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Liver resection for non-cirrhotic hepatocellular carcinoma in South African patients

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Abstract

Background. We describe the clinicopathologic features and outcome of South African patients who have undergone hepatic resection for hepatocellular carcinoma (HCC) arising in a non-cirrhotic liver.

Methods. We utilised the prospective liver resection database in the Surgical Gastroenterology Unit at Groote Schuur Hospital, Cape Town, to identify all patients who underwent surgery for HCC with non-cirrhotic liver parenchyma between 1990 and 2008.

Results. Twenty-two patients (10 men, 12 women, 3 black, 19 white, median age 47 years, range 21 - 79 years) underwent surgery for non-cirrhotic HCC. Sixteen patients had non-fibrolamellar HCC (Group 1); 6 patients had fibrolamellar HCC (Group 2). Group 1 had a median age of 55 years, and 6 (38%) were men; group 2 had a median age of 21 years, and 5 (83%) were men. Most patients had a solitary tumour at diagnosis; median largest tumour diameters in Groups 1 and 2 were 10 cm (range 4 - 21) and 12 cm (range 4 - 17), respectively. Patients in Group 1 underwent extended right hepatectomy (*N*=3), right hepatectomy (*N*=3), left hepatectomy (*N*=3), partial hepatectomy (*N*=7), cholecystectomy (*N*=6), and appendicectomy (*N*=1). Patients in Group 2 underwent extended right hepatectomy (*N*=1), right hepatectomy (*N*=1), left hepatectomy (*N*=2), segmentectomy (*N*=2), and portal lymphadenectomy (*N*=3). Recurrence rates in Groups 1, 2, and overall were 81%, 100% and 86%, respectively. Median overall survival was 46 months, with 1-, 3-, and 5-year survival rates of 95%, 59% and 45%, respectively. In Group 1, median survival was 39 months, with 1-, 3-, and 5-year survival rates of 100%, 56% and 38% respectively. In Group 2, median survival was 61 months, with 1-, 3-, and 5-year survival rates of 83%, 67% and 67%, respectively.

Conclusion. Despite aggressive surgical resection, HCC arising in normal liver parenchyma has a high recurrence rate and an ultimately poor outcome. This finding is similar to both the recent international experience of non-cirrhotic HCC and local experience of fibrolamellar HCC.

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy in adults, and is the fifth most common solid tumour worldwide. The overall incidence is increasing; HCC is now the third leading cause of cancer-related deaths globally, trailing only lung and stomach cancers.[1-3] Because HCC has a highly aggressive biological behaviour, occurrence and mortality rates are almost equal.[4,5] HCC is especially prevalent in regions of Asia and sub-Saharan Africa, where the annual incidence reaches 500 per 100 000 population, compared with less than 3 per 100 000 in Western countries.[5,6] The high incidence of HCC in Asia and sub-Saharan Africa is mainly attributed to the frequency of chronic hepatitis B virus (HBV) infection, which is often complicated by cirrhosis, with lesser contributions from dietary exposure to the fungal toxin, aflatoxin B1 and chronic hepatitis C virus infection. Chronic liver disease predisposes to cirrhosis because low-grade liver cell damage and mitosis render hepatocyte DNA more susceptible to genetic alterations.[7]

The presence of cirrhosis and underlying viral hepatitis influences the clinical presentation and surgical management of HCC. Over 90% of HCC occurs in patients with macronodular cirrhosis, which is the most frequent risk factor for HCC.[8] The annual risk of HCC in a cirrhotic liver is about 3%.[7] In most populations, approximately 10% of HCCs occur in normal liver parenchyma. However, in black patients, as many as 40% of HCCs arise in a normal liver.[9] Until recently, limited reports have separately considered non-cirrhotic HCC.[10-17] When black patients with HCC and cirrhosis were compared with those without cirrhosis, no differences were found in age, clinical features,

hepatic function, serum alpha-fetoprotein concentrations, or hepatitis B virus status.[18] It has been shown that chronic HBV infection occurs as often in black patients with HCC in the absence of cirrhosis as it does in those with cirrhosis.[19] In this study, we assessed the clinicopathological features and outcome of patients with non-cirrhotic HCC following curative liver resection at a tertiary centre in South Africa.

Patients and methods

Patient selection

In this single-centre retrospective cohort study, we used the prospective liver resection database in the Surgical Gastroenterology Unit at Groote Schuur Hospital to identify patients who underwent surgery for hepatocellular carcinoma between 1990 and 2008. All patients in the study were offered surgery as the initial treatment for their primary liver tumour. All patients had preoperative viral serological testing, laboratory assessment of liver function, computed tomography and transabdominal ultrasonography to evaluate tumour characteristics, location and tumour relationship to portal and hepatic veins. Preoperative biopsy of the tumour was not performed. Patients underwent liver resection if resectable disease were present, based on findings from cross sectional imaging, adequate estimated post-resection hepatic function, and pre- and intra-operative absence of extrahepatic tumour.

Surgical technique

Details of the operative technique have been previously described.[20,21] In brief, patients were explored through a bilateral subcostal incision with a vertical midline upward extension to the xiphoid cartilage. Intraoperative ultrasound was used to detect any unsuspected tumours in the contralateral lobe and tumour invasion of portal or hepatic veins, and to define the relationship and proximity of the tumour margin to major intrahepatic vessels. The plane of the proposed parenchymal transection was marked on the liver surface using diathermy. The appropriate lobe was fully mobilised, and parenchymal transection was performed using an ultrasonic dissector. Haemostasis was achieved using diathermy and argon beam coagulation and suturing. Intermittent hepatic inflow occlusion was used selectively depending on blood loss during parenchymal transection. On completion, the transected liver surface was treated with argon beam coagulation and Tisseel. The resection area was routinely drained using silastic closed suction drains.

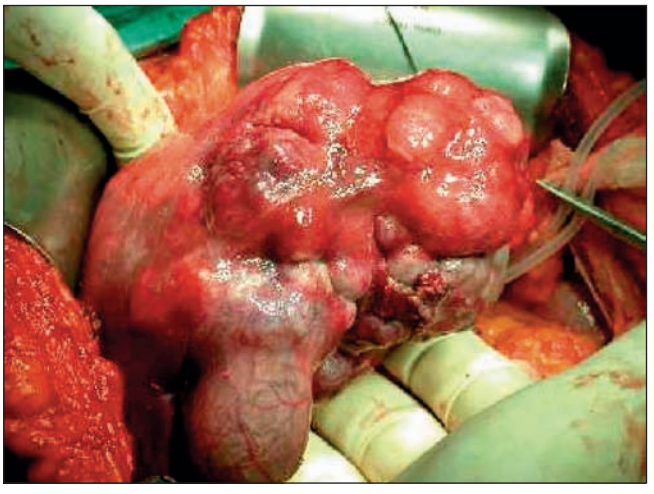

Fig. 1. Fibrolamellar hepatocellular carcinoma in a 21-year-old patient with normal liver parenchyma, before resection.

Histopathological analysis

The liver resection specimens were fixed in formalin after inking the resection margins. Tissue samples of both tumour and adjacent liver were placed in cassettes and processed to form paraffin-embedded tissue blocks. Tissue sections were cut with a thickness of 3 μm and stained with haematoxylin and eosin. A single pathologist (MLL) analysed all the specimens without prior knowledge of the clinical data. Histopathological analysis of tumour tissue included classification as either well, moderately or poorly differentiated HCC according to World Health Organization criteria, the presence or absence of vascular invasion, lymph node metastasis, and the status of resection margins. Histopathological analysis of background non-tumour liver focussed on the following information for each specimen:

- hepatic fibrosis was evaluated using the Metavir fibrosis score, which ranged from 0 - 4 (0: no fibrosis, 1: portal fibrosis without septa, 2: portal fibrosis with few septa, 3: numerous septa without cirrhosis, 4: cirrhosis)
- hepatic inflammation was assessed as present or absent and, if present, further classified as predominantly polymorphonuclear or predominantly lymphoplasmacytic
- steatosis was quantified by the percentage of benign hepatocytes containing steatotic vesicles, and classified into 4 groups: <5%, 6 - 33%, 34 - 66%, and >66% of hepatocytes affected.

Data collection

We collected clinical information from the existing prospective database, hospital files, laboratory and pathology reports, and patient interviews. The following data were reviewed: patient demographics, imaging studies including ultrasound and computerised tomography, serology, surgical procedures, postoperative morbidity, histopathological features of the resected specimens, and evidence of recurrence and outcome during follow-up. Follow-up was obtained by personal communication with patients, patients' families and referring physicians. Follow-up was calculated as the interval from the date of operation until 1 February 2009.

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.[22] We used the modified Clavien-Dindo classification[23] of surgical complications to score surgical outcomes, in which Grade I refers to any deviation from the normal postoperative course without the need for pharmacological treatment (excluding antiemetics, antipyretics, analgesics, diuretics or electrolytes) or surgical, endoscopic, or radiological interventions; Grade II complications are defined as those requiring pharmacological treatment other than the basic drugs allowed for Grade I complications, including blood transfusions and total parenteral nutrition; Grade III encompasses complications that require surgical, endoscopic or radiological intervention; Grade IV includes life-threatening

complications, such as organ dysfunction, that require intensive care; and Grade V refers to death.

Results

Over an 18-year period, 31 patients with HCC underwent liver resection; 9 patients had evidence of hepatic viral infection and/or cirrhosis, and were excluded. Twenty-two patients (10 men, 12 women, 3 black, 19 white, median age 47 years, range 21 - 79) underwent surgery for non-cirrhotic HCC. Sixteen patients had non-fibrolamellar HCC (Group 1); 6 patients had fibrolamellar HCC (Group 2). Group 1 had a median age of 55 years, and 6 (38%) were men; group 2 had a median age of 21 years, and male predominance (83%). No patient had a family history of HCC. Serum α-fetoprotein (AFP) was raised in 5/16 (31%) of Group 1 patients; all Group 2 patients had normal serum AFP levels (Table I).

In Group 1, we performed 3 extended right hepatectomies, 3 right hepatectomies, 3 left hepatectomies, and 7 partial hepatectomies. In Group 2, we performed 1 extended right hepatectomy, 1 right hepatectomy, 2 left hepatectomies and 2 segmentectomies, and 3 patients also had an extensive portal

TABLE I. CLINICOPATHOLOGICAL FEATURES AND OUTCOMES OF PATIENTS WITH NON-CIRRHOTIC HEPATOCELLULAR CARCINOMA

Characteristics	Total HCC (*N*=22)	Group 1 – non-FLC (*N*=16)	Group 2 – FLC (*N*=6)
Median age, yrs (range)	47 (21 - 79)	55 (22 - 79)	21 (21 - 42)
Male	10 (45%)	6 (38%)	4 (67%)
Underlying liver disease (cirrhosis/hepatitis B/hepatitis C)	0	0	0
Elevated AFP	5 (23%)	5 (31%)	0
Total operative duration (min.)	248 (120 - 570)	263 (120 - 570)	233 (185 - 360)
Median total intra-op ischaemic time (min.)	53 (10 - 260)	53 (10 - 260)	53 (10 - 75)
Median longest intra-op ischaemic time (min.)	25 (10 - 65)	30 (10 - 51)	24 (10 - 65)
Median number of times clamp applied	3 (1 - 6)	3 (1 - 6)	3 (1 - 5)
Intra-op blood transfusion required	8 (36%)	7 (44%)	1 (17%)
Median intra-op blood transfusion (ml) (8 patients)	750 (500 - 1500)	500 (500 - 1500)	1 000
Median duration of ICU admission	2 (0 - 6)	3 (0 - 6)	2 (2 - 5)
Median duration of hospital stay	8 (5 - 24)	9 (5 - 24)	8 (8 - 21)
Post-op complications	6 (27%)	5 (31%)	1 (17%)
Median tumour size, cm (range)	12 (4 - 21)	10 (4 - 21)	12 (4 - 17)
Multiple tumours	9 (41%)	7 (44%)	2 (33%)
R0/R1/R2 resection	18/4/0	13/3/0	5/1/0
Vascular invasion	11 (50%)	9 (56%)	2 (33%)
Regional lymph node metastasis	3 (14%)	0	3 (50%)
Differentiation (well/moderate/poor)			
well	8 (36%)	4 (25%)	4 (67%)
moderate	12 (55%)	11 (69%)	1 (17%)
poor	2 (9%)	1 (6%)	1 (17%)
Metavir fibrosis score 0/1/2/3/4	12/4/3/1/0	10/3/2/1/0	2/1/1/1/0
Metavir fibrosis score ≤ 2	19 (86%)	15 (94%)	4 (80%)
Inflammatory activity present	11 (50%)	10 (63%)	1 (20%)
Steatosis <5%	8 (36%)	8 (50%)	0
Recurrence	19 (86%)	13 (81%)	6 (100%)
Median overall survival, months (range)	46 (7 - 159)	39 (14 - 159)	61 (7 - 69)
Overall 1-year survival rate	21 (95%)	16 (100%)	5 (83%)
Overall 3-year survival rate	13 (59%)	9 (56%)	4 (67%)
Overall 5-year survival rate	10 (45%)	6 (38%)	4 (67%)

HCC = hepatocellular carcinoma; AFP = α-fetoprotein.

TABLE II. CLINICOPATHOLOGICAL FEATURES AND OUTCOMES OF 22 PATIENTS WITH NON-CIRRHOTIC HEPATOCELLULAR CARCINOMA

Patient	Age (yrs)	Sex	Type	Serum AFP	Size (cm)	Number of tumours	Surgery	Number of segments resected	Recurrence	Alive	Post-op survival (months)
1	46	F	HCC	N	16.5	1	PHx (segs 2,3), appendicectomy	2	Lung	No	60
2	68	M	HCC	N	4.5	1	PHx (seg 4), cholecytectomy	1	Liver	No	42
3	62	M	HCC	-	-	1	PHx (segs 6,7,8)	4	CA HOP	No	72
4	48	F	HCC	↑	20	3	R hepatectomy	4	Lung/bone	No	27
5	29	F	HCC	↑	-	1	L hepatectomy	4	Liver	No	153
6	28	F	HCC	↑	10	2	R hepatectomy, cholecytectomy	4	Liver	Yes	50
7	22	F	HCC	N	11	1	R hepatectomy	4	No	Yes	159
8	51	M	HCC	N	-	1	Extended R hepatectomy	5	Liver	No	72
9	58	F	HCC	↑	14	1	Extended R hepatectomy, cholecytectomy	4	Liver	Yes	33
10	79	M	HCC	N	6	1	PHx (segs 5,6,7), cholecytectomy	3	Liver	No	15
11	68	F	HCC	N	10	1	PHx (seg 5,6)	2	No	Yes	24
12	45	F	HCC	-	19	1	PHx (segs 2,3)	2	Liver	No	80
13	74	F	HCC	-	15	1	L hepatectomy, cholecytectomy	3	Liver/Portal vein	No	36
14	48	M	HCC	↑	10.5	1	PHx (segs 4,5,8)	4	No	Yes	19
15	64	M	HCC	N	17	1	L hepatectomy, cholecytectomy	4	Liver	No	32
16	71	F	HCC	N	9.5	1	Extended R hepatectomy	5	Lung	No	14
17	21	F	FLC	N	10	1	PHx (segs 4,5,6), PL	3	Liver	Yes	60
18	21	M	FLC	N	12	1	PHx (segs 2,3), PL [1997]; PHx (seg 4), PL [2001]	2 + 1	Liver	Yes	62
19	42	M	FLC	N	17	1	Extended R hepatectomy	5	Liver	Yes	23
20	21	M	FLC	N	12	2	L hepatectomy	4	Liver	No	62
21	40	F	FLC	N	4	1	L hepatectomy	4	Liver	No	69
22	21	M	FLC	N	14	2	R hepatectomy, PL	4	Liver	No	7

M = male; F = female; AFP = α-fetoprotein (↑ = >10 ng/ml, N = <10 ng/ml); L = left; R = right; PHx = partial hepatectomy; seg/s = segment/s; R hepatectomy = segs 5-8; extended R hepatectomy = segs 4-8; L hepatectomy = segs 2-4; extended L hepatectomy = segs 2-5,8; PL = portal lymphadenectomy.

lymphadenectomy with resection of large overtly involved lymph nodes around the hepatic artery and coeliac axis. One patient required a second resection and portal lymphadenectomy for recurrent tumour 4 years after the first resection (Table II). In addition to liver resection, 6 Group 1 patients and 5 Group 2 patients had a cholecystectomy as part of the procedure, 2 patients in Group 2 underwent portal lymphadenectomy for regional lymphatic tumour metastasis, and 1 patient in Group 1 had an appendicectomy.

Twenty-one of the 22 resections were performed using portal vein and hepatic artery inflow occlusion of the liver (Pringle manoeuvre). The median total ischaemic time was 53 minutes (range 10 - 260); the median longest intra-operative ischaemic period was 25 minutes (range 10 - 65); and the median number of times the clamp was applied was 3 (range 1 - 6). Fourteen operations were performed without the need for a blood transfusion. Eight patients received a median intra-operative blood transfusion of 750 ml (range, 500 - 1 500). The total operation duration overall was 248 minutes (range 120 - 570); in Group 1, the total operation duration was 263 minutes (range 120 - 570), and in Group 2, 233 minutes (range 185 - 360).

In Group 1, 6 of the 16 patients had postoperative complications: patient 7 had a Dindo Grade III intra-abdominal bile leak that required percutaneous drainage; patient 9 had a Dindo Grade II pleural effusion following partial diaphragmatic resection; patient 11 had a Dindo Grade II postoperative pneumonia that resolved with antibiotics and physiotherapy; patient 14 had a Dindo Grade II pneumonia and pleural effusion and a Grade III subphrenic abscess requiring laparotomy 12 days after liver resection; patient 15 had a Dindo Grade I acute urinary retention that resolved with urinary catheterisation; and patient 16 had a Dindo Grade III pleural effusion requiring intercostal drain insertion, and a Dindo Grade IV Staphylococcus aureus septicaemia and hepatic encephalopathy which prolonged her ICU and hospital stay. In Group 2 (FLC), one patient had a Dindo Grade II postoperative complication (superficial abdominal wound sepsis requiring oral co-amoxyclavulanic acid).

The median duration of hospital stay overall was 8 days (range 5 - 24); in Group 1 the median duration was 9 days (range 5 - 24), and in Group 2, 8 days (range 8 - 21). The median duration of ICU admission overall was 2 days (range, 0 - 6); in Group 1 the median duration was 3 days (range 0 - 6), and in Group 2, 2 days (range 2 - 5). There were no perioperative deaths.

The median greatest tumour dimension in Group 1 was 10 cm (range 4 - 21cm), and the median greatest tumour dimension in Group 2 was 12 cm (range 4 - 17 cm). Multiple tumours were present in 7/16 (44%) of Group 1 patients and 2/6 (33%) of Group 2 patients. Overall, 18 patients had R0 resections and 4 patients had R1 resections. Histological vascular invasion was present in 11 patients (Group 1 = 9, Group 2 = 2). Regional lymph node metastasis was demonstrated in 3 patients (all from Group 2). Eight tumours were well differentiated (Group 1 = 4, Group 2 = 4), 12 tumours were moderately differentiated (Group 1 = 11, Group 2 = 1), and 2 tumours were poorly differentiated (Group 1 = 1, Group 2 = 1). Background hepatic fibrosis was seen in 9 (Group 1 = 6, Group 2 = 3) patients; median Metavir scores in Groups 1 and 2 were 0 and 1 respectively. Inflammatory activity in surrounding liver parenchyma was present in 11 (Group 1 = 10, Group 2 = 1) patients. Eight patients in Group 1 had background steatosis affecting more than 5% of hepatocytes, while no patients in Group 2 had steatosis in more than 5% of benign hepatocytes. We were unable to assess background liver fibrosis, inflammation or steatosis for patient 19 (slides unavailable).

The median follow-up from date of operation was 132 months (range 24 - 213). No patients were lost to follow-up. Overall, recurrence occurred in 19 patients (86%); Groups 1 and 2 had similar recurrence rates: 81% and 100% respectively. Median overall survival for the 22 patients was 46 months, with 1-, 3-, and 5-year survival rates of 95%, 59% and 45% respectively. In Group 1 (normal liver parenchyma, *N*=16), median survival was 39 months (range 14 - 159), with 1-, 3-, and 5-year survival rates of 100%, 56% and 38% respectively. Patients in Group 2 (*N*=6) had a better prognosis: median survival was 61 months (range 7 - 69), with 1-, 3-, and 5-year survival rates of 83%, 67% and 67% respectively.

Discussion

Sub-Saharan Africa is one of 3 geographical regions worldwide where HCC occurs commonly.[4] A number of differences exist between HCC in sub-Saharan Africa and HCC in other parts of the world. In sub-Saharan Africa, HCC generally presents at a younger age and with a striking male predominance in black, compared with industrialised, populations.[5] Although the prognosis of HCC is poor in all geographical regions, it is especially grave in blacks, in whom the annual tumour fatality ratio is 0.97.[4] In this study, we analysed the outcome of 22 patients with hepatocellular carcinoma which arose in non-cirrhotic livers. While HCC arises most often in cirrhotic livers, the 22 patients in this study with HCC and non-cirrhotic liver parenchyma who underwent resection represent less than 5% of the total number of patients with HCC seen during the 18-year study period, 95% of whom had multicentric HCC and established cirrhosis at presentation. The median age of patients in our study was 47 years, with a wide range of 21 - 79. The patients with non-fibrolamellar HCC (group 1) included mostly women with a higher median age than fibrolamellar HCC patients (group 2), which comprised younger men. This is in contrast to the usual 4:1 male predominance of HCC in the literature,7 but is typical of the younger age at diagnosis among patients with fibrolamellar HCC.[21]

Because of the absence of underlying liver disease and consequent lack of surveillance, HCC in non-cirrhotic patients is usually diagnosed only when the tumour becomes symptomatic. In our study, most tumours were large at diagnosis (median 12 cm overall), with a similar median diameter in groups 1 and 2 (10 cm and 12 cm), which is consistent with international trends.[11,12,24] Brancatelli[24] reported a mean tumour diameter of 12.4 cm in non-cirrhotic HCC patients, Lang[12] documented a mean diameter of 9 cm, and Dupont-Bierre[11] a mean tumour diameter of 8.5 cm. Recent studies suggest that, in comparison with cirrhotic HCC, non-cirrhotic HCC is more likely to present with a single dominant mass, as well as more frequent macrovascular invasion, poorer differentiation and more aggressive tumour behaviour.[13,25]

In recent years, both selection criteria and liver resection techniques have evolved. Improvements in perioperative technique, including the use of an ultrasonic dissector, a reduction in blood loss and the need for blood transfusion, intermittent warm hepatic ischaemia, maintenance of a low central venous pressure, and

shorter procedure times, have contributed to safer surgery and improved outcomes with fewer postoperative complications.[20,21,26] In most series, a blood transfusion is necessary in less than 10% of resections, and operative mortality is less than 3%.[27] Postoperative morbidity has been significantly associated with the degree of underlying liver dysfunction, small liver remnant volume, blood loss, transfusion and co-morbidities.[28] In our study, the median duration of hospital stay overall was 8 days (range 5 - 24). There were no postoperative deaths, and 7 of the 22 patients had postoperative complications, of whom one required a laparotomy for a subphrenic abscess, one a percutaneous drain for a bile leak, and one a chest drain for a pleural effusion after resection of part of the right hemidiaphragm owing to tumour adherence.

The routine use of intra-operative ultrasonography allows precise localisation and staging of the tumour, and also facilitates anatomical resections. We performed major resections (right, left and extended hepatectomies) in every Group 1 (*N*=16) and Group 2 (*N*=6) patient. Aggressive operation, as we performed, is advocated in the treatment of non-cirrhotic HCC, regardless of the degree of fibrosis.[10-12] From an oncological perspective, anatomical resections that may include satellite lesions are superior to limited resections without a surrounding margin.[27] Pathological studies of resected tumours support this notion[26] but some authors have challenged the benefits of a safety margin,[29] and robust evidence is lacking. In our study, 18 of the 22 patients had an R0 resection, and 4 had an R1 resection with microscopic tumour in the thrombus at the portal vein resection margin; in these 4 cases, however, the parenchymal resection margins were clear. The risk of vascular invasion and dissemination increases with size,[30] but some tumours may grow as a large single mass with no evidence of vascular invasion. In these, the risk of recurrence is not significantly increased compared with smaller tumours.[27]

Following resection, tumour recurrence rates exceed 70% at 5 years, including recurrence owing to dissemination and *de novo* tumours.[27] Tumour recurrence occurred in 86% of our patients, which is higher than the reported recurrence rate.[10,11] The higher rate of recurrence in our study may be partially explained by the size of the primary tumour and the frequency of microscopic vascular invasion, which was present in 11 of 22 patients. Some studies suggest that histopathological features are predictive of recurrence and overall survival.[14,27] We did not observe a correlation between degree of differentiation and tumour recurrence, as the majority of tumours were moderately differentiated. Multiple tumours, macroscopic vascular invasion and tumour grades are reported to be poor prognostic factors associated with tumour recurrence and diminished survival.[11,12] However, despite later clinical presentation and more aggressive tumour behaviour, patients with non-cirrhotic HCC are more likely to survive resection and have a better prognosis than patients with cirrhotic HCC.[13,25,31]

The most powerful predictors of recurrence in the absence of extrahepatic spread are the presence of macro- and microscopic vascular invasion.[27] This likelihood of vascular invasion increases as tumour size and number increase,[32] which suggests that most recurrences are due to dissemination from the primary tumour and not metachronous tumours developing in a cirrhotic liver.[27] Furthermore, recurrence due to dissemination is more likely to appear during the first 3 years of follow-up.[27,32] Microscopic vascular invasion, multiplicity and size of tumours have been shown to be independent risk factors for decreased overall long-term survival in multivariate analysis.[33] Margin positivity is associated with local recurrence, but the absolute width of the margin is less important. Poon *et al*. have demonstrated that recurrence is probably due to dissemination by both the portal venous system for intrahepatic metastases and multicentric carcinogenesis for multisegmental metastases, while proportionally less recurrence occurs locally.[29] Moreover, Poon *et al*. propose that the presence of venous invasion and satellite nodules are important predictors of recurrence, irrespective of the margin status.[29]

Treatment of tumour recurrence is a poorly investigated area.[27] While a solitary recurrence may benefit from repeat resection, most patients with recurrence after primary resection present with multifocal disease, which can be attributed to intrahepatic primary tumor dissemination.[29] This usually reflects advanced tumour stage, and there is scant evidence that any further treatment provides a survival advantage. While a number of retrospective analyses suggest that some patients with recurrent tumour may be candidates for salvage transplantation, this option is not supported by an analysis of clinical outcomes.[27] Most recurrences – and especially those that appear early during follow-up – are due to tumour dissemination and demonstrate more aggressive pathobiology than the primary tumors.[34]

In our study, in Group 1 patients (non-fibrolamellar HCC), median survival was 39 months, with 1-, 3-, and 5-year survival rates of 100%, 56% and 38%, respectively. Among non-cirrhotic HCC patients, other recent studies have reported post-resection 1-, 3-, and 5-year survival rates of 85%,[10-12] 43 - 70%[10-14,35] and 29 - 64%[10-15,31] respectively. Our overall 3- and 5-year-survival rates of 59% and 45%, respectively, compare favourably with the reported data, considering the median size of the tumours in our resected specimens. Comparatively, our fibrolamellar HCC cases fared better, with a median postoperative survival of 61 months and a 5-year survival rate of 67%. Our series suggests that, despite aggressive surgical resection, HCC arising in normal liver parenchyma has a high recurrence rate and an ultimately poor outcome. These findings are similar to both recent international experience of non-cirrhotic HCC and local experience of fibrolamellar HCC.[2]

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