tumour embolisation with Lipiodol.

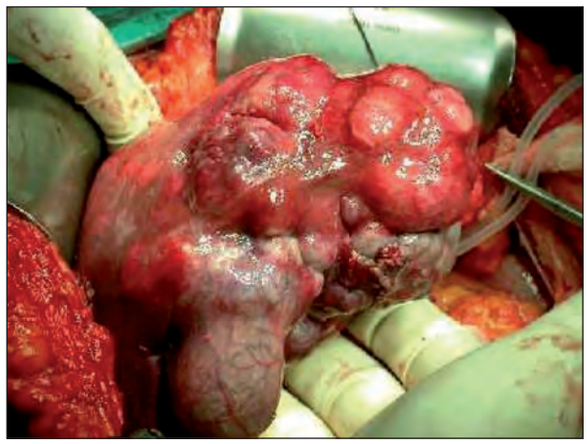

Fig. 2. Fibrolamellar carcinoma involving segments 4, 5 and 6.

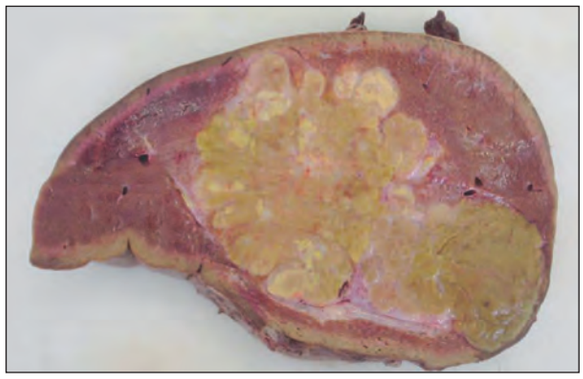

Fig. 3a. A 140×85×130 mm fibrolamellar carcinoma replacing the right hepatic lobe (patient 6, Table II).

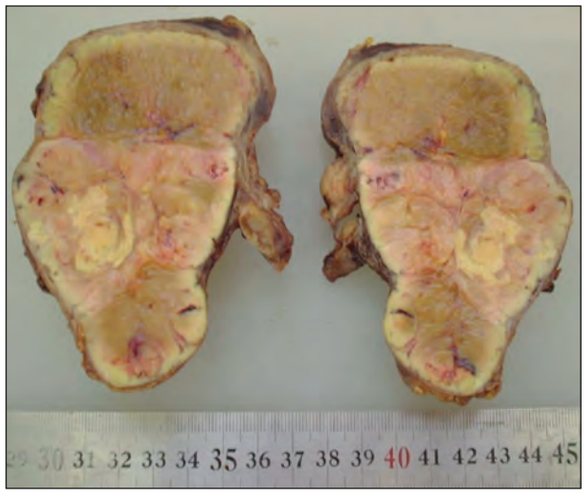

Fig. 3b. Resected 11 cm lymph node containing tumour metastases.

Discussion

While HCC is one of the most common malignancies globally, resulting in over one million deaths annually, FLC is rare, with an age-adjusted incidence rate of 0.02/100 000 compared with 1.9/100 000 for HCC.[10] FLC occurs worldwide, and accounts for 0.85% of primary hepatic malignancies in the West; unlike typical HCC, it is thought to be more prevalent in the USA and Europe than in Africa and Asia.[2,10] There are no associations with cirrhosis, hepatotoxins, α_1-antitrypsin deficiency and haemochromatosis, and fewer than 10% of patients show evidence of hepatitis B and C viral infection.[1,2,11] FLC most frequently presents in adolescents and young adults (mean age 23 years) in non-cirrhotic livers with no prior liver disease,[2-4,11,12] and accounts for 13 - 22% of HCC in younger patients.[10,13] Over 90% of cases occur in patients <35 years old, with <5% occurring in patients >50.[1,2] Typical HCC affects males predominantly, but FLC affects both sexes equally.[1,2,10] Our series demonstrated a male predominance, with a median age of 21 years at the time of diagnosis. About 10% of FLC patients show a mildly elevated serum AFP (often <200 ng/ml), in contrast with HCC patients, who frequently show elevated levels.[2,11,12] None of our patients had a raised serum AFP at either time of diagnosis or recurrence.

The macroscopic and microscopic appearance of FLC is distinctive. Grossly, FLC occurs as a large, single, non-encapsulated, lobulated mass, ranging in size from 5 - 25 cm, and sharply demarcated from normal liver parenchyma (Fig. 3).[2,4,5] Eighty to 90% of cases demonstrate a solitary mass – as in all the patients in our series – but the tumour may also appear with small peripheral satellite lesions, as a bilobed mass or, rarely, as diffuse multifocal masses.[2,12] Some publications have reported that both hepatic lobes were equally affected,[1] while others contended that the left lobe was predominantly involved.[2] Three of our patients had left-sided tumours, and a fourth patient had a central tumour involving both lobes. Fibrous tissue compartmentalises the tumour, often coalescing into a central stellate scar (20 - 60%).[2,11,12] Regional lymph node involvement is an indicator of poor prognosis.[14] Distant metastases are seldom seen.[1,2,6]

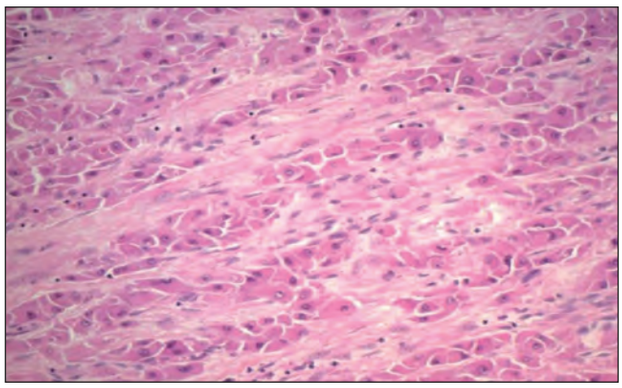

Fig. 4. Histopathological features of fibrolamellar carcinoma demonstrating large, pleomorphic, intensely eosinophilic cells arranged in sheets separated by fibrous lamellae.

Controversy surrounds the question of whether, cirrhosis notwithstanding, FLC demonstrates more favourable biological behaviour than typical HCC. Some series have demonstrated a better survival rate in FLC patients compared with HCC patients,[3,10,12] which may be attributable to a preponderance of FLC patients with localised and resectable tumours. The median survival for unresected FLC is 12 months; the 5-year recurrence-free survival of patients with presumed successful resections is only 18%.[14] The largest population-based study (using the Surveillance, Epidemiology, and End Results (SEER) database) showed superior survival in FLC by comparing the FLC group (*N*=68) with the entire HCC group (*N*=7 896), but did not analyse patients with and without cirrhosis separately in multivariate analysis. El-Serag reported that 5-year survival for FLC patients – of 32% – was considerably better than the 5-year survival for HCC patients, of 6.8%. By separating the HCC group into those with underlying liver disease and those without, some studies have concluded that the better survival in FLC patients might be due to the absence of cirrhosis rather than the unique clinicopathological features of the tumour.[15] In a recent review of the clinicopathological features of FLC, Torbenson[7] concluded that the overall prognosis of FLC was better than that of typical HCC, and similar to that of HCC arising in non-cirrhotic livers. Other recent studies of children and young adults with FLC have also failed to show a more favourable prognosis.[8,13] Katzenstein *et al*. found no difference in prognosis, median survival, or incidence of surgical resectability at diagnosis between FLC and HCC in a cohort of 46 children, and concluded that clinical staging, rather than histological subtype, had the most influence on outcome.[13]

Our overall 5-year survival rate was 57%, with a median survival of 60 months. In published case series, overall 5-year survival rates (in both resectable and unresectable cases) vary between 26% and 31%.[8,10] Among our resectable FLC cases, 5-year survival was 67%, with a median post-operative survival of 61 months. Following resection, overall 5-year survival rates increase to between 45% and 80%;[14-17] the highest median survival reported is 112 months.[14,16] In typical HCC patients, the prognosis is considerably worse: Stipa *et al*. reported a post-resection 5-year survival rate of 37% with median survival of 37 months; 13 patients with unresectable disease had a median survival of 12 months, and no patient survived beyond 5 years.

The recommended therapeutic approach for FLC is complete surgical resection. Curative resection can prolong patient survival in cases of recurrent local disease, limited metastatic spread and/or recurrent lymphadenopathy.[2,5,6,17] In reported series, relapse rates are high, ranging from 64 - 100%.[14,16,17] In our series, recurrence occurred in all patients. The high likelihood of late tumour recurrence necessitates regular follow-up imaging studies in FLC patients.[2,5,14] In inoperable cases, intra-arterial or systemic chemotherapy may render the tumour operable, allowing an attempt at curative resection.[2] Orthotopic liver transplantation (OLT) and total hepatectomy may be considered for patients with nonresectable tumours confined to the liver;[4,11] extra-hepatic disease, distant metastases, nodal involvement and vascular invasion are contraindications to liver transplantation. Limited affordability and availability restrict the use of OLT, but newer innovative approaches may overcome these obstacles; these include adult live-related donors, split-liver techniques or the potential use of marginal donor organs.[17]

Conclusion

Our series suggests that despite (*i*) a high resection rate of solitary lesions with clear tumour resection margins, and (*ii*) absence of underlying liver disease, FLC has a high recurrence rate with an ultimately poor clinical outcome. These findings concur with recent international experience of FLC.

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