Liver resection for hepatocellular and fibrolamellar carcinoma in a South African tertiary referral centre.

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DECLARATION

I, Yalda Ziaei, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy in adults and is the fifth most common solid tumour worldwide with a variable prevalence based on underlying risk factors and geography. The incidence has risen over the past several decades and HCC is now the third leading cause of cancer-related deaths globally, after lung and stomach cancers, with a 5-year survival rate less than 20% and recurrence rates as high as 88%. More than 80% of global HCCs occur in sub-Saharan Africa (SSA) and Eastern Asia where the incidence ranges from 4.8 to 8.3 per 100,000 per year in different regions of SSA with the highest incidence in the western central Africa compared to less than 3 per 100 000 in Western countries. Hepatocellular carcinoma has become a significant public health concern in SSA and is now the second leading cancer in men and the third for women, occurring in particular in young adults. Unfortunately only a small proportion of patients in SSA with HCC are treated with curative intent. Data are scarce, but studies consistently report that curative-intended treatment is pursued in less than 1% of patients in SSA with HCC. Fibrolamellar carcinoma (FLC) was until recently regarded as a variant of HCC occurring in young patients with a relatively good prognosis but is now recognized as a distinct clinical entity with consistent chimeric fusion protein (DNAJB1-PRKACA) expression by FLC tumours.

The optimal treatment of HCC and FLC is influenced by the stage of the disease, the degree of liver impairment, and patient performance status. Currently, the therapeutic strategy is based on international guidelines and the Barcelona Clinic Liver Cancer (BCLC) staging system in which potentially curative treatment for early-stage HCC includes resection, transplantation and ablation. Surgical resection is the treatment of choice in patients without cirrhosis and in those with cirrhosis and well-preserved hepatic function. Despite advances in surgical techniques and perioperative care, hepatectomy remains a high-risk surgical procedure with complications occurring in up to 40% of resections. This adds a significant burden to individual patients by adversely affecting quality of life and increasing length of hospital stay, readmission rates, and healthcare costs. Recurrence despite curative-intent treatment is as high as 88% and is due to tumour multifocality, size ≥5 cm, macroscopic vascular or microscopic lymphovascular invasion, elevated alfa-fetoprotein (AFP) levels and impaired liver function. Previous publications from our unit have reported earlier data on resection for HCC and FLC. The aim of this research was to assess the peri-operative outcome and survival of patients with HCC and FLC following curative liver resection at a tertiary referral centre in South Africa.

In this study a retrospective analysis was done of all liver resections for HCC and FLC at Groote Schuur Hospital and the University of Cape Town Private Academic Hospital between January 1990 and December 2021. Three resection groups were compared, (i) HCC occurring in normal livers, (ii) HCC occurring in cirrhotic livers, and (iii) fibrolamellar carcinoma. Post-operative complications were classified according to the expanded Accordion severity grading system. Median overall survival (OS) and 95% confidence intervals (CI) were calculated.

Forty-eight patients were included in the study, 25 with HCC in non-cirrhotic livers, 15 in cirrhotic livers and eight for FLC. Thirty-six patients (75%) underwent a major resection. No mortality occurred but 16 patients (33%) developed grade 1 to 4 complications. Thirty-three patients (68%) developed recurrence of HCC following their initial resection of whom 29 (60%) ultimately died. Median OS was 64.2m, 95% CI [29.7-84.6], 61.9m, [28.1-95.6] and 31.7months, [1.5-61.8] for patients with HCC in non-cirrhotic livers, FLC and HCC in cirrhotic livers respectively.

Liver resection for HCC and FLC was a safe procedure with no mortality, but one-third of patients had associated post-operative morbidity. The high long-term recurrence rate remains a major obstacle in achieving better survival results after resection.

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CHAPTER 1

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide (1) and the most common primary malignancy of the liver. HCC is a major cause of cancer deaths worldwide and has the sixth-highest morbidity and the fourth highest mortality in the world (2, 3) with an approximate 5 year survival rate of 18% (4).

Most HCCs occur in low socio-economic countries, especially in SSA and Southeast Asia. The incidence of HCC in these regions accounts for approximately 80% of newly diagnosed cases (5). The incidence data for HCC in most sub-Saharan countries are based on non-population-based registries, positive histological reports, or estimates of incidence, because there are no reliable statistics regarding the true incidence (5, 6).

Risk factors for HCC such as chronic hepatitis, alcohol abuse, fatty liver and steatohepatitis, obesity, diabetes, nicotine use and hemochromatosis are largely attributed to the prevalence of the disease (4). The high incidence of HCC in Asia and SSA is mainly attributed to the frequency of chronic hepatitis B virus (HBV) infection, which accounts for high incidences of HCC in non-cirrhotic livers and is often complicated by cirrhosis, and lesser contributions from dietary exposure to iron or aflatoxin B1 and chronic hepatitis C virus (HCV) infection (7). Different aetiological factors for HCC result in the diversity and variant incidences of the disease across different regional areas and ethnic groups (4).

The age of onset of HCC varies in different parts of the world. In Japan, North America and European countries, mean age of presentation is above 60 years while patients tend to be younger in East Asia and some African countries (8). The younger age group in Africa, especially in SSA, is due to the higher incidence of hepatitis resulting in HCC. The bimodal age distribution in this group and the higher incidence of foetal-to-maternal transfer of the hepatitis results in HCC in younger age group (9).

Unfortunately, most patients present with advanced disease and the triad of jaundice, abdominal pain, and distention, with about 60% of patients having cirrhosis. An estimated 93% of patients die within 1 year of onset of symptoms (7). While 40% of patients in high-income countries are diagnosed early, 95% of patients in SSA countries present at an advanced or terminal stage (6, 7).

Until 2000, treatment for hepatocellular carcinoma was limited to a small number of options. With a dismal proportion of patients eligible for treatment other than best supportive care, results were not encouraging (5). The treatment of HCC is classified into two main categories, those having curative intervention and those who are treated with palliative intent, with resection and liver transplantation and in selected patients, percutaneous ablation, offering the potential of cure while other modalities such as trans-arterial and systemic therapies considered as palliative treatment.

Hepatocellular carcinoma has become a significant public health concern in SSA and is now the second leading cancer in men and the third for women, occurring in particular in young adults. Data on HCC in SSA are limited. This is largely due to difficulty in accessing medical practitioners, especially for patients living in rural areas. Many rural patients prefer to go to traditional healers (witch-doctors, nyangas) due to cultural beliefs. Other limitations hampering accurate data collection are secondary to a lack of experienced trained personnel available to maintain a detailed HCC registry as well as the lack of a comprehensive and accurate population survey (9).

Only a few HCC surgical series have been reported in SSA (10-13). In order to resolve these deficiencies, an analysis of outcome was undertaken in a HPB unit tertiary centre in South Africa. This study evaluated the pathology, surgery, peri-operative morbidity and mortality in a series of patients who underwent resection.

CHAPTER 2

LITERATURE REVIEW

Epidemiology

Hepatocellular carcinoma is the 6th most common cancer worldwide and the most common primary malignancy of the liver (1). The ratio between incidence and mortality is approximately 1 which indicates the aggressiveness of the disease (4, 7, 14). In 2020, HCC was ranked the third highest cause of mortality and accounted for 8.3% of all deaths (7).

Although globally the diagnosis of HCC peaks between 60 and 70 years (4) a cohort study from a tertiary referral centre in SSA showed a median age of 45 years in patients with HCCs and 32.5 – 37.5 years in those with HBV-induced HCC (8).

HCC predominantly affects men (4) with a male-to-female ratio of 2:1–4:1 (15). In 2020, HCC was the fifth most common cancer in males and the seventh most common in females worldwide (15). In SSA, HCC is the second most common cancer in males and the third most common cancer in females with male to female ratio of 3:1 to 4:1 (7).

The incidence of HCC varies by geographic region and ethnicity. Age of exposure to risk factors plays an important role in this scenario. Most patients will develop an HCC with the background of liver cirrhosis and viral hepatitis, alcohol, non-alcoholic fatty liver and steatohepatitis as the major risk factors (4). China, Southeast Asia and SSA have the highest incidence of HCC followed by central and Southern Europe countries. The lowest incidence rates are reported in Northern Europe, the Middle East, Oceania, North and South America (15) (Figure 1)

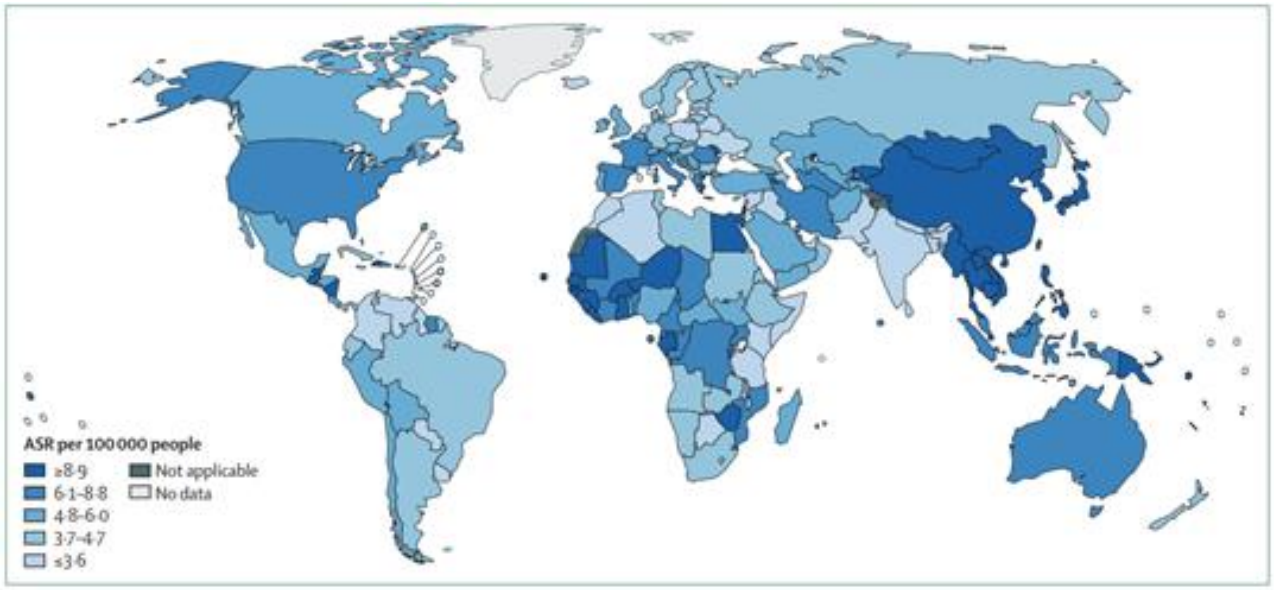

Figure 1. Worldwide incidence of liver cancer, 2020 (4) (With permission from the Internations Agency for Research on Cancer. ASR=age-standardised rate)

The true incidence of HCC in Africa is underestimated and is estimated to have a 40% undercount of HCC in Africa resulting in a 20% underestimation of HCC worldwide (1, 5). This is largely due to lack of registries in SSA, the lack of population screening and increased death from the chronic viral hepatitis, lack of HCC surveillance in high risk populations as well as health care limitations in some of these countries (1, 9). The recent incidence of HCC in SSA is shown in Table 1.

Ten African countries (Egypt, The Gambia, Guinea, Ghana, Liberia, Burkina Faso, Senegal, Guinea-Bissau, Mauritania, and Cape Verde) are among the 25 countries with the highest age-standardised rates of HCC per 100 000 population. Egypt has the highest incidence of HCC incidence followed by the Gambia. (7).

In SSA, most HCCs are diagnosed at an advanced stage and are inoperable. Only 5% present with Barcelona Clinic Liver Cancer Classification (BCLC) stage A-B in contrast to 40% presenting with the same stage in European countries and 72% patients in BCLC stage D versus 15% (7).

	Incident cases	Age-standardised incident rate per 100 000 population	Deaths	Age-standardised mortality rate per 100 000 population
Western sub-Saharan Africa	17630	8.4	16887	8.1
Central sub-Saharan Africa	6072	6.1	5716	5.9
Eastern sub-Saharan Africa	12326	5.0	11542	4.8
Southern sub-Saharan Africa	2601	4.6	2447	4.3

Table 1. Regional variation in hepatocellular carcinoma in sub-Saharan Africa (7), Data are from BLOBOCAN 2020

Clinical Presentation

The growth of HCC is characteristically silent in nature which may delay diagnosis for as long as 3 years from the time of development (16), especially in cases of non-cirrhotic HCC (17). As a result, patients are unaware of their disease and will present very late in the course of their disease (9).

The clinical presentation of HCC is known to vary considerably and generally relates to the extent of hepatic reserve (Table 2) (16). The commonest presentation of HCC is abdominal pain which occurs in about 52% of patients (17). Pain is most often felt in the right hypochondrium, epigastrium or lower right anterior chest and may radiate to the right side of the back or tip of right shoulder. The pain is initially described as unremitting dull and aching which progresses in severity as the disease progresses (9).

As HCC usually arises in patients with underlying cirrhosis, deterioration of hepatic function as a result of cirrhosis will result in hepatic encephalopathy, jaundice and ascites (16). In a series of Black patients in Southern Africa, 52.4% of the males and 49.1% of the females complained of either a mass in the upper abdomen or generalized swelling caused by ascites. Haematemesis may be an initial complaint in populations with HCC because of co-existence of long standing cirrhosis (9) and portal hypertension.

Presentation	Manifestations
Asymptomatic	
Liver dysfunction	- Ascites - Jaundice - Hepatic Encephalopathy - Variceal Bleed
Complications of tumour growth	- Abdominal pain - Weight loss / Cachexia - Abdominal mass - Obstructive Jaundice - Tumour rupture
Para-neoplastic syndrome	- Hypoglycaemia - Hypercalcaemia - Polycythaemia - Feminization syndrome - Diarrhoea - Cutaneous manifestations
Distant metastasis	

Table 2. Presentation and manifestations of hepatocellular carcinoma (16)

Complications related to the tumour growth can be the initial presenting finding in non-cirrhotic patients whose tumours can grow without restriction as a result of adequate hepatic reserve. This is common in SSA and other regions where chronic hepatitis B virus (HBV) infection related HCC is more prevalent (16). These patients are more likely to present with signs and symptoms of long-standing malignancy such as weight loss, anorexia, malaise and abdominal distension (18).

Large subcapsular HCC can spontaneously rupture into the peritoneal cavity and end with catastrophic results. This usually occurs if the tumour sustains blunt trauma or outgrows its blood supply. Presentation in this situation can range from abdominal pain and peritonism to shock (16).

Extrahepatic manifestations of HCC, which are more common in non-cirrhotic HCC (16, 17), can be the result of distant metastases or para-neoplastic syndrome. Most common sites of metastases are lung, bone and adjacent visceral organs (16). Twenty-five per cent of non-cirrhotic HCC initially present with extra-hepatic metastases (17).

Patients with HCC may rarely present with a paraneoplastic syndrome. If present, this can manifest as hypoglycaemia, hypercalcaemia, polycythaemia and feminisation syndrome (19). As a result of increased

production of secretory peptide, patients may present with watery diarrhoea which can lead to electrolyte abnormalities if severe (20). Cutaneous manifestations occur rarely and are mainly seen in association with chronic liver disease rather than HCC. Examples include porphyria cutanea tarda and pityriasis rotunda (16).

On physical examination, hepatomegaly is the most common physical finding. The liver may be hard with irregular palpable borders. Hepatomegaly can be appreciated in cases of non-cirrhotic or early cirrhotic HCC as a result of a mass. In advanced cases of cirrhosis, the liver may be shrunken and not palpable (16). Hepatocellular carcinomas are almost always larger in Black Africans and Asia-Pacific patients than they are in patients in resource-rich countries with low incidence of the tumour (9).

Ascites is present in approximately one-half of Black Africans with HCC at the time of diagnosis. The degree of fluid accumulation is usually mild to moderate at the time of admission and can progress as the disease progresses. Fourteen percent of Southern African patients present with tense ascites as result of tumour invasion into the hepatic veins. In these patients, the whole liver is enlarged because of venous congestion and may be difficult to palpate and clinically examine the liver in detail (9).

Twenty-five to 41% of patients may present with jaundice at the time of admission (21). The incidence of jaundice is 33.6% in males and 28.6% in females. While the most common type of jaundice is the non-obstructive type, 12% of Southern African patients have been reported to have HCC complicated with obstructive jaundice which is considered a rare and unusual presentation for HCC (9).

Patients with fibrolamellar carcinoma traditionally present with chronic gastrointestinal symptoms, abdominal pain and distension. On examination, a mass may be palpable as well as findings of ascites(22). In rare circumstances, fibrolamellar carcinoma can present with gynecomastia secondary to high levels of aromatase expression and mental status change secondary to hyperammonaemia and acquired ornithine transcarboxylase deficiency (17, 22). Other rare manifestations include deep vein thrombosis, Budd-Chiari syndrome, non-bacterial thrombotic endocarditis and fulminant liver failure (17).

Natural History

HCC has a poor prognosis in all geographical regions, but the prognosis is especially grave in resource-constrained regions that have a high incidence of the tumour (9). The incidence of HCC is increasing in

low-incidence countries and even in some high-incidence countries because of the growing incidence of HBV, HCV and obesity-related liver disease (23).

Malignant transformation is thought to result from cirrhosis, viral integration into the hepatocyte genome with tumourogenesis or after years of hepatic regenerative activity in which inflammatory cytokines, growth factors and other mediators prompt genetic alterations within hepatocytes via oxidative stress (16). In a multivariate analysis, liver cell dysplasia was found to be a major risk factor for HCC occurring in 24% of all HCC and 53% of those positive for hepatitis B surface antigen (24).

The first widely accepted staging system to predict survival which incorporates tumour biology and hepatic function was that proposed by Okuda et al (16, 25). Improperly identifying patients for specific treatment was one of the main drawbacks of this staging system. The Cancer of the Liver Italian Group Programme (CLIP) (26) had a more mathematically sound criterion to better explain variability in survival (16). The Barcelona Clinic Liver Group (BCLC) staging system is thought to be more directed to specific therapy depending on the stage of the patient (27).

Despite advances in medicine, the overall survival is poor. The 12 month fatality ratio of patients with HCC is the highest of any human tumour (9). Median survival rate is reported to be less than 6 months (16, 23). Most patients are not a candidate for curative intent intervention. The only palliative treatment which has been shown to be of benefit is TACE (23).

Diagnosis

Biochemistry

Conventional liver function tests (LFT) are of no great value in HCC diagnosis. LFT derangement is nonspecific and cannot differentiate between HCC and other liver lesions or cirrhosis (9, 28).

Tumour markers

Serum tumour markers are a useful and important adjunct for the detection of HCC. There are four main groups which include oncofoetal antigens, glycoprotein antigens, enzymes with iso-enzymes and cytokines (29). The most widely used tumour marker is Alpha-fetoprotein (AFP) which is a glycoprotein and has three forms of glycoforms (APF-L1, AFP-L2 and AFP-L3) as per their binding capacity to lectin lens agglutinin. AFP levels are elevated usually in 60-80% of patients. (30).

Values of 10-20 ng/ml are considered normal for AFP and levels more than 400 ng/ml are regarded as diagnostic. Higher levels are usually associated with a poorer prognosis (29). Sensitivity and specificity of AFP is 41 – 65% and 80-94% when the cut-off value of 20ng/ml is used (30). This sensitivity further declines in non-cirrhotic patients. In high risk patients, elevated levels of AFP suggest a diagnosis of HCC but does not exclude an HCC diagnosis when the AFP levels are normal or low (17).

Levels of AFP can differ in different geographic locations. The highest levels of AFP are seen in patients with HCC in sub-Saharan black Africans with mean concentrations of 70,000 – 80,000 ng/ml and can exceed one million. No obvious correlation is found in Black African patients between serum AFP and other clinical or biochemical changes occurring in HCC such as degree of differentiation, stage of tumour, survival and its association with HBV (9).

Despite being a good serum marker, AFP has some limitations as well. False positive AFP levels can be detected during pregnancy, active liver disease, embryonic and some gastrointestinal tumours. While small tumours can express AFP in lower than detected ranges, larger tumours can delay or express higher levels than detected rate, resulting in negative results in all of them (30).

AFP levels are normal in the majority of patients with fibrolamellar carcinoma (17) with only 10% of patients showing mild elevation in AFP (11). Transcobalamine I, also known as Haptocorrin (HC) is found to be elevated in the serum of young patients with fibrolamellar carcinoma and is used as a tumour marker for this disease. Haptocorrin is not specific for fibrolamellar carcinoma and can be found in chronic myeloid leukaemia and sporadic cases of breast cancer as well (31). Less frequently, fibrinogen and neurotensin levels can also be elevated (32).

Des-γ-carboxyprothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an effective tumour marker for HCC. High serum level predicts higher risk of vascular invasion, higher recurrence rate and worse overall survival (33, 34). DCP is highly recommended for screening especially when combined with AFP as it increases the sensitivity. But it's not recommended for recurrence screen as the level tends to be high after curative treatment even if pre-treatment levels were low (33). Due to lower sensitivity and specificity of test in Black Africans with HCC (9), the use of the test is limited in these population.

Alpha-L-Fucosidase (AFU) is a lysosomal enzyme present in all mammalian cells. AFU level significantly rises 6–9 months before ultrasonographic imaging can depict the case (35). Sensitivity can reach to 85%

with specificity of 91% for HCC detection (36). Montesar et al. recommend use of AFU for HCC detection especially in cirrhotic patient as it was correlated with significant elevation of AFU in these group of patients (35). One of limitation of AFU is its inability to distinguish HCC from liver cirrhosis (37) and that might result in increased false positive results when this test is used.

Other tumour markers such as γ-Glutamyl Transferase, tissue polypeptide antigen, immunoreactive calcitonin and Glypican-3 are not recommended as tumour markers for HCC. They did not show to be diagnostically superior to AFP for detection of HCC. Some of these markers are also non-specific and can be found in non-malignant liver lesions or other malignancies (9).

Liver imaging

Ultrasonography

Ultrasonography (US) is a non-invasive test that allows determining the size, location, morphology and vascular involvement of liver lesions (17). This mode of imaging is widely used for surveillance with sensitivity of 60-80% and specificity of 45-94%. The sensitivity of the test can increase to 53-87% when done by experienced professionals (38).

Contrast-enhanced US (CEUS) has become popular due to its capacity for stable and real time observation with improved detectability of peripheral blood flow under vascular phase imaging (39). In addition, its dye is safe to be used in patients with nephropathies and other contrast allergies (17). The microbubbles of Sonazoid accumulates in the reticuloendothelial tissue such as Kupffer cells. This property will allow differentiating between benign and malignant lesions in the post vascular phase. Deeply located lesions and blind spots can be missed however on the imaging (39).

The appearance of HCC on US is variable and non-specific ranging from hypo or hyperechoic lesions with or without heterogeneity or necrotic areas. The role of ultrasound is limited to the detection of tumours <2 cm and tumours in a liver with a heterogeneous background and diffuse nodular pattern (17)

To characterise various nodules in a cirrhotic liver, it is important to evaluate the blood supply to the nodule. In advanced HCC, a nodule is seen to be supplied by abnormal arteries, while in regenerative and dysplastic nodules, normal hepatic arteries and portal veins can be seen supplying the lesion (40).

A systematic way of performing and reporting ultrasound features has been suggested by Ultrasound Liver Imaging and Reporting Data System (US LI-RADS) and shown in Table 3. This can further help in management recommendation (41).

Category	Criteria
LR-1	Simple cyst, classic hemangioma, focal fatty change, or focal fatty sparing
LR-2	Nodule size <10 mm, no AP enhancement, no washout, no additional enhancement patterns OR LI-RADS 3 observa- tion stable for ≥2 years
LR-3	Nodule size ≥10 mm, no AP enhancement, no washout, no additional enhancement patterns OR nodule size <10 mm, AP enhancement, no washout OR nodule size <20 mm, no AP hyperenhancement, and washout (≥60 seconds)
LR-4	Nodule size ≥10 mm, AP hyperenhancement, no washout OR nodule size <10 mm, AP hyperenhancement, and wash-out OR nodule size ≥20 mm, no AP hyperenhancement, and washout (≥60 seconds)
LR-5	Nodule size 10 mm, AP hyperenhancement, and washout
LR-M	Nodule of any size and washout (<60 sec) OR marked washout within 2 minutes OR rim enhancement and washout
LR-NC	Not categorizable due to image degradation or omission
LR-TIV	Tumor within the portal vein, hepatic vein, or both

Table 3. Contrast-enhanced US LI-RADS Diagnostic Categories (42)

Note-Arterial phase (AP) hyperenhancement is defined as diffuse enhancement with unequivocal nodule hypervascularity and no evidence of peripheral globular or rimlike enhancement. LI-RADS= Liver Imaging Reporting and Data System, LR-1 = definitely benign, LR-2-probably benign, LR-3 intermediate malignancy probability, LR-4 probably hepatocellular carcinoma (HCC), LR-5 - definitely HCC, LR-NC = cannot be categorized due to image degradation, LR-TIV = tumor in vein, and LR-M = probably or definitely malignant but not HCC specific.

CT

With the new advances in understanding HCC specific radiologic findings, the diagnosis of HCC can be safely done without need of histological sample in most of cases. The AASLD and EASL guidelines state that the diagnosis of HCC can be made radiologically if a new mass measuring ≥1 cm is found that demonstrates arterial hyper-enhancement and venous washout in a cirrhotic liver using either multiphasic contrast computed tomography (CT) or MRI (8).

Computed tomography has a high sensitivity (55-91%) and specificity (77-96%) in diagnosing HCC (43). For lesions larger than 1cm in size, using either CT or MRI is sufficient. For lesions between 1-2 cm in size, EASL-EORTC guidelines recommend using both modalities in non-expert centres (44).

The main diagnostic criteria on CT scan include hypervascularization on the arterial “wash-in” phase and washout during portal phase of enhancement, which is similar in cirrhotic and non-cirrhotic livers. On non-contrasted phase, CT shows hypo-attenuation. HCC lesions are usually well-circumscribed and encapsulated. Other specific features of lesions such as fat involvement, foci of haemorrhage and necrotic areas are more commonly seen in non-cirrhotic HCC (17).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is superior to CT for the diagnosis of HCC (17). Sensitivity of MRI for HCC detection can reach 89-100%. For lesions between 1 and 2cm, specificity can reach to 84% and 47% respectively. Because of its lower availability and higher cost, the use of MRI is limited, especially in resource-poor countries (38).

The HCC appearance on T1 sequences depends on the degree of fibrosis, necrosis and the presence of fat, but most commonly appears hypo-intense on T1 and hyper-intense on T2 images (17). Up to 30% of HCC nodules can be isointense on T2-weighted images and 12% to 50% can display a hyper-intense signal on T1-weighted images which is explained by the presence of fat, copper, iron, protein, and glycogen within the lesion (43). In the contrasted phase, HCC shows enhancement in the late arterial phase and is isointense to the liver parenchyma on portovenous phase and hypointense on the delayed images (45), (figures 2 & 3).

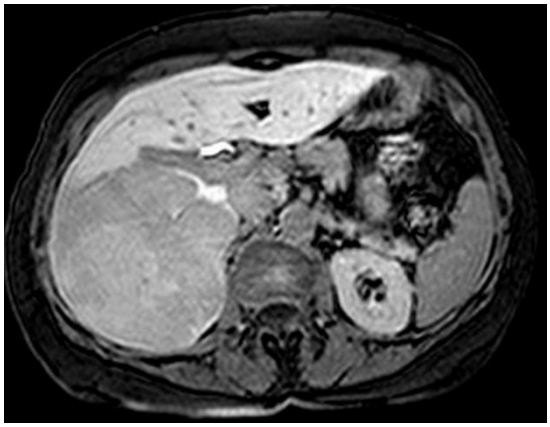

Figure 2. Right liver lobe HCC

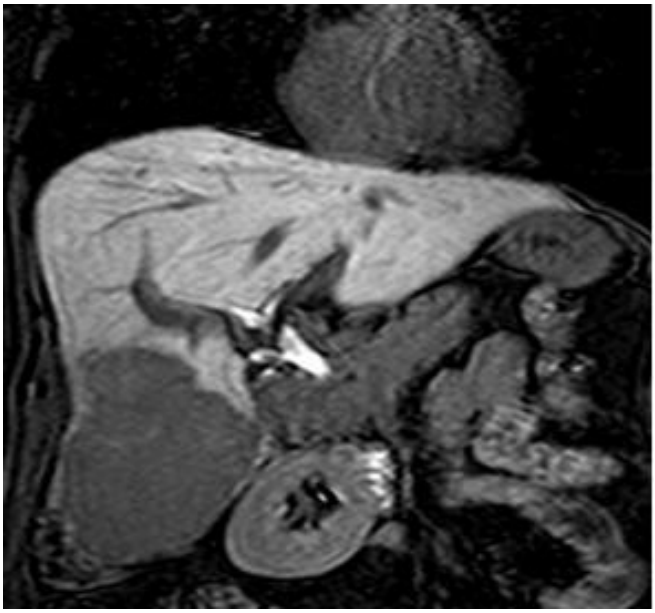

Figure 3. HCC involving liver segments 5 and 6

The presence of intra-lesional fat signifies a better prognosis. This finding can be detected more easily on MRI compared to CT or CEUS. A high fat content is seen in 10-17% of non-cirrhotic HCCs and in 36% of well differentiated HCCs (17). A non-cirrhotic liver represents a challenge in differentiating between HCC and benign liver lesions such as focal nodular hyperplasia and hepatocellular adenoma (17).

Diffusion Weighted Imaging (DWI) measures diffusion of water molecules. In HCC, cells are smaller than normal hepatocytes resulting in high number of cells per voxel and restricting the water diffusion. This will result in higher signal intensity on DWI images compared to normal liver parenchyma (46).

DWI can be also useful for assessing prognosis, and predicting and monitoring response to treatment (46). A recent study showed that DWI has a lower sensitivity (60.7%) for the detection of local HCC recurrence after transarterial chemoembolization (TACE) compared to contrast-enhanced imaging (82%) (43). In patients with a high risk of HCC recurrence, the use of Gadoxetic acid liver MRI and DWI may improve the differentiation of non-specific new arterial enhancing foci from early hypervascular HCC recurrence in patients with non-occlusive findings on extracellular liver MRI with high specificity (90.9%) and positive predictive value (95.8%) (47).

Another proposed use for the DWI is its prediction of the histopathological grade of HCC. A lower mean ADC has been reported in moderately to poorly differentiated HCC compared to well-differentiated HCC. Muhi et al. observed a 95% early recurrence rate in patients with tumour ADC of ≤0.898 × 10−3 mm2/s (48).

DWI shows promise as an imaging biomarker, since restricted diffusion can indicate the presence of progenitor cell markers, vascular endothelial growth factor (VEGF) expression and microvascular invasion. A summary is presented in Table 4 (46).

Tumour Grade	ADC	Potential association
High differentiation	Good diffusion	No reported association
Well differentiation	Moderate diffusion	No reported association
Poor differentiation	Restricted diffusion	Presence of progenitor cell markers 1
Scarce differentiation	Scarce diffusion	Presence of progenitor cell markers 1, vascular endothelial growth factor (VEGF) expression2-51, and microvascular invasion52.

Table 4. Role of DWI as a biomarker (46)

<u>Positron emission tomography</u>

Glucose metabolism of cancer cells are significantly higher when compared to normal cells. Like glucose, fluorine-18-fluorodeoxygluose (FDG) is also taken up by the cancer cells via glucose transporters (49). Sensitivity of FDG positron emission tomography/CT (18F-FDG PET/CT) for HCC is reported to be between 40 and 60% (49) and is not satisfactory in detecting well differentiated HCC (50, 51).

Due to low sensitivity of FDG-PET, other radionuclides have been used with more promising results. ^{11}C-acetate is a precursor for phospholipid synthesis with a higher MRI sensitivity for HCC than PET and is used for monitoring the tumour response post loco-regional treatment. Another useful radionuclide is ^{11}C-choline which has proved to be useful in imaging and therapeutic management of HCC (52).

A systematic review and meta-analysis has recommended dual tracer PET imaging which increases the diagnostic accuracy of HCC. The authors reported that FDG-PET was better in cases of poorly differentiated HCC while radiolabelled choline PET/CT is more valuable in detecting other HCCs (49).

Liver biopsy

Non-invasive diagnostic criteria for HCC have only been validated in patients with cirrhosis who have been followed up with six-month interval ultrasound examinations. Furthermore, the diagnosis of HCC in nodules <1cm especially in non-cirrhotic patients can be challenging if the nodules do not show the characteristic features of HCC (53). Therefore, EASL guidelines strongly recommend a liver biopsy to confirm the diagnosis of a HCC in non-cirrhotic livers (53, 54). AASLD guidelines do not recommend a biopsy for lesions >1cm if two different imaging studies yield concordant findings (17).

Liver biopsy is done under CT or US guidance with varying degrees of sensitivity (66%-93% based on tumour size, operator experience, and needle size) and 100% specificity and positive predictive value (17, 53). The diagnostic accuracy is lower in lesions < 3 cm (50%-83%) (55).

Besides the histological diagnosis for doubtful cases, tissue is sampled for investigations in clinical trials. The histological sample is reported for HCC histotype, grade, vascular invasion, morpho-molecular type, expression of phenotypic markers of prognostic impact such as CK-19 and the degree of fibrosis of the non-neoplastic liver tissue (53).

Major problems with histopathological examination of HCC include differentiating well-differentiated HCC with benign lesions such as regenerative nodules, dysplastic nodules, focal nodular hyperplasia (FNH) and hepatocellular adenoma (HA) (Figure 4) (56). Similar features between HA and HCC include relative monomorphic hepatocytes and lack of true portal tracts as well as thin-walled unpaired arteries and in the background of steatosis and focal loss of reticulin, differentiation between the two can be diffuclt (57). On the other side of the spectrum, histological differentiation betweeen HCC and cholangiocarcinoma or metatstatic carcinoma can be challenging as well (56).

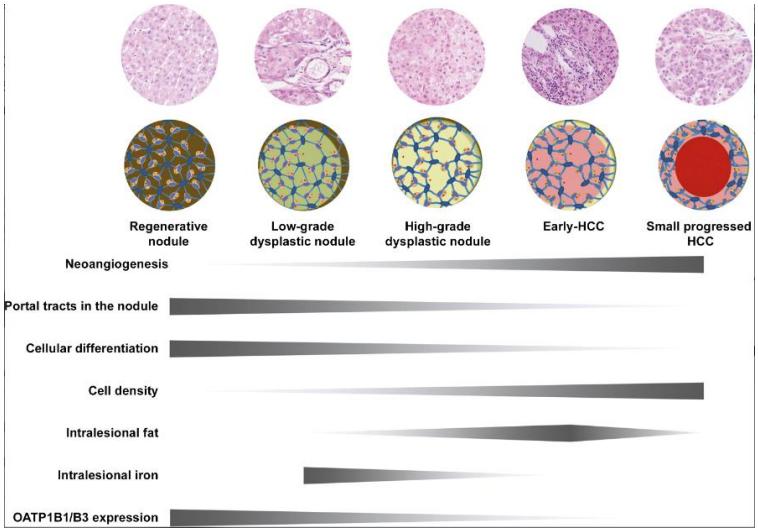

Figure 4. Temporal development of histopathologic changes during hepatocarcinogenesis and their imaging correlated (58)

The role of a liver biopsy is limited because of the fear of seeding thorough the needle tract. The larger the needle diameter and the number of passes, or the lower the degree of tumour differentiation, the higher the risk of seeding (55). The real risk is unclear. A meta-analysis by Silva et al in 2008, showed the incidence of needle tract tumour seeding following HCC biopsy was 2.7% overall and 0.9% per year (59). Later studies showed a lower incidence rate of less than 1% (53, 60, 61).

Diagnostic laparoscopy

Even though laparoscopy is a widely used diagnostic tool for a variety of intra-abdominal and hepatobiliary malignancies (62, 63), the use of laparoscopy specifically for patients with HCC is still largely undefined (62). Operative morbidity is estimated to be 5% with mortality of 0% (64).

Proper assessment of the utility of staging laparoscopy is critically dependent on the extent and quality of the preoperative imaging. Patients with liver cirrhosis, major vascular invasion and bilobar tumours were identified to benefit more from diagnostic laparoscopy prior to an attempted resection (62).

Combining diagnostic laparoscopy with intra-operative ultrasound can optimize patient selection for curative hepatic resection and may discover unresectable disease in as many as 63% of patients (65, 66). The addition of intra-operative ultrasound confirms the location and number of lesions diagnosed by

conventional imaging with higher quality and definition. (65). On the other hand, challenges with this technique can include difficulty in maintaining close probe contact with a nodular liver surface and difficulty in delineating regenerative nodules from neoplastic lesions in cirrhotic patients (64).

Pathology

Non-cirrhotic HCC

While HCC commonly arises in a cirrhotic liver, approximately 10% occur in non-cirrhotic livers in most populations. Some studies have found that this figure may be as high as 20% in the general population (67). This rate increases to 40% in black patients (10, 68). Non-cirrhotic HCC has a bimodal age distribution with peaks at the 2nd and 7th decades of life (67). HCC occurs more commonly in males irrespective of the underlying liver disease and cirrhosis (69).

These HCCs occur usually in chronic HBV infection and in patients with non-alcoholic fatty liver disease (NAFLD). BCP T1762/A1764 mutation and high HBV viral load are independent factors for HCC in non-cirrhotic patients. Older age, African American and Asian race are also considered risk factors in these patients (17). Due to the increasing incidence of NAFLD in the Western World, the incidence of non-cirrhotic HCC is likely to increase in future (67, 68). Differences between HCC and NCHCC are summarized in Table 5.

Studies have shown that non-cirrhotic HCC tends to have a poorer differentiation and more aggressive behaviour (10). Because of the normal underlying liver tissue, HCC in non-cirrhotic patients are usually diagnosed late (67, 68). These patients do not present with symptoms until the lesions is large in size and by the time the diagnosis is made, the HCC is at an advanced stage which requires more extensive surgery to achieve a R0 resection (68).

The risk of tumour recurrence exceeds 70% at 5 years after resection. In the absence of extra-hepatic disease, the presence of vascular invasion and positive resection margins are risk factors for high recurrence rates (10, 70). Surprisingly patients with non-cirrhotic underlying livers have higher recurrence rates which has been attributed to higher rates of resection compared to the need for transplant in cirrhotic patients. No recurrence rate difference was noticed when comparing specific procedures in cirrhotic and non-cirrhotic patients (70).

Multiple tumours, large tumour size, non-R0 resection and lympho-vascular invasion are poor prognostic factors. R0 resection, although non-statistically significant, can impact on patient survival (69). Peri-operative morbidity and mortality are 29.5% and 2.7% respectively, which is lower than cirrhotic liver resection (17, 68).

	HCC	NCHCC
Epidemiology	Eighty percent of HCC develop in a cirrhotic background. A unimodal age distribution (peak in 7th decade) noted. Male:female ratio - 3:2	Twenty percent of tumours develop in a non-cirrhotic liver. A bimodal age distribution (peak in 2nd and 7th decade) noted. Male:female ratio- 2:1
Risk factors	Development of cirrhosis from any aetiology can progress to HCC. Hepatotropic viruses, environmental and life-style factors (alcohol, tobacco), metabolic conditions (nonalcoholic fatty liver disease, diabetes mellitus, obesity) play a predominant role noted	NCHCC develops without a background of underlying cirrhosis. Viral (HBV, HCV infection) and non-viral risk factors (obesity, diabetes mellitus, toxin exposure, germline mutations and genetic disorders) noted
Clinical features	Symptoms could be related to underlying cirrhosis (from portal hypertension) or HCC (early satiety, upper abdominal pain) itself. Paraneoplastic signs such as hypercalcemia, hypoglycaemia have been reported	Generalized fatigue, abdominal pain and weight loss are common symptoms. Can present at late stage with large tumour burden, extrahepatic metastasis
Diagnosis	High quality cross-sectional imaging (CT/MRI) are used with typical arterial phase hyper-enhancement and portal venous washout. LI-RADS classification is used in classification of radiological findings in HCC	Although CT and MRI are increasingly utilized for diagnosis, liver biopsy are utilized in patients when cross-sectional imaging is equivocal. LI-RADS classification cannot be utilized for NCHCC and instead tumor characteristics (size, imaging features) are utilized for staging
Treatment	Given the underlying cirrhosis, liver transplant candidacy need to be evaluated for HCC patients. Resectability of the lesion, amount of liver reserve, vascular invasion, performance status determine the treatment outcomes	Antiviral treatment recommended when aetiology of NCHCC is HBV/HCV. Surgery remains the main treatment modality. Systemic and local therapy options are increasingly being utilized for NCHCC

Table 5. Key differences between non cirrhotic hepatocellular carcinoma and hepatocellular carcinoma (67)

A recent retrospective study in Germany evaluated overall survival (OS) in patients with non-cirrhotic HCC post-resection. The median OS was 35 months with 3 and 5 year survival rates of 64% and 47%, respectively. Tumours less than 3cm in diameter, unifocal lesions, no vascular invasion and normal serum

AFP were associated with significantly better OS (68). A recent systematic review analysis in China showed 5 years OS and Disease Free Survival (DFS) after non-cirrhotic HCC resection ranged from 30 – 61.4 and 24.01 – 58% respectively. No significance difference in outcome was seen when late and early stage non-cirrhotic HCC liver resection was compared (69).

Heptatocellular carcinoma in cirrhosis

The incidence of liver cirrhosis has steadily been increasing during the past 30 years in the USA, while cirrhosis-related mortality decreased by 22% (71). Approximately 80% of HCCs develop in a background of liver cirrhosis (67). Liver cirrhosis has a 2.79 to 45 fold increase risk for HCC compared to non-cirrhotic patients (72). Viral hepatitis, alcohol-associated liver disease (ALD) and non-alcoholic steatohepatitis (NASH) are major risk factors for cirrhotic HCC (73).

The complex architecture of the liver makes the surgery challenging. The challenge for resection in cirrhotic livers is even higher because of the impact of surgical stress and trauma imposed on borderline liver function and the impaired ability for liver regeneration in cirrhotic livers. Important aspects to be considered during liver resection is the functional status (including evidence of portal hypertension) and the future liver remnant (74).

Liver resection in cirrhotic patients is associated with higher morbidity and mortality (71). Child B and C categories are independent factors for increased morbidity. In the early 1980s, the mortality rate after resection was high and ranged from 16% to 26%. In recent years with new advances in surgical techniques and improved perioperative care, the mortality rate has decreased to 5% (75).

Impaired liver function, especially coagulopathy, hyperbilirubinaemia and hypoalbuminaemia have been found to be associated with poor outcome after liver resection (68). Although liver cirrhosis is a major cause of post-operative HCC recurrence due to hepatocarcinogenesis, the pattern and annual rate of post-operative recurrence is still unclear (76). Studies have shown the highest rate of recurrence in cirrhotic HCC is seen after loco-regional therapy. This rate decreases after a major resection and lowest risk is after liver transplantation (73).

Fibrolamellar carcinoma

Fibrolamellar carcinoma (FLC) was considered to be a rare variant of HCC in the 4th WHO classification of tumours of the digestive system which was published in 2010 (77). The term “fibrolamellar” has been

applied in view of the thick fibrous collagen bands surrounding the tumour cells,. Other terminologies such as eosinophilic HCC with lamellar fibrosis, HCC with polygonal cell type and fibrous stroma, eosinophilic glassy cell hepatoma and fibrolamellar oncocytic HCC have been used in the past (11).

Unlike HCC, viral hepatitis and liver cirrhosis are not considered risk factors. Less than 10% of all FLC have a background of liver cirrhosis (78). Historically, FLC was considered as subtype of HCC. But given the histological appearance, the origin from non-cirrhotic liver and association with low AFP, FLC is now considered a unique entity (22).

Due to rarity of the disease, most publications are small case series. Fibrolamellar carcinoma compromises 1 to 9% of HCCs (79, 80). While some single institutional studies report a male predominance, results from the United States' National Cancer Data Base state that there is a female predominance (80). FLC occurs more commonly in a younger age group but also appears to have two peak incidences with the another group occurring between 70 and 79 years (80, 81).

Fibrolamellar carcinoma are usually large and single tumours with well-defined margins that demonstrate rapid growth outgrowing the blood supply and have central scars (78). Unlike HCC, alpha-feto protein levels are not elevated. Instead, high levels of aromatase, B12 binding protein and neurotensin can be expected with these tumours (22). The disease is associated with DNAJB1-PRKACA fusion mutation (80). The same gene mutation is also found in other pancreaticobiliary tumours, resulting in the question of the primary stem cell of FLC (22).

Currently no randomized control trials have been done to determine the most efficacious chemotherapy regimen and no neoadjuvant/adjuvant chemotherapy has shown improved survival post disease resection (78, 82). The best outcome is achieved by complete surgical resection (81). Even when a R0 resection is achieved, recurrence rates are as high as 71% (78, 80, 82). Most patients (approximately 60%) are stage IV at the time of diagnosis with perihilar lymph nodes the most common site of metastases (80).

Association between hepatocellular carcinoma and cirrhosis

The majority of HCC positive patients in the world have underlying liver cirrhosis. Two mechanisms of HCC development have been postulated in cirrhotic patients.

An underlying chronic inflammatory process in cirrhotic patients results in the formation of regenerative nodules. These regenerative nodules can undergo dysplasia and become malignant. This transformation is in keeping with nodular pattern of growth with surrounding capsule resulting in nodular type of HCC (83).

The second mechanism is by the more direct effect of viral hepatitis integrating into the hepatocyte genome. This may result in a number of molecular events ending with neoplastic transformation. The gene incorporation is independent of the regeneration nodules and can occur in any region of the hepatocyte with more rapid spread of the disease (83).

Several models have been developed to predict the risk of HCC in patients with liver cirrhosis. The ADRESS-HCC model which was based on a cohort of cirrhotic patients from the National Liver Transplant data base, showed that the overall incidence of HCC was 2.9 per 100 person per year (73). Age, sex, race, diabetes, aetiology and severity of cirrhosis were statistically associated with HCC development. The Toronto HCC risk index (THRI) was based on a cohort of cirrhotic patients secondary to HCV, HBV, ALD and NAFLD. The 10 year incidence in this model was 23% for HBV, 21% in HCV (7% in HCV achieving sustained virologic response), 18% in ALD and 13% in NAFLD. Despite different models available, challenges remain how to incorporate these risk-based models into clinical practice (73).

Aetiology

Chronic hepatitis B infection

The hepatitis B virus is member of hepatotropic DNA virus family, called the *Hepadnaviridae* (9). Hepatitis B is a partly double-stranded DNA virus (84) which infects humans and higher primates only. As a result, the hepatitis B virus causes acute and chronic infection in the liver with progression of chronic inflammation into malignancy (9).

Chronic HBV infection accounts for most of the HCCs worldwide with an annual incidence of 0.2% in all HBV chronic infections older than 40 years and 3-8% in patients with HBV with liver cirrhosis (85). The risk of HCC development increases in patients with Hepatitis C virus (HCV) and Human immune-deficiency Virus (HIV) co-infections (86), black Africans, high viral load (more than $1X10^4$ copies), cirrhosis and positivity of E-antigen (9). Mortality rate increases in male, advanced age and black African people (1, 7).

Compared to other causes of HCC, HBV-related HCC tends to affect a younger population. Up to one third of infected patients will not have cirrhosis associated with HCC. In these patients, HBV can directly intergrate with the hepatocyte DNA resulting in genomic instability and direct mutagenesis (86). The remaining patients develop HCC in the context of liver cirrhosis as a consequence of chronic inflammation and development of premalignant lesion, a pathophysiology which is not completely understood (7).

The rate of HBV-related HCC is decreasing in high prevalence areas of HBV infection. This is mainly because more than 90% of countries worldwide have incorporated a HBV vaccine programme into their health system, resulting in a dramatic decrease in HBV-related HCC (87).

Chronic hepatitis C infection

Chronic hepatitis C infection is a *Hepacivirus* within the *Flaviviridae* family (9) and is an enveloped RNA virus (88). The lack of proof-reading capability of the RNA-dependant RNA polymerase results in high mutational rate and variation in genomic structure. As a consequence of type, multiple genotypes of the virus are known (9).

The 5 year risk of developing HCC in patients with chronic HCV infection ranges from between 1 to 13% (7). Multiple pathophysiological factors contribute to the development of HCC in these patients. First is the development of cirrhosis as a result of chronic inflammation (89, 90). The inflammatory cascade results in fibrosis starting mainly in the peri-portal region and ending with liver cirrhosis pre-disposing to HCC formation. While the inflammatory cascade is considered an indirect pathway of carcinogenesis, HCV can directly interrupt signal transduction pathways which control cell survival, proliferation and transformation. (89)

Achieving sustained virological response (SVR) results in regression of fibrosis. This phenomenon is easier to occur in the context of mild to moderate fibrosis (89). Effective anti-viral treatment to achieve SVR has shown to significantly reduce the risk of HCC. The risk reduction was observed more in patients with cirrhosis compared with patients in different stage of fibrosis (91). Due to the continuous risk of HCC in patients with established cirrhosis or established fibrosis, EASL and AASLD guidelines recommend lifelong surveillance in these patients even after achieving SVR (89).

Besides the above mentioned factors, co-infection with HBV, untreated HIV, obesity, diabetes and insulin resistance as well as steatohepatitis can further increase the risk of HCC development (7, 15).

Alcohol

The World Health Organization (WHO) Global Status Report on Alcohol and Health estimated that 2.3 billion people are current alcohol drinkers, who consume an average of 32.8 g of pure alcohol per day (92). Chronic alcohol use has been linked to the development of multiple malignancies. This risk starts with a dose as low as 10 g/1unit/day (93). Doses of 80g/day for more than 10 years have been associated with HCC development and increasing the risk by approximately 5 folds (94).

In USA and Europe, alcohol is the second most common risk factor for cirrhosis and HCC formation. Age older than 55 years and thrombocytopaenia were reported to be independent risk factors for the development of HCC in alcoholic cirrhosis patients (8).

Alcohol can be considered the main cause for development of HCC as result of liver cirrhosis as well as co-factor when combined with other aetiological factors such as viral hepatitis (94). The carcinogenic effect of alcohol is via the direct effect of acetaldehyde. The metabolites result in the formation of reactive oxygen species and DNA damage with impaired repair (7, 93).

Aflatoxin B1

Aflatoxins are mycotoxins that contaminate staple cereals and oilseeds. Aflatoxins exert potent carcinogenic properties resulting in formation of HCC especially when Aflatoxin B1 (AFB1) is produced by Aspergillus Flavus and Aspergillus parasiticus (8, 17).

The carcinogenic effect of AFB1 is the result of mutations in the TP 53 tumour suppressor gene, substituting arginine for serine (8).The highest exposure is in SSA, southeast Asia and China (17) with high level documentation beyond the WHO safety level of 30 µg/kg (7).

The synergistic action of HBV with AFB1 has been reported (8, 17). Meta-analysis studies in China, Taiwan and SSA, confirms these findings. These studies have shown in patients with AFB1 toxicity and positive HBsAG, odds ratio for HCC formation is 73·0 (95% CI 36·0–148·3) comparing to AFB1 or HBV exposure alone with OR 6·37 (3·74–10·86) and 11·3 (6·75–18·9), respectively (7)

Dietary iron overload in sub-Saharan Africa

Secondary iron overload is seen with different haematological disorders (17). In SSA, this is mainly seen in Black African people in association with the consumption of traditional beer which is as high as 82mg/L in iron content (7). The risk of HCC secondary to iron overload in southern Africa is 10·6 (95% CI 1·5–76·8) (95).

Excess iron produces free radicals and reactive oxygen species resulting in oxidative stress, lipid peroxidation, protein modification, DNA damage, necrosis and apoptosis of hepatocytes (with consequent exhaustion of antioxidant defences and promotion of mutagenesis), frequent mitosis, and hepatic fibrosis (7, 96)

Treatment

Transarterial therapies

Trans-arterial chemoembolization (TACE) is an established treatment for intermediate stage HCC (97). Barcelona Clinic Liver Cancer (BCLC) algorithm has defined the indication for TACE in HCC. The 2022 guideline (figure 5) indicated TACE should be used in the second sub-group of intermediate stage. The intermediate stage is defined as multifocal HCC with preserved liver function, no cancer related symptoms (performance status 0) and no vascular invasion or extra-hepatic spread. A second sub-group is compromised of patients without the option of a liver transplant who have preserved portal flow and a defined tumour burden (27).

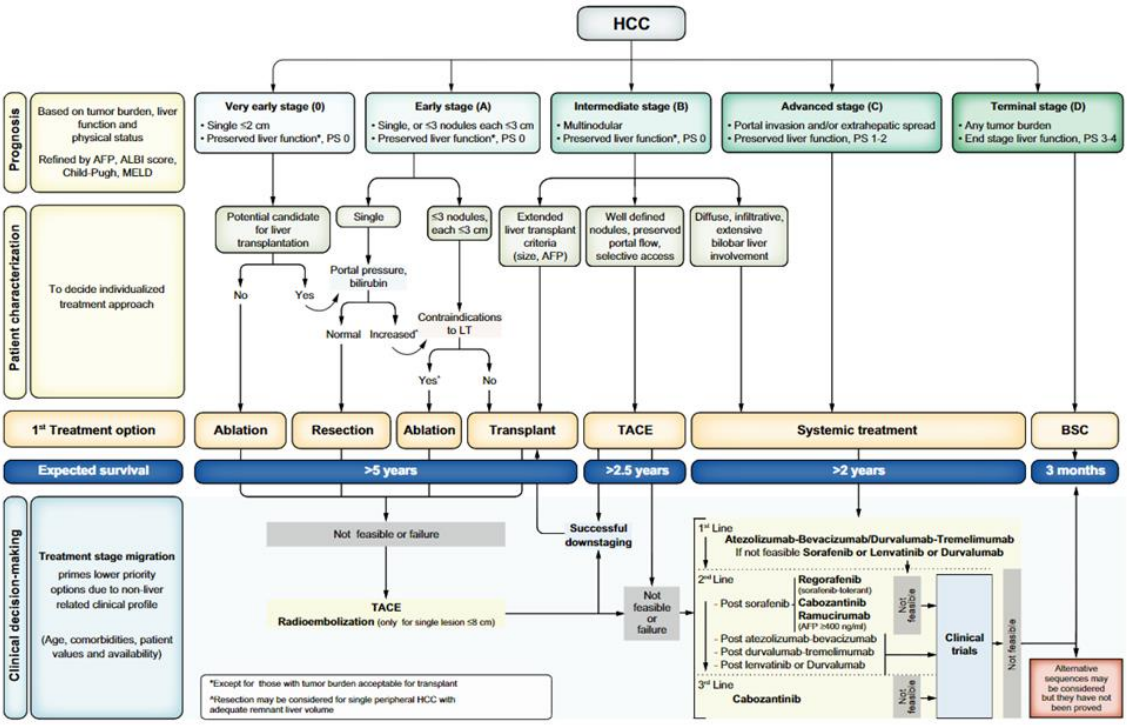

Figure 5. BCLC staging and treatment strategy in 2022 (27)

The BCLC system established the prognosis in accordance with the 5 stages that are linked to first-line treatment recommendations. The expected outcome is expressed as the median survival of each tumour stage according to the available scientific evidence. Individualised clinical decision-making, according to the available data on November 15, 2021, is defined by teams responsible for integrating all available data with the individual patient's medical profile. Note that liver function should be evaluated beyond the conventional Child-Pugh staging. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; ECOG-PS, Eastern cooperative Oncology Group-performance status; LT. liver transplantation; MELD, model of end-stage liver disease; TACE, transarterial chemoembolization.

The BCLC system also incorporates the treatment migration concept in that TACE should be used in patients with early-stage HCC in whom the recommended treatments are not feasible or have failed. The use of TACE is also supported by other staging systems, such as the Japanese Integrated Staging (JIS) scoring system (98), the Chinese University Prognostic Index (CUPI) (99), and the Hong Kong Liver Cancer (HKLC) staging system (100), all of which have been validated in Eastern Asian populations (101).

In June 2014, the revised Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma, proposed by the Japan Society of Hepatology (JSH), suggested TACE should to be the first choice of treatment in Child-Pugh A/B patients with four or more HCC tumour nodules. The combination of TACE and ablation were indicated for lesions less than 4 in number and nodules exceeding 3cm, if resection was not indicated (98).

TACE is also used as neoadjuvant therapy prior to liver transplantation. TACE is mainly used for patients while waiting on the list or as down staging of tumour burden to accepted criteria for transplantation. Use of conventional TACE (cTACE) while waiting for transplantation is associated with 3-13% waitlist dropout which is lower than expected (101). Moreover, cTACE has been shown to reduce HCC recurrence after LT and to improve post-transplant overall survival, especially when the period on the waiting list exceeds 6–12 months (101, 102).

The superiority of TACE over best supportive care has been shown for advanced HCC with portal vein thrombosis in randomized clinical trials (101, 103, 104) and meta-analysis (105). In real world clinical practice, TACE is used as first line treatment for up to 50% of BCLC stage C HCC patients (101, 106).

Multiple scores have been developed to aid in patient selection either for first time TACE use or re-TACE. Predictive values of these scores have not been demonstrated. Instead, tumour burden, BCLC stage at baseline, Child-Pugh score and radiological responses are used for decision making and consideration of alternative therapy (101). A summary of scores and their components are presented below in Table 6.

	To decide for 1st TACE		To decide for re-TACE	
	STATE	**HAP**	**ART**	**ABCR**
	Baseline (before 1st TACE)			
Albumin	In g/L as score points	36 g/dL (1 point)	-	-
Bilirubin	-	>37 µmol/L (1 point)	-	-
Tumor load	Beyond up-to-seven criteria (-12 points)	Max tumor diameter >7cm (1 point)	-	-
CRP	≥1 mg/dL (-12 points)	-	-	-
BCLC stage	-	-	-	A (0 point) B (2 points) C (3 points)
AFP	-	> 400 ng/mL (1 point)	-	≥200 ng/mL (1 point)
			After 1st TACE	
Child-Pugh score	-	-	1-point increase (1.5 point) ≥2 point increase (3 points)	≥2 point increase (2 points)
Radiologic tumor response	-	-	No (1 point)	Yes (-3 points)
AST	-	-	>25% increase (4 points)	-
Score range	Depends on serum albumin level (range greater than ART)	From 0 to 4	From 0 to 8	From -3 to +6

Table 6. Parameters used to calculate STATE, HAP, ART, and ABCR scores (101)

BCLC: Barcelona Clinic of Liver Cancer; AFP: alpha-foeto-protein; CRP: C-reative protein; STATE: selection for transarterial chemoembolization treatment; HAP: hepatoma arterial-embolisation prognostic; ART: Assessment for Retreatment; ABCR: Alpha- foeto Protein, BCLC, Child-Pugh, Response.

TACE can be given in conventional methods with the administration of lipiodol or by using Drug-eluting beads (DEB-TACE). The Lipiodol used in cTACE may cross the sinusoids into the portal venules and cause ischemia. This is turn will result in hepatic dysfunction and increase liver toxicity. While in the DEB-TACE, the embolic material will remain within the arteries (97). In PRECISION V trial, lower incidence of

hepatotoxicity and systemic adverse effects was seen with use of drug-eluting beads loaded with doxorubicin (107). Despite these advantages of DEB-TACE, no increased survival benefit was seen when compared to cTACE (108).

Hepatic artery embolization will cause tumour necrosis. High concentration of concomitantly used chemotherapy agent will retain in the tumour and lead to additive necrosis effect. On the other hand, regurgitation of the portal flow into the tumour from surrounding sinusoids facilitates tumour survival. High incidence of recurrence after TACE is secondary to this phenomenon. Local recurrence after TACE is reported to be 46, 58 and 63% at two, three and five year interval, respectively (109).

Tumour number, tumour size, PVT, and hepatic function were found to be predictors of the TACE response (97). In a randomized control trial done by Lo et al, tumour diameter of ≤5 cm was of a good prognostic factor (110). Sub-segmental TACE has the strongest anti-tumour effect compared to cTACE (109).

TACE has low mortality rate. In a study done by Takayasu et al, the incidence of mortality was calculated to be 0.5% (44 out of 8510 patients) (111). Post TACE syndrome manifests as fever and abdominal pain and usually appears several days post procedure. Other serious complications include post TACE syndrome, hepatic abscess and ischemic complications such as hepatic infarct, hepatic insufficiency, cholecystitis and bile duct necrosis (109).

The exact dose, frequency and best type of chemotherapy to be used with TACE are unknown. Doxorubicin, epirubicin, idarubicin, mitomycin C and cisplatin are some of the known chemotherapy agents used in TACE (101). Burrel et al (112) and Malagari et al (113), reported relatively good outcomes with use of doxorubicin DEB with median survival rate of 48.6 and 43.8 month, respectively. In the PERCISION V trial, six month response rates were 52% in DEB-TACE vs 44% in cTACE indicating non-inferiority of the DEB (107). Although there is no significant evidence from randomized control trials to replace cTACE for DEB-TACE, the efficacy of DEB-TACE for cTACE-resistant advanced HCC is promising (109).

The superiority of combined treatment of TACE and radiofrequency ablation (RFA) has been demonstrated in multiple randomized control trials (114, 115). Patients undergoing combined cTACE and RFA treatment had significantly better overall survival and recurrence-free survival than patients treated with RFA alone. This combined treatment can be considered as an alternative to surgical resection where there is a high likelihood of operative complications or similar to resection or in difficult positions

of the tumour when resection is considered (101). The combination of TACE with systemic therapy has also been investigated in multiple trials (116-119). None of above trials showed any clinical benefit from the combined therapy.

Ablation

Surgical resection and liver transplant are considered the standard curative therapies for HCC. When surgery is not possible, local ablation can be used as an alternative curative treatment (120). Ablations are most commonly performed percutaneously. Sometimes due to position of tumour (proximity to the diaphragm, vital visceral structures and major vessels or bile ducts), surgical ablation can be considered.

While tumour size and location are well-proven factors regarding the procedure feasibility and tumour control rate, tumour aggressiveness, the addition of a non-hypervascular hepatobiliary phase, hypointense nodules on gadoxetic acid enhanced MRI was recently found to be an important imaging biomarker related to survival after ablation (121).

Most commonly used ablation techniques for HCC are further categorized into thermal (Radiofrequency ablation – RFA and Microwave ablation – MWA) (101, 122, 123) and chemical (ethanol injection). Less commonly used ablation techniques are Cryo-ablation which is the other spectrum of thermal ablation and Irreversible Electroporation (IRE). A summary of the different ablation modalities is shown in Table 7.

Ablation modality	Temperature manipulation	Mechanism	Advantages	Disadvantages	Outcomes
Percutaneous ethanol injection (PEI)	No, non-thermal	Dehydration, induce coagulation, ischaemia	Cost-effective	Multiple sessions required	LR: 33% at 5 years
Radiofrequency ablation (RFA)	Yes, heat induction	Alternating current (460 kHz) between probe and tissue, induce coagulation, ischemia	Improved surgical margins compared to PEI	Skin burn, heat sink, bile duct injury	HCC size ≤ 3.5 cm, LR: 14% at 5 years
Microwave ablation (MWA)	Yes, heat induction	Water vibration producing heat (2400 MHz), induce coagulation, ischaemia	Synergy from multiple probes allow for larger ablation zones	Declining efficacy for HCCs > 4.0 cm, bile duct injury	HCC size > 5.0 cm, LR: 50%
Cryoablation (CA)	Yes, freezing	Ice ball formation from freeze, tissue death	Ability to see ablation zone (ice ball) during procedure	Bleeding/cryo shock	LR: 23% at 5 years
Irreversible electroporation (IRE)	No, non-thermal	Electric field alters cellular membrane, disruption exchange, cell death	Preserve bile duct allowing treatment of central tumours	Incomplete cell death at margins	LR: 32% at 3 years

Table 7. Summary of ablation modalities and associated characteristics (124)

Legends. LR Local recurrence; HCC hepatocellular carcinoma

Percutaneous ethanol injection (PEI) was an influential technique established in the early 1990s. Direct alcohol injection into small HCC tumour leads to cell dehydration, catalysing the coagulation cascade and leading to a fibrous scar. Sometimes multiple injections over course of few weeks are required in the same session if small calibre needles are used (124). The recommendation is usually for 4-6 treatment sessions over a few weeks (125).

The effect of PEI is not as widespread with involvement of surrounding tissues like the thermal ablations and surrounding satellite lesions can be missed during treatment. RFA has been shown to be superior to PEI with 1- and 2-years local recurrence-free survival rates of 98% and 96% in RFA vs 83% and 62% in PEI, respectively (124).

Thermal ablation for HCC has an excellent outcome and is performed in a more minimally invasive manner (121). RFA was developed in 1990 for the percutaneous treatment of HCC. RFA utilizes radiofrequency alternating current to induce heat between the percutaneously placed probe and the surrounding tissues ultimately leading to tissue coagulation necrosis and death. The best outcomes with RFA are seen with HCC lesions less than 3.5 cm with local recurrence rate of 14% and survival rate of 64%. (124).

Multiple randomized controlled trials have compared RFA with surgical resection for early-stage HCC. Results from these studies are contradictory (126). While studies from Chen et al (127) and Feng et al (128) showed similar survival between RFA and surgery, Huang et al (129) and Liu et al (130) demonstrated inferiority of RFA in terms of survival and local recurrence (126). A recent systematic review and meta-analysis comparing liver resection with local ablation therapies for HCC lesions within the Milan Criteria showed that liver resection was superior to RFA in terms of recurrence free survival and incidence of local recurrence. Moreover, liver resection was associated with better oncologic outcomes than MWA or RFA plus TACE (131).

Microwave ablation has recently gained popularity around the world because of its intrinsic advantages of faster ablation with high temperature and less susceptibility to the heat-sink effect when compared to RFA (121). MWA was originally developed in the 1970s as an adjunctive surgical technique to help control bleeding during surgical hepatectomies. Using energies along the microwave spectrum, this ablation modality disturbs water within the tumour and immediately adjacent surrounding tissues to generate extreme heat that ultimately causes coagulation and cell death (124).

Beside the heat-sink effect, MWA causes less skin burns as it does not uses a grounding pad. Larger zones of ablation can be done with MWA by placing multiple probes close to each other and creating a synergistic effect (124). A complete pathological response can be found in approximately 80% of cases of HCC (size between 5-7 cm) treated with MWA (124, 132).

Multiple studies have compared MWA and RFA (133-137). A meta analysis of 16 studies involving 2,062 patients by Huo et al (133) compared MWA vs. RFA. Few of the included studies showed better 6-year survival with MWA, while collectively there was no difference in 1-5 year overall survival, disease free survival, local recurrence and adverse events. A more recent meta-analysis showed similar therapeutic effects with MWA and RFA (135). In a randomized controlled trial by Yu et al (134), MWA was found to be superior with a higher thermal efficacy. The reported therapeutic outcomes of MWA for HCC were

promising with technical success rates ranging from 88% to 95%; progression-free survival rates of ≤92 and 5-year survival rates ranging from 43% to 60% (121, 134).

Resection

Curative treatment of HCC such as liver resection, liver transplantation and ablation can have a good outcome for the patient. Overall 5 year survival rates can reach to 50-70% if patients are diagnosed at an early stage (138). While liver resection is one of the main curative options for early HCC in patients with cirrhosis, it is considered the treatment of choice in non-cirrhotic HCCs eligible for resection. The absence of cirrhosis allows for larger and more complex resections, with recorded morbidity and mortality rates of 4 and 33%, respectively after major hepatic resections (139).

A comparison between anatomical and non-anatomical liver resections shows discrepant results. Theoretically, anatomical liver resections should improve clinical outcomes by reducing the risk of satellite distribution through the anatomical pedicle. This can explain the high local and liver recurrence rate which is as high as 80% in some patients. (4). The advantage of surgical resection is the availability of a histopathological specimen which can predict the recurrence such as microvascular invasion and/or satellite lesions (8). Adjuvant therapy with Sorafenib has not shown to be beneficial (140).

The aim of surgical resection is to achieve complete resection with negative margins while preserving as much liver volume as possible, thereby minimizing the risk of post-hepatectomy liver failure (PHLF) (141). Eligibility for resection is determined by tumour burden, liver function, extent of hepatectomy, expected volume of future liver remnant, presence of portal hypertension and other co-morbidities (8, 139). Figure 6 summarizes and compares different guideline criteria for HCC liver resection (138, 142, 143).

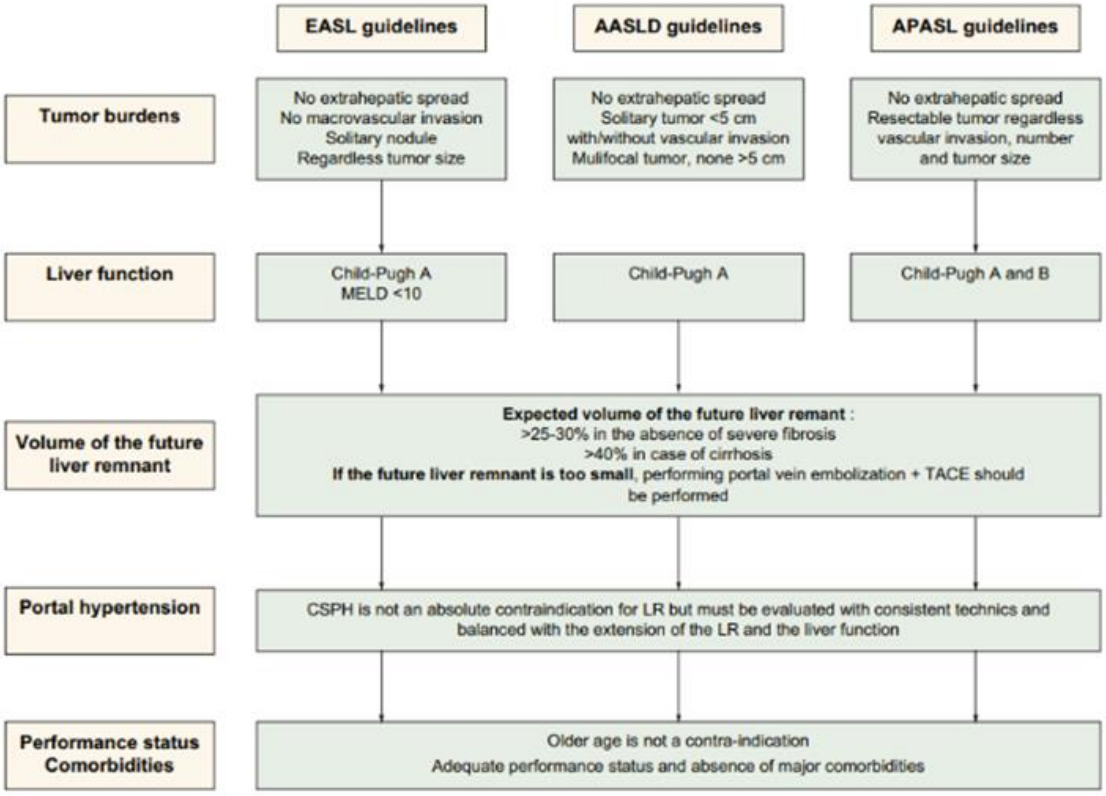

Figure 6. Current indication for liver surgery according to EASL, AASLD and APASL guidelines (139)

Previously, the resection criteria for cirrhotic HCC in western countries were defined as a single tumour, bilirubin <1 mg/dl with no portal hypertension. The overall survival in these patients was close to that of liver transplantation (5-year overall survival of 74% for liver resection and 69% for liver transplantation). In recent years, the criteria for resection has expanded (139).

The Child-Pugh score is calculated pre-operatively to estimate the liver function. Patients with a Child-Pugh score of B or C are considered high risk for surgery and may have liver failure even after a minor hepatectomy (139). The model for end-stage liver disease (MELD) score was recently incorporated into the EASL guidelines (138). Scores of 9 and above are associated with low overall survival post liver resection (144). The Albumin and Bilirubin (ALBI) score, Indocyanine green (ICG) clearance and ultrasound-based assessment of liver stiffness are other models used to assess functional status of the liver (4)

Clinically significant portal hypertension (CSPH) is defined as a Hepatic Venous Pressure Gradient (HVPG) >10mmHg and is considered to be a predictive factor for liver failure and death post liver resection (4,

139). Indirectly, the presence of portal hypertension is based on the presence of varices, splenomegaly and a low platelet count of <100,000 per µl (4). In CSPH, the extent of surgery is proportionate to the degree of post resection liver decompensation with mortality rates reaching 25% after major hepatectomies vs. 9% in minor hepatectomies (139).

Once the diagnosis of HCC is made, staging and a clinical decision assessment of the patient's performance status and presence of other co-morbidities is important. Metabolic syndrome, cardiovascular and respiratory diseases can influence surgical decision making as these are associated with higher post-operative complication rates (139).

When a HCC lesion is ≥2 cm, consensus from all guidelines are for liver resection as the first line of treatment. Differences in guidelines come when the tumour is found to be <2cm in diameter. While EASL and APASL guidelines prefer RFA as first line of treatment, liver resection remains the first choice in AASLD guidelines if feasible. When liver resection was compared to RFA, both had similar overall survival (139). RFA was associated with lower cost (139).

A small volume of future liver remnant (FLR) can result in PHLF and death, especially in cirrhotic patients. Different mechanisms have been reported for pre-operative augmentation of the FLR. Portal vein embolization (PVE) will aid in re-directing the portal flow to the FLR and liver hypertrophy. This process can take up to 4-6 weeks (145). The addition of sequential TACE to PVE has been proposed to prevent tumour growth between PVE and liver resection (139). This is associated with greater hypertrophy and longer DFS compared to PVE alone in retrospective studies (139, 146, 147)

High-dose trans-arterial radioembolization (TARE) of the portion of the liver to be resected induces atrophy of the treated lobe and compensatory growth of the FLR. Radio-embolization effect usually takes longer time (approximately 3 months) compared to PVE but has the advantage of treating the tumour at the same time (141).

Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) consists of right portal ligation and in situ splitting of the liver parenchyma (Stage 1), followed by completion of the hepatectomy (Stage 2) (139). The process of hypertrophy is very short, taking about 7-12 days (141). 90 day mortality is high with ALPPS and is estimated to be between 11 and 31% (139, 141). When ALPPS was compared with PVE, although higher resection rate was seen in ALPPS, but the short and long term outcomes were comparable with PVE (141, 148)

Surgical techniques

The various types of liver resection can be classified into anatomical and non-anatomical liver resections with further subclassification of anatomical into minor and major resection. Anatomic resection is defined as any type of complete excision of at least one segment based on Couinaud's classification containing the tumour together with the related portal vein branch and the corresponding hepatic territory (figure 7), while non-anatomical resection is defined as local resection or enucleation without regard to Couinaud's segmental or sectoral structure (149, 150).

A systematic review and meta-analysis by Sun et al. advised an anatomical liver resection in HCC for well-preserved liver function especially if microvascular invasion was likely. Anatomical liver resection was found to have higher rate of overall survival and disease free survival (149). Anatomical liver resection is associated with slightly higher operative time compared to non-anatomical resection, whereas post-operative complications, blood loss and intra-operative transfusion rates were comparable in both groups (149).

Several types of abdominal wall incisions can be used for a liver resection and depend ultimately on the tumour size and anatomical location and the surgeon's preference. The traditional incision is a bilateral subcostal incision with an upward midline extension if needed. A J-incision is another commonly used incision which provides good liver exposure and can be extended into thoracic cavity if needed. In cases of a small liver resection, an upper midline laparotomy may be sufficient (151).

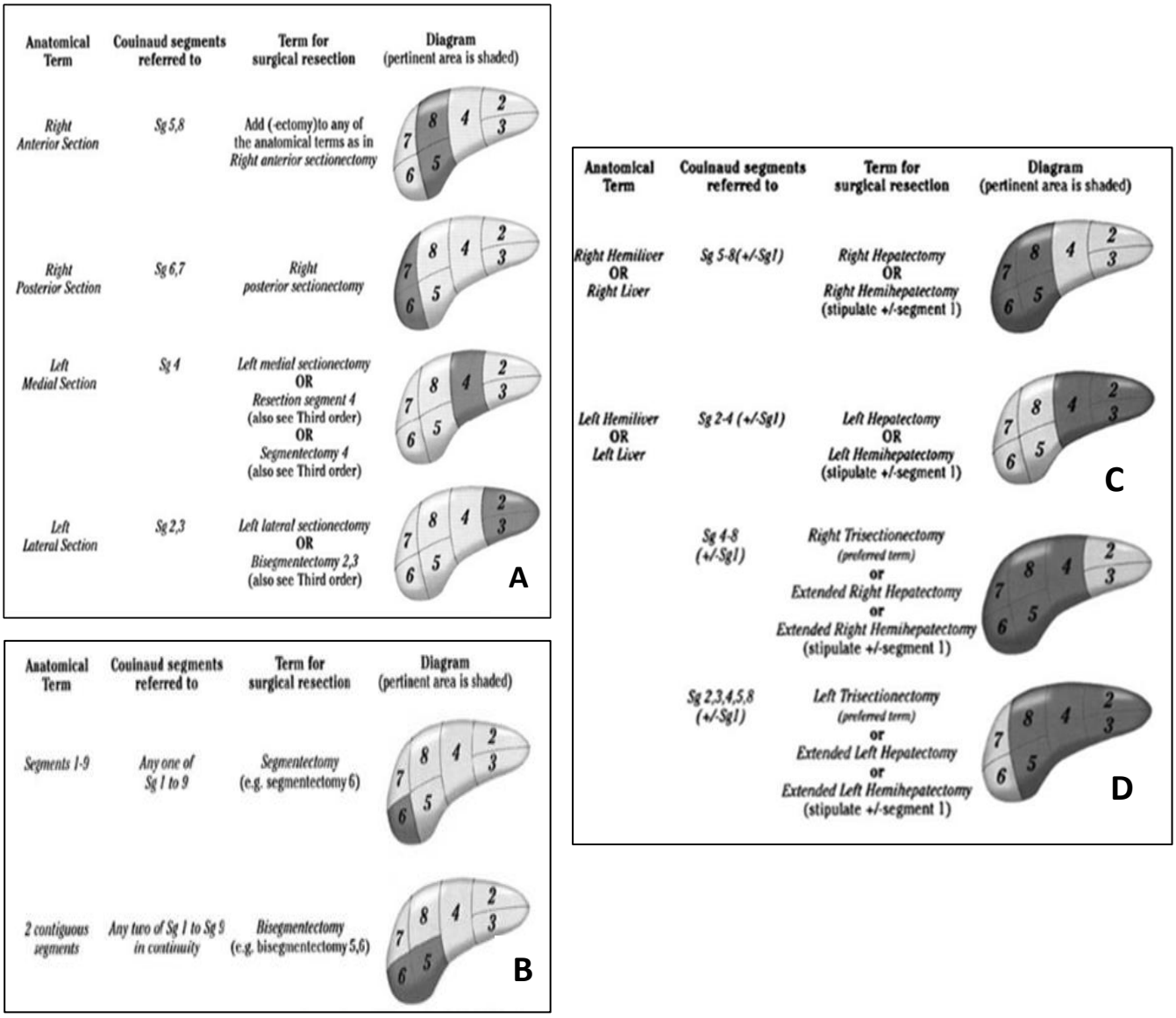

Figure 7. Anatomical classification of hepatectomy (152)

4A. Minor liver resection, nomenclature for second-order division anatomy; 4B. Minor liver resection, nomenclature for third-order division anatomy (for clarity, segments 1 and 9 are not shown in the image); 4C. Major liver resection, nomenclature for first-order division anatomy; 4D. Major liver resection

The hepatectomy starts by mobilizing the “to be resected” liver segments for proper exposure by dividing the attachments including the coronary ligaments (figure 8). Once the liver is fully mobilized, the hilar dissection can progress followed by transection of the liver parenchyma from the anterior surface towards the IVC along the principal planes. Lastly, the hepatic veins are ligated and divided the specimen is removed (153). A hanging manoeuvre for parenchymal dissection has been described by Belghiti et al. (154), where a tape passes between anterior surface of IVC and liver.

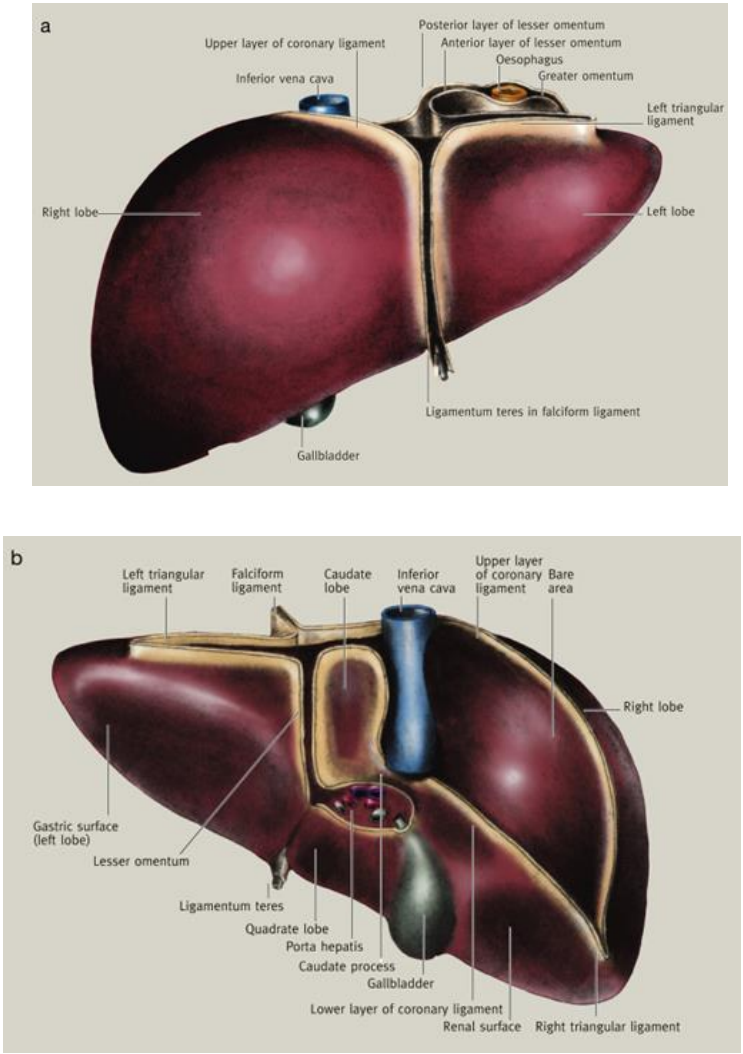

Figure 8. Attachments and relations of the liver (155) a. anterior liver, b. posterior liver

Blood loss and a peri-operative transfusion can have negative impact of the patient, and therefore various techniques have been described to reduce blood flow during liver surgery (Table 8). The Pringle manoeuvre is the oldest and simplest way to reduce blood loss during hepatectomy. This is achieved by encircling the hepatoduodenal ligament with vascular tape or a vascular clamp. The Pringle manoeuvre can be applied continuously for up to 60 and 30 minutes in the non-cirrhotic and cirrhotic liver, respectively. Intermittent clamping (inflow clamp for 15-20 minutes followed by 5 minutes of clamp release) can extend the clamping period if needed. While there is no difference in total blood loss and volume of blood transfusion between continuous and intermittent Pringle manoeuvre, a cirrhotic liver tends to tolerate continuous Pringle manoeuvre poorly (153).

Occlusion of liver inflow	**Non-selective**	- Continuous Pringle manoeuvre - Intermittent Pringle manoeuvre
	Selective	- Hemi-hepatic vascular occlusion - Segmental Vascular occlusion
Occlusion of liver inflow and outflow (interruption of venous backflow)	- Total hepatic vascular exclusion (THVE) - Hepatic vascular occlusion with preservation of Caval flow	
Control of CVP (<5 cm H2O)		

Table 8. Various vascular occlusion techniques to reduce blood loss during liver resection (156)

Complete control of bleeding is not achieved by a Pringle manoeuvre alone as there will be back bleeding from the liver parenchyma with the added disadvantage of ischaemic reperfusion injury to the remnant liver parenchyma. On the other hand, this is very well tolerated by the patient as there are minimal haemodynamic changes (153). Ischaemic reperfusion injury can be minimized with the use of ischaemic preconditioning (IP). This technique is based on a short period (10 minutes) of hepatic perfusion clamping followed by an equivalent period (10 minutes) of reperfusion before the start of a prolonged continuous Pringle manoeuvre (157), first described by Clavien et al (158). The use of allopurinol, acetylcysteine, adenosine, intervention in the inflammatory cascade and in situ cooling of the liver under total hepatic exclusion are other known techniques that minimize ischaemic reperfusion injury (156).

Selective vascular control can be approached extra-hepatic or intra-hepatic. The first extra-hepatic approach was described by Lortat-Jacob et al. while performing a right hepatectomy (159). In this technique, the free edge of the lesser omentum is opened, the portal triad is identified and followed untill

their divisions with division and transection of the appropriate side. The hepatic veins can be easily identified and transected extra-hepatically (160). Intra-hepatic vascular control entails dissection of the anterior surface of the liver until the pedicle is reached which is then divided (161). This technique can be associated with considerable bleeding as there are no identifiable boundaries and pedicle control is done after parenchymal dissection (160). Total hepatic vascular exclusion (THVE) reduces blood loss by occluding inflow and outflow. This technique mitigates the risk of retrograde bleeding and reduces the risk of air embolism. However THVE is technically more difficult necessitating full liver mobilization with exposure of inferior vena cava (IVC) (162). The biggest disadvantage of this technique is the severe haemodynamic compromise of the patient and approximately 15% of patients cannot tolerate the procedure (163). A low central venous pressure (CVP) of < 5cm H_2O is advised for safe liver resection. Higher CVP pressures will result in increasing blood loss as a consequence of high hepatic vein pressure (156, 164). This can be achieved by combination of posture change, fluid restriction, diuretics, vasodilators and anaesthetic agents (165).

Finger fracture (166) or Kelly clamp crushing (167) has been the standard technique for transection of liver parenchyma in the past (165). With new advances in technology, specific instruments have been developed to aid in parenchymal dissection such as ultrasonic dissector, water jet, Harmonic Scalpel (Harmonic Scalpel, Ethicon Endo-Surgery, Cincinnati, OH, USA), Ligasure (Valley Lab, Tyco Healthcare, Boulder, CO, USA) and Tissue-Link (Tissue Link Medical, Inc., Dover, NH, USA) dissecting sealer (153, 165). Staplers can be used in liver surgery for inflow and outflow control, parenchymal dissection as well as transection of hepatic pedicles in major hepatectomies (168). A radiofrequency assisted device applies radiofrequency energy to pre-thermocoagulate the liver parenchyma before parenchymal division inducing coagulative necrosis around the probe (162). In a systematic review by Gurusamy et al., no significant differences in mortality or morbidity (including bile leaks) were seen post-liver parenchymal dissection irrespective of the method used (169). A meta-analysis of techniques of liver parenchymal dissection reported more rapid and less blood loss with clamp crush technique otherwise the rest of the techniques had a similar outcome in terms of mortality, morbidity, liver failure, intensive care/high care stay and length of hospital admission (170). Radiofrequency liver resection is associated with greater amount of tissue necrosis compared to other techniques (162, 171) leading to infections, hence it is generally reserved for ablating liver tumours that are unresectable (162).

Between 20 to 80% of liver resections are done laparoscopically. The most favourable indications for laparoscopic resections are solitary lesions, ≤5cm in diameter and in the periphery of segments 2 to 6 of

liver (172). Laparoscopic liver surgery is divided into minor resections (non-anatomical wedge resection, left lateral resections, and/or removal of anterior segments which include 4b, 5 and 6) and major resections (right and left hepatectomies, trisectionectomy and resection of posterior segments including 1, 4a, 7 and 8) (173). Advances in technology and technical skills have led to more advanced laparoscopic resections (173, 174). Depending on the type of liver surgery, the position of the port placement can differ and depends mainly on the surgeon's preference. Hepatic transection can be performed using either electrosurgical devices with staplers reserved for larger structures, or staplers to divide parenchyma and major structures without the aid of portal triad clamping. As in open liver surgery no single method of parenchymal transection has been shown to be superior (172). Demarcation of the line of dissection post portal vein ligation, can be difficult to reproduce in the laparoscopic surgery. Use of Indocyanine green (ICG) can help in real-time identification of hepatic tumours and segmental boundaries, thus aiding in navigation during laparoscopic liver surgery (175). Studies have shown reduced bleeding, decreased post-operative morbidity and shortened hospitalization with laparoscopic surgery compared to open liver resection, longer operative time in laparoscopic group and no change in long-term oncological outcomes in either groups (139, 173, 176).

The introduction of robotic technology in the field of liver surgery makes technically difficult minimally invasive surgical procedures such as posterior sectionectomy and tumours located in superior segments 4a and 8 more feasible (177). The system allows three-dimensional views of the operative field, has tremor filtration capacity, and permits 7° of freedom which allow surgeons to dexterously perform delicate dissections and precise intra-corporeal suturing (178). For experienced liver surgeons who are only familiar with an open approach, the learning curve for robotic-assisted surgery may be less steep compared with conventional laparoscopic surgery (179). In earlier studies, no significant difference in peri-operative outcomes were reported when comparing robotic with laparoscopic surgery (178, 180). A recent meta-analysis which compared laparoscopic and robotic liver surgery, found that robotic surgery was associated with longer operative time, less blood loss and re-admission rates and had comparative outcomes in terms of complications, blood transfusion and conversion rates (179). Rates of disease-free survival and overall survival at 2 years have been reported to range from 72–84% and 94–98%, respectively, in well-selected patients. Considering the cost of the robotic surgical devices compared to laparoscopic equipment, robot-assisted procedures needs to be better described before applying this technique for the treatment of HCC (139)

Complications post hepatic resection

With advances in surgical techniques and a better understanding of the pathophysiology and function of liver, morbidity and mortality from liver resection has reduced substantially. Current morbidity rates are estimated to be around 20-45% with mortality rates of 2-4% (3, 181-184). Post-operative complications have been defined by the modified Clavien Classification in 2004 which is shown in Table 9.

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anaesthesia
Grade IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

Table 9. The Clavien-Dindo Classification of Surgical Complications. (185)

*Brain haemorrhage, ischaemic stroke, subarachnoidal bleeding, but excluding transient ischaemic attacks. CNS, central nervous system; IC, intermediate care, ICU, intensive care unit.

Post-operative complications result in a longer hospital stay and possibly poorer outcomes in oncological liver resection (181, 186, 187). The exact reason for a worse long-term outcome post complications is not clear. Various theories have been postulated. Some authors believe that severe complications may result in a prolonged period of immunosuppression secondary to septicaemia, thus allowing further tumour proliferation and a worse survival (186). The risk of complications post-surgery is related to the presence of liver cirrhosis, operative time, blood loss, peri-operative transfusion and tumour size (182). A systematic review of 72 papers by Longchamp et al evaluated the predictors of complications after liver surgery. Considering the low evidence of available data and their impact, pre-operative ASA score, liver cirrhosis, blood loss requiring blood transfusion and operative time were noted to be the most important factors predicting higher complication rates (181). In another study done by Yanjie Hu in Western China, length

of incision, BMI, operative time and bleeding were the factors correlating with post-operative complications (3)

Haemorrhage, bile leak, liver failure, pleural effusions and surgical site infections are the most common post-hepatectomy complications (183). The International Study Group for Liver Surgery (ISGLS) has defined bile leak as "fluid with an elevated bilirubin level in the abdominal drain or intra-abdominal fluid on or after post-operative day three or the need for radiological intervention (i.e. interventional drainage) owing to biliary collections or re-laparotomy due to biliary peritonitis. The elevated bilirubin level in the drain or intra-abdominal fluid is defined as a bilirubin concentration at least three times higher than the serum bilirubin level measured at the same time". The incidence of a bile leak is 3.6 - 12% in patients after hepatectomy without biliary reconstruction and 0.4 – 8% in patients with biliary reconstruction post liver resection (188-190). The placement of an abdominal drain and intra-operative blood loss especially more than 500ml were independent risk factors for post-operative bile leak (182). Abdominal drain placement is associated with higher detection of mild-moderate bile leak which possibly may not have any clinical significance. Not placing a drain does not increase the need for post-operative intervention and major bile leaks are not missed. In fact, it has been shown that routine placement of abdominal drains after hepatectomy may be harmful (188). Most bile leaks are self-limited and no further intervention is required. The International Study Group for Liver Surgery graded bile leaks from Grade A-C are detailed in Table 10. The incidence of patients requiring further intervention for a bile leak is 1.7 – 3.2% (188).

Grade	Definition
A	Bile leakage requiring no or little change in patients' clinical management
B	Bile leak requiring a change in patients clinical management (e.g. additional diagnostic or interventional procedures) but manageable without a re-laparotomy. Or: a Grade A bile leakage lasting for > 1 week
C	Bile leakage requiring re-laparotomy

Table 10. International Study Group for Liver Surgery (ISGLS) definition for biliary leak

Post hepatectomy liver failure (PHLF) is one of the most serious complications after a major liver resection. The ISGLS defines PHLF as a postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, which is characterized by an increase in INR or a need for administering clotting factors to maintain a

normal INR) and hyperbilirubinemia on or after postoperative day 5. If INR or serum bilirubin concentration is increased pre-operatively, PHLF is defined as an increasing INR and increasing serum bilirubin concentration on or after postoperative day 5, compared with the values of the previous day. Other causes for the observed biochemical and clinical changes such as bile duct obstruction should be excluded. The ISGLS grades of PHLF are shown in Table 11. The incidence of PHLF is higher after liver resection for HCC and hilar cholangiocarcinoma (191). The reported incidence of PHLF ranges widely from 0.7 to 34% depending on the definition used (191-193). Risk factors for PHLF are mentioned in the Table 12.

Grade	Description
A	PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient.
B	B PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment.
C	PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment.

Table 11. ISGLS definition for PHLF

Patient related	**Age** **Diabetes mellitus** **Obesity**
Liver related	Cholestasis Steatosis/cirrhosis CALI
Surgery related	Hypotension Massive bleeding Liver ischaemia Remnant liver volume Infection/sepsis Portal hypertension

Table 12. Risk factors for post hepatectomy liver failure (194)

The occurrence and resolution of PHLF is closely related to optimum liver regeneration. The mainstay of clinical management still remains early identification of PHLF and instituting general care of the critically ill patient with the focus on organ support, sepsis control and provision of the optimal environment for liver regeneration. (191).

The Centres for Disease Control (CDC) and Prevention define Surgical Site Infection (SSI) as a wound infection that occurs within 30 days of an operative procedure or within a year if an implant is left in place and the infection is thought to be secondary to surgery (195). SSI is common after all types of surgery and is classified into superficial, deep incisional, and organ/space (182). Post-hepatectomy, organ/space SSI rates of 4.7 – 25% have been reported (190).

Renal failure post-hepatectomy is closely associated with PHLF and hepatorenal syndrome and haemodialysis can be used in selected patients. Ascites is commonly seen in patients with liver dysfunction and cirrhosis post-surgery. Reducing the patient's portal flow is the main focus of treatment which can be achieved by medical management followed by more invasive approach. Bleeding is another common complication and is secondary to inadequate haemostasis intra-operatively or secondary to a coagulation abnormality. Respiratory disorders are less commonly seen (182).

Intra-operative blood loss

Bleeding is a common complication during liver resection. Intra-operative blood loss leads to hemodynamic instability and relative ischaemia of the future liver remnant. This in turn can lead to lymphocyte dysfunction and an immunocompromised status of the patient after significant blood loss (196). Reported blood loss during major hepatectomies is reported to range between 200 and 2000 mls, which is an independent predictor of morbidity and mortality associated with liver resection (197, 198)

Risk factors for bleeding are divided into pre-operative and intra-operative factors. These risk factors are summarized in the Table 13 (199)

Peri-operative risk factors	Intra-operative risk factors
Hb concentration < 12.5 g/dl	Tumour characteristics (Type, size, location, presence of vascular involvement)
Thrombocytopenia	Extent of hepatic resection
Coronary artery disease	Concomitant extrahepatic organ resection
Pre-operative biliary drainage	Operative time
Presence of background liver disease, eg. Cirrhosis	

Table 13. Risk factors for bleeding (199)

Co-ordination between the anaesthesiologist and surgeon is crucial in the management of intra-operative blood loss. As there are strong associations between major blood loss and patient morbidity, it is of the utmost importance to implement strategies to decrease blood loss and need for peri-operative blood transfusion (197)

Reducing central venous pressure (CVP) is commonly used during liver surgery. CVP can be reduced by several techniques, but the optimum technique is yet to be found (197, 200). A systematic review and meta-analysis by Michael et al assessed the efficacy of lowering CVP during liver resection. In their study, the authors found that lowering CVP can reduce intra-operative blood loss and need for transfusion and this practice was encouraged. However, no impact was seen on improving outcomes in terms of morbidity and hospital stay (200).

Portal pedicle clamping was first described by J.H. Pringle in 1908 (201). The 'Pringle' manoeuvre involves manual temporary occlusion of the hepatic portal venous and arterial inflow. Most commonly intermittent compression is performed for 10-20 min with release of occlusion for 5 minutes (199). The effect of intermittent Pringle Manoeuvre (IPM) has been evaluated in a number of studies. It is believed that safe liver surgery can be done without need of IPM. A drawback to IPM is liver ischaemia and reperfusion injury which can trigger the oxidative stress cascade resulting in immune response and inflammation leading to more liver cell damage and post-operative complications (202). IPM not only does not affect significant blood loss or need of blood transfusion, studies have shown that it can adversely result in post-operative ascites and pleural effusion. (202)

The Pringle manoeuvre controls liver blood inflow but does not affect the outflow and can still result in bleeding from hepatic vein backflow. Selective hepatic vascular exclusion (SHVE) can selectively isolate the inflow and outflow to the liver without compromising the blood supply of the future liver remnant. More precise dissection is needed with SHVE. A recent meta-analysis compared Pringle manoeuvre with SHVE. The result showed a significant reduction in mortality, overall complications, blood loss, blood transfusion, air embolism, liver failure and multi-organ failure when SHVE was used (203).

Intra and post-operative blood transfusion

Liver resection and transplant are curative procedures for liver malignancies. Blood loss is a major cause of morbidity during liver resection and is treated with packed red blood cells (RBCs) transfusion. Different studies with different timelines reported different percentages of blood transfusion post-hepatectomies.

The National Inpatient Sample (NIS) which was carried out between 1998 and 2004 reported that 56.8% of patients required a blood transfusion while the National Surgical Quality Improvement Program (NSQIP) reported a lesser percentage of patients requiring blood transfusion (199). The latter study was done between 2007 and 2012. This difference in the transfusion required can be attributed to more advances in the surgical techniques and adopting more parenchymal sparing approach (204).

Blood transfusion is known to increase peri-operative morbidity (184, 199, 205). Reported complications rates post-hepatectomy in patients with blood transfusion are 17-64% versus 5-33% in patients who did not receive blood transfusion (199, 206).

Transfusion of packed red blood cells can have immunomodulatory effects on post-operative patients making them more susceptible to infection and impairing anti-tumour activity. Transfusion can also result in acute lung injury and other organ failures as part of their pro-inflammatory process (199).

Long term, blood transfusion is known to decrease the survival and increase risk of cancer recurrence (206). This is believed to be multifactorial, not only related to post transfusion adverse effect but also to be secondary to suboptimal resection in case of increase blood loss intra-operative. (199, 205). Recent studies have contradicted the above observation. A study by Yamashita et al evaluated the survival impact of blood transfusion during HCC liver resection. Yamashita et al used 11 propensity scores associated with tumour-related factors, liver function such as Indocyanine green (ICG) and surgical factors such as blood loss. Their retrospective study concluded that peri-operative blood transfusion did not influence survival after hepatic resection for HCC (204). Their results were further supported by Tan et al who also concluded that intraoperative blood transfusion had no significant impact on the survival outcomes in patients who receive curative resection in primary HCC (207).

Transplantation

Liver transplantion (LT) is the best curative treatment in cirrhotic patients fulfilling transplantation criteria, as transplantion can cure both the tumour and the underlying liver disease (139). Although initial studies have shown disappointing results with high recurrence rates due to a lack of precise guidelines and selection criteria (17, 208). Recent studies are in favour of better long-term survival post transplantation for patients with chronic liver disease, limited HCC and no vascular invasion (209).

In patients with small HCC that meet the Milan Criteria (single tumours ≤5cm or multiple tumours ≤3 nodules and ≤3cm), excellent long-term survival of more than 70% at 10 years and low recurrence have been documented (209). The Milan criteria are still the safest and most commonly used for HCC liver transplantion (210).

Restrictive criteria within Milan is a major disadvantage. With an increasing number of HCCs worldwide, we are facing an increasing pressure of enlarging the donor pool and extending the criteria (Table 14) for transplantation. Patients with HCC beyond the Milan criteria that still might benefit from liver transplantation, can be managed in two different ways. The first is by using extended criteria while the other is down-staging the lesion with the use of other treatment options to meet the Milan criteria (208). While expanded criteria showed a subgroup of patients who may benefit from liver transplantion outside the Milan criteria, the European Metroticket system (Figure 9) has shown "the further the distance, the greater the price" (211).

Transplantation criteria	Tumour morphology	Tumour biology	Tumour grading	Clinic
Milan	Single nodule ≤5 cm or 3 nodules all ≤3 cm	-	-	-
UCSF	Single nodule ≤6.5 cm or 3 nodules all ≤4.5 cm with TTD ≤8 cm	-	-	-
Up-to-7	Biggest nodule diameter + number of nodules ≤7	-	-	-
TTV/AFP	Total tumor volume ≤115 cm^3	AFP ≤400 ng/mL	-	-
ETC	Size: no limit; number: no limit	-	Biopsy of the largest nodule not poorly differentiated	No cancer related symptoms
Kyoto	≤10 nodules each ≤5 cm	DCP ≤400 mAU/mL	-	-

Table 14. Criteria for the selection of liver transplantation candidates among HCC patients (210)

HCC, hepatocellular carcinoma; UCSF, University of California San Francisco; TTV/AFP, total tumor volume/alpha-fetoprotein; ETC, extended Toronto criteria; DCP, des-γ-carboxyprothrombin.

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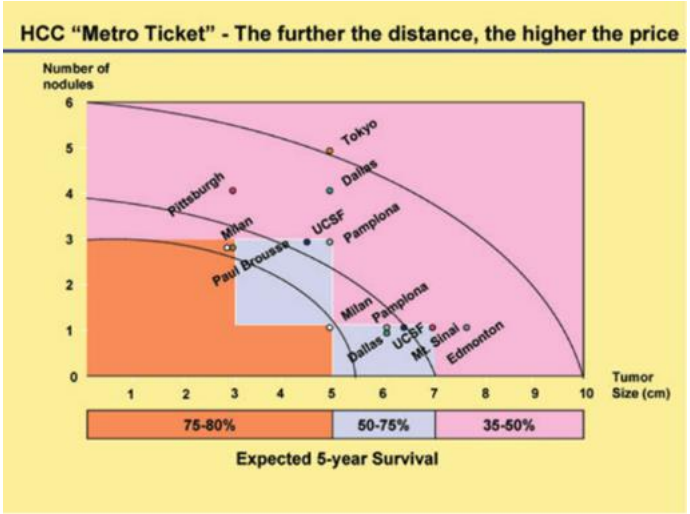


Figure 9. HCC "Metro Ticket" (212)

Besides HCC, LT is considered the best treatment option for a wide range of other liver pathologies (210, 213) which requires high organ demand. Organ shortage and a long waiting list is associated with risk of drop out due to tumour progression (139). The transplant community has placed strict criteria for liver transplantation in order to prioritize patients based on their clinical condition in the waiting list. MELD score is used to assess the urgency of transplantation in cirrhotic patients with an exceptional point given to HCC patients to compensate for the time-related risk of progression of disease beyond treatment (210). The most recent change in allocation policy mandates a 6-month observation period in HCC patients before priority listing and a maximum score of 34 points (214).

Salvage transplantion has emerged as the new paradigm for patients with early HCC and compensated liver cirrhosis (139). With organ shortage, salvage LT is an alternative and promising curative strategy for HCC recurrence or deterioration of liver function after primary liver resection (139, 215). A recent meta-analysis by Guerrini et al, showed that salvage LT offers comparable technical outcomes but slightly lower survival outcomes with respect to primary LT (215). Better patient selection for the resection first approach and early detection of recurrence may improve outcomes of salvage LT (216). When comparing salvage LT with curative loco-regional therapy, systematic review by Wang et al., showed the superiority of salvage LT (217).

CHAPTER 3

RESEARCH STUDY

Hepatocellular carcinoma has become a significant public health concern in SSA and is now the second leading cancer in men and the third for women, occurring in particular in young adults (3, 6). Unfortunately only a small proportion of patients in SSA with HCC are treated with curative intent. Data are scarce, but studies consistently report that curative-intended treatment is pursued in less than 1% of patients in SSA with HCC. Fibrolamellar carcinoma (FLC) was until recently regarded as a variant of HCC occurring in young patients with a relatively good prognosis but is now recognized as a distinct clinical entity with consistent chimeric fusion protein (DNAJB1-PRKACA) expression by FLC tumours (7).

The optimal treatment of HCC and FLC is influenced by the stage of the disease, the degree of liver impairment, and patient performance status. Currently, the therapeutic strategy is based on international guidelines and the Barcelona Clinic Liver Cancer (BCLC) staging system in which potentially curative treatment for early-stage HCC includes resection, transplantation and ablation. Surgical resection is the treatment of choice in patients without cirrhosis and in those with cirrhosis and well-preserved liver function. Despite advances in surgical techniques and perioperative care, hepatectomy remains a high-risk surgical procedure with complications occurring in up to 40% of liver resections. This adds a significant burden to individual patients by adversely affecting quality of life and increasing length of hospital stay, readmission rates, and healthcare costs. Recurrence, despite curative-intent treatment, occurs more often in patients with tumour multifocality, tumour size ≥5 cm, macroscopic vascular or microscopic lymphovascular invasion, elevated alfa-fetoprotein levels and impaired liver function. Previous publications from our unit have reported earlier data on resection for HCC and FLC. This study assessed the peri-operative outcome and survival of patients with HCC and FLC following curative liver resection at a tertiary referral centre in South Africa.

Patients and Methods

Patient Selection

The prospective database in the Surgical Gastroenterology and Hepatopancreatobiliary (HPB) Unit at Groote Schuur Hospital was used to identify patients who underwent liver resection for histologically confirmed hepatocellular carcinoma at Groote Schuur Hospital and the University of Cape Town Private

Academic Hospital between January 1990 and December 2021. Clinical information was collected from the database, hospital files and laboratory and pathology reports. Patient demographics, imaging studies, surgical procedures, postoperative morbidity and histopathological details of the resected specimens were reviewed. Data analysis included and compared the three histological HCC subtypes, those occurring in a (i) normal liver, (ii) cirrhotic liver (iii) fibrolamellar variant. The Brisbane 2000 nomenclature was used to define the segmental extent of the resections and the expanded Accordion classification of surgical complications (218) was used to score surgical outcomes (219). This study was approved by the University of Cape Town Human Research Ethics Committee (HREC REF: 131/2022).

Radiologic assessment

The major imaging modalities used in the diagnosis in this study included transabdominal ultrasound (US) and triple- or four-phase contrast-enhanced CT (CE-CT) for tumour detection and characterization and segmental orientation, depiction of biliovascular anatomy and assessment of tumour encroachment on, or proximity to, vital vascular and biliary structures. Detailed volumetry was performed in patients with a marginal future liver remnant (FLR). When necessary, MRI (MRI) was performed with MRI contrast agents, including gadopentetate dimeglumine (Magnevist®) and Gadoxetate disodium (Primovist®) (Bayer Schering Pharma, Berlin, Germany) used at the discretion of the radiologist.

Surgical Technique

Details of the operative technique have been described previously (10-13). In patients with a FLR <25% of the total functional parenchymal volume a portal vein embolization (PVE) was performed to increase the size of the FLR. In brief, patients were explored through a subcostal incision positioned in relation to the tumour and the liver segments to be resected. For large or central tumours a bilateral subcostal incision with a vertical midline extension to the xiphoid cartilage was used. The costal margins were elevated using an Omni-tract® or Thompson® fixed body wall retractor. Intraoperative US was used to define the relationship of the tumour to vascular structures including portal pedicles, hepatic veins and the inferior vena cava (IVC). Mobilization of the liver by division of the peritoneal attachments was performed as appropriate for the planned resection. For right-sided sectoral resections and hemi-hepatectomies, the relevant hemi-liver was fully mobilized, including exposure of the extrahepatic hepatic veins and retrohepatic IVC. At the discretion of the surgeon and when applicable and possible, selective control of the vessels supplying the resected liver (portal vein and hepatic artery) was achieved. After the desired

demarcation line was demonstrated by temporary occlusion of the vessels, the vessels were transected and after having been secured by suture ligation or linear stapler. The plane of the planned parenchymal transection was marked on the liver surface using diathermy and parenchymal transection was performed using a Cavitron Ultrasonic Surgical Aspirator (CUSA®). Haemostasis was secured using argon beam coagulation and suture or Ligaclip® ligation for larger vessels. Vascular inflow control was used selectively in cycles (application for 20 minutes and release for 10 minutes). As a rule the hepatic vein(s) were transected after the parenchymal resection or when there were signs of venous back-bleeding, usually when a sufficiently low CVP could not be achieved, during the transection. On completion, the transected liver surface was inspected for bile leaks and sealed using Tisseel®. The resection area was routinely drained using closed silastic suction drains. Intermittent calf compression stockings and subcutaneous Clexane (40mg daily) were used as deep vein thrombosis prophylaxis.

Anaesthetic management

For anaesthesia a defined institutional protocol for LR was used. Radial artery and central venous catheters were inserted and arterial and central venous pressures (CVP) were continuously measured. IV fluids were restricted to 1–1.5 mL/kg/h during the extrahepatic dissection with a target CVP <5cm H2O during parenchymal transection to minimize hepatic venous congestion and reduce blood loss. On completion of the parenchymal transection, the cumulative fluid deficit was replaced to replenish the intravascular volume and preserve renal function.

Statistical analyses

The data were analysed using Stata version 11 (StataCorp. 2009. Stata: Release 11. Statistical Software. College Station, TX: StataCorp LP). For bivariate analysis, the Pearson chi square or Kruskal-Wallis tests were used for categorical variables, and the non-parametric Wilcoxon rank-sum test for numerical variables. Univariate and multivariate logistic regression models were used to evaluate the odds ratios (OR) and 95% confidence intervals of clinical variables (while excluding collinearity). All statistical tests were two-tailed and a p-value <0.05 was considered statistically significant. Descriptive statistics as appropriate were used to present clinical and treatment characteristics and outcome of the study subjects.

Results

A total of 601 elective liver resections were performed during the study inclusion period of which 48 (8%) were the primary operation for HCC or FLC. During the same period 529 patients with a confirmed diagnosis of HCC were assessed in the unit of whom 40 (7.6%) were resected. Twenty-five resections (52%) were performed for HCC in non-cirrhotic livers, 15 (31%) in patients with cirrhotic livers and 8 (17%) for FLC. Patient demographics and operative details are shown in Table 15. The median age of the total cohort was 48 years (range 17-79), the majority of whom were men (62.5%). The viral status was known in 32 patients of whom 13 (27%) had chronic hepatitis B infection, eight in the non-cirrhotic and five in the cirrhotic groups, and one had hepatitis C. Seven patients (15%) had pre-operative radiological intervention, of whom six had trans-arterial embolization (TAE) [bland embolization n=4; trans-arterial chemo-embolization (TACE) n=2] and one had a portal vein embolization (PVE). Thirty-six (75%) major resections were performed. The median operating time was 240 min (range 120-570), median blood loss was 725 ml (range 80-2500) and intra-operative blood transfusion was required in 13 patients. Two of the 12 minor resections required a blood transfusion.

	Total n=48	**Non-cirrhotic livers n=25 (52.1%)**	**Cirrhotic livers n=15 (31.2%)**	**Fibrolamellar carcinoma n=8 (16.7%)**
Male **Female**	30 18	13 12	12 3	5 3
Age **median** **range**	48 18-79	49 21-79	51 18-74	22 19-67
No of segments resected	range 1-5 median 3	range 2-5 median 3	range 1-4 median 3	range 2-5 median 3
Surgery duration in minutes	range 120-570 median 240	range 120-570 median 245	range 120-480 median 195	range 185-295 median 233
Estimated intra-operative blood loss in ml	range 80-2500 ml median 725 ml	range 80-2500 median 700	range 300-1800 median 800	range 300-1500 median 850
Intra-operative blood transfusion	13	7	4	2

Table 15. Patient demography and operative details

Post-operative outcomes are summarized in Table 16. The median post-operative hospital stay for the whole cohort was eight days (range 5-32 days), nine days (range 6-32 days) in patients with complications compared to eight days (range 5-24 days) in patients without complications. Sixteen patients (33%) developed Accordion grade 1 to 4 complications. The highest complication rate (50%) occurred in resections for FLC. The most frequent complications were bile leaks (n=5) and intra-abdominal collections

(n=4), followed by wound infection (n=3), pneumonia (n=2), and acute kidney injury (n=2). Two of the patients with bile leaks were treated conservatively with spontaneous resolution, two underwent ERCP and stenting and one had percutaneous aspiration of a biloma. Two patients required re-exploration, one for bleeding and another for a subphrenic collection which was not amenable to ultrasound-guided percutaneous drainage. There was no in-hospital or 30-day mortality.

Thirty-three patients (68%) developed recurrence of HCC following their initial resection of whom 29 ultimately died. The most common site of recurrence was the liver which occurred in 29 (60%) patients, five of whom also had extra-hepatic metastatic disease (lung, lymph nodes, omentum, abdominal wall and vertebrae). Four patients (8.3%) had only extra-hepatic metastatic recurrence. One patient had a repeat resection of a segment 4 recurrence one year after the initial right hemi-hepatectomy. A year later, she had percutaneous US guided microwave ablation of a left liver recurrence and remains disease-free five years later.

	Total n=48	HCC in non-cirrhotic livers n=25 (52.1%)	HCC in cirrhotic livers n=15 (31.2%)	Fibrolamellar carcinoma n=8 (16.7%)
Days in ICU	46 patients range 1-6 days	23 patients range 1-6 days	15 patients range 1-6 days	8 patients range days
Days in hospital	range 5-32 days median 8 days	range 5-32 days median 10 days	range 5-24 days median 7 days	range 6-21 days median 8 days
Post-operative complications	16 (33%)	8 (32%)	4 (26.6%)	4 (50%)
Accordion severity grading				
1	5	2	2	1
2	3	1	1	1
3	6	3	1	2
4	2	2	-	-
5	-	-	-	-
6	-	-	-	-

Table 16. Post-operative outcome in 48 patients undergoing liver resection

Thirty-three (69%) patients have died (29 due to recurrence and four due to other causes) at a median of 952 days (range 51-5740) (median: 31.7m) Median overall survival (OS) for the total cohort after surgery was a median of 57.2 months, 95% CI [29.7 - 84.6]. At three years the overall survival was 58%, and at 5 years was 48% (Figure 10). Patients with a normal liver had a median survival of 64.2 months, 95% CI [29.7 - 84.6], for patients with FL HCC 61.9 months, 95% CI [28.1 - 95.6] and patients with a cirrhotic liver 31.7 months 95% CI [1.5 - 61.8]. The overall comparison of the three groups was not statistically significant, *P*= 0.275 (Figure 11).

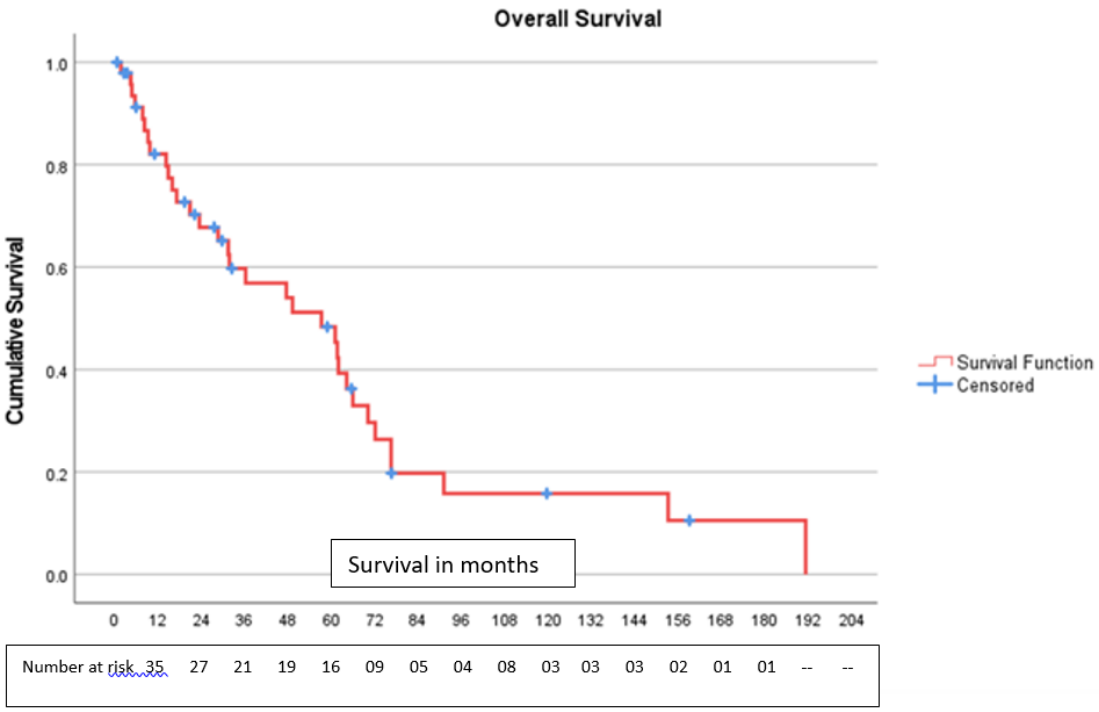


Figure 10. Kaplan-Meier for overall survival of the total cohort

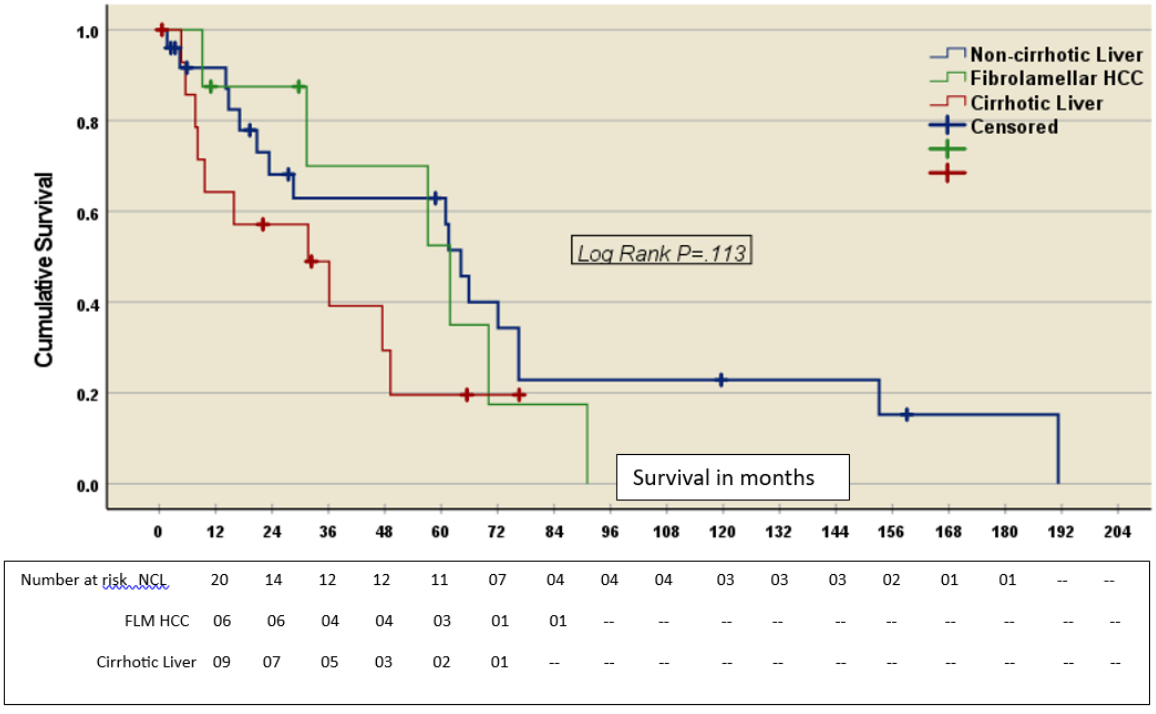


Figure 11. Kaplan-Meier overall survival estimates for patients with non-cirrhotic livers, cirrhotic livers and fibrolamellar carcinoma

Discussion

Hepatic resection is the most widely used method for curative intended treatment of HCC and FLC (4, 5, 7). In this retrospective cohort analysis of 40 liver resections performed for HCC and eight for FLC, there was no in-hospital or 30-day mortality, although one-third of patients had one or more post-operative complications. Major resections were performed in 75% of patients, a quarter of whom required an intra-operative blood transfusion. On long-term follow-up 33 (69%) patients developed recurrent disease, predominantly in the residual liver. Median OS was best in patients who had HCC in non-cirrhotic livers, followed by patients with FLC and worst in patients with HCC in cirrhotic livers.

Of salient interest in this series was that more than 60% of the resected HCCs were in patients with non-cirrhotic livers, likely due to the oncogenic pathway of chronic HBV infection causing HCC in younger patients, which differs from the predominantly cirrhosis pathway seen in low incidence regions (220, 221). Like sub-Saharan Africa, Asia is also known to have HBV as their primary risk for HCC in controversy to HCC in North America, Europe, Japan and Egypt which is mainly secondary to HCV (1). Multiple studies in Asia have been done comparing the prognosis of HBV related HCC between young and elder patient. Some authors found better long term outcome in young patients (222, 223), while others reported more advanced tumour factor and poorer prognosis (224, 225). The most recent multicentre study in China indicated better liver function and more aggressive tumour with worse prognosis in younger age groups (226). Given that over 70% of HCC cases in developing countries are linked to HBV, the pressing challenge now is to guarantee the availability of the vaccine in these regions (227).

Most patients in SSA present late with advanced disease when cure is not possible and there is evidence that HCC in SSA follows a more aggressive course than elsewhere (228). Comprehensive international multicentre retrospective studies have compared HCC outcome in Egypt and SSA (229). Patients in SSA were diagnosed with more severe liver dysfunction (Child-Pugh scores B and C 64% vs. 93%), worse Eastern Cooperative Oncology Group performance status (ECOG 2-4 15% vs. 67%), and advanced BCLC stage (BCLC stage D 7% vs. 72%). In total, Africa has 102 establishments that provide cancer treatment, with 38 located in South Africa (230). Lack of enough tertiary facilities, proper HCC surveillance, absence of trust in health system and poor seeking health behaviours in SSA can be all attributed to the worse outcome of the disease (6, 231, 232).

Eight (16%) patients in this study had FLC, a tumour typically affecting a younger age group without underlying liver disease. These tumours display a unique histological pattern distinctly different from HCC and were designated with a unique WHO classification number in 2010 (82, 233). Several factors in FLC are associated with a poor prognosis include lymph node metastases, multiple tumours, metastatic disease at presentation, and vascular invasion (82).

Despite advances in surgical technique and perioperative management which have reduced mortality and morbidity rates for HCC and FLC resection, one third of patients in our study had postoperative complications. In large published series from high-volume referral centres operative mortality rates of less than 3% are reported, however post-operative complication rates remain substantial and exceed 35% (75, 234). Risk factors for postoperative morbidity include underlying liver dysfunction, a small liver remnant volume, major blood loss, perioperative transfusion and underlying co-morbidities. In most series, a blood transfusion was necessary in less than 10% of resections (75, 234).

Although the 5-year overall survival following surgical resection within the Barcelona Clinic Liver Cancer (BCLC) criteria is around 70%, a main drawback of resection is the high incidence of tumour recurrence in the liver, which occurs in up to 80% of patients (4, 235). The overall three- and five-year survival rates in this study were 58% and 48% which is in sharp contrast to survival reported in contemporary Asian series (236). A systematic review and meta-analysis study by Hassanipour et al. (236) evaluated the survival rate after liver resection in Asian countries. A total of 63 studies were included and the one-year, three-year and five-year survival rates of LC were 34.8 % (95 % CI; 30.3-39.3), 19 % (95 % CI ; 18.2-21.8) and 18.1 % (95 % CI ;16.1-20.1) respectively.

Differences in the development of countries can be attributed to different incidences of death from cancer between different counties (237). Human Development Indices and Indicators (HDI) has been used as guide and is a relative measure of life expectancy, education, quality and education level, and in general, is the living standards in human societies (236). Studies have confirmed the relation between HDI and the cancer survival (237-240). Although the overall survival rate in the systematic review and meta-analysis of Asian series were lower than our study, specific countries with high HDI such as South Korea and Japan had a high survival rate similar to advanced countries such as Europe and North America (236).

The results in terms of long-term survival however vary considerably among series because of variation in resection criteria. Resection outside these criteria result in lower survival rates, but some patients will

benefit from 5-year OS rates in excess of 50% (4, 241). The majority of patients in this study fell outside the resection criteria of the BCLC staging system. In our cohort OS for FLC and HCC occurring in non-cirrhotic livers were similar, with a trend of worse survival in HCC occurring in cirrhotic livers. In our study HCC recurred in 33 patients, most commonly involving the liver, but five had associated extra-hepatic metastases. The most powerful predictors of recurrence are the presence of vascular invasion and/or additional tumour sites besides the primary lesion. Risk factors for poor survival after HCC recurrence include histologically poorly differentiated tumours, tumour multifocality, large size (≥5 cm), vascular invasion, high preoperative AFP levels, R1 resection, and the presence of impaired liver function.

Accurate data on outcome after HCC resection in SSA are scant. A literature search for HCC in PubMed, PubMed Central, Scopus Web of Science, Africa Wide and the Cochrane databases up to September 2022 identified only four papers that provided specific outcome after HCC resection apart from the published studies from our unit (11, 242). Of these four, two were from Nigeria (243, 244), and one each from Sudan (245) and Uganda (246) (Table 17). The Muhammad study from Nigeria included 35 patients all of whom had ruptured HCCs and only 3 had a major liver resection (243). In the Enwezor study five of 60 HCC patients underwent a resection with a 60% operative mortality and 0% survival at 26 months (244). The Harrison study from Uganda reported that only ten of 120 patients underwent resection with a 20% operative mortality rate (246). In the study from Sudan 44 patients with HCC had resections [major (>3 liver segments) n=8; moderate (1-3 segments) n=4; minor<1 segments n=32)] with a major complication rate of 36.4% and a 30-day operative mortality of 9.1% (245).

This study has several specific limitations. Despite the fact that the data generated are from a high volume tertiary academic centre, patient numbers are small and may reflect an inherent referral, selection and treatment bias. A further limitation is that our study included patients who underwent a liver resection over a period of 30 years, during which time changes in operative techniques and perioperative management may have affected post-operative morbidity rates. A strength of this study is the prospective documentation of a robust dataset conducted in a single centre using uniform criteria in consecutive patients providing reliable granular data. Although this study may not completely reflect the population of patients treated at all tertiary referral centres, the analysis provided data not typically collected or available in large administrative databases. Because data about resections for HCC in SSA and reports on outcome after surgery are limited, this study provides important and very relevant missing information.

In conclusion, hepatic resection is the treatment of choice in patients with resectable HCC. A major concern in this study is the low resection rate of 7.6% of all patients presenting with HCC. Resection was safe with no mortality but despite applying optimal surgical techniques and peri-operative care one-third of patients had associated post-operative morbidity. The high long-term recurrence rate remains a major obstacle in achieving better survival results after liver resection.

Author	Country of Study	Study Period	No. of patients (males) (females)	Mean / Median age (range) yr.	Main aetiology of HCC	Liver Cirrhosis	HCC treatment	Outcome
Muhammad et al. (243)	Nigeria	1975-1987	35 (26) (9)	Mean 44 (20-70)	HBV (70%)	94%	Wedge excision n=27 (77.1%) Hepatic artery ligation n=5 (14.3%) Liver resection n=3 (8.6%)	16 (46%) patients died within 35 days of laparotomy (mean survival: 22 days) 6-month survival: n=2 (5.7%)
Enwezor et al. (244)	Nigeria	1988	60 (48) (12)	(20-40)	HBV	85%	Liver resection n=5 (8.3%) BSC (91.7%)	Liver resection group: 0% survival at 26 months BSC group: 0% survival at 15 months
Elsanousi et al. (245)	Sudan	2002-2013	44 (32) (12)	Mean 58.6 (40-75)	Not Specified	47.7%	Liver resection (100%)	30-day mortality: n=4 (9.1%)
Harrison et al. (246)	Uganda	1969-1972	34 (24) (12)	Mean 38 (16-65)	Not Specified	Not Specified	Liver resection n=10 (29.4%) Hepatic artery infusion n=6 (17.6%) Systemic chemotherapy n=7 (19.4%) BSC n=7 (19.4%)	Liver Resection: Median survival of 7 mo. Hepatic artery infusion: Median survival of 6 months BSC: Median survival of 1 month

Table 17. Publications detailing specific outcome after HCC resection in sub-Saharan Africa
Legends: BSC: Best supportive care. HCC: Hepatocellular carcinoma

CHAPTER 4

CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

CONCLUSIONS

Hepatocellular carcinoma poses a significant global health challenge, particularly in SSA where survival is poor and has lagged compared to other continents. Overcoming these challenges requires innovative approaches to improve overall patient outcome. This study which examined the role of liver resection for HCC and FLC within the South African context, provided interesting and valuable information. The research, conducted in the Surgical Gastroenterology Unit at Groote Schuur Hospital and the University of Cape Town Private Academic Hospital and which spanned three decades, used meticulous prospective data collection and patient follow-up to analyze liver resection outcome in a specialist surgical unit. The study examined patient demographics, surgical technique, radiologic assessment, and post-operative care, which contributed to a comprehensive understanding of the challenges and outcomes associated with liver resections for HCC and FLC.

The analysis showed that with careful patient selection and applying precise surgical technique, major liver resections could be achieved with no mortality and acceptable morbidity. One-third of patients experienced complications following surgery which prolonged hospital stay. Although there was no in-hospital or 30-day mortality, the occurrence of post-operative complications underscores the need for ongoing refinement in surgical techniques and peri-operative care to further improve patient outcome.

In addition, the study findings highlighted the unique characteristics of HCC and FLC in patients with non-cirrhotic livers, which is often attributed to the oncogenic pathways related to chronic HBV infection. The data reflect a distinct pattern of disease presentation and progression in these patients, which necessitates a tailored approach to diagnosis and treatment.

Despite the challenges and complexities of liver resections for HCC and FLC, this study underscores the importance of surgical intervention as a curative treatment option. However, the high rate of disease recurrence, particularly within the liver, poses a significant hurdle in achieving long-term survival benefits. This emphasizes the ongoing need for innovative approaches to address disease recurrence and further improve overall patient outcome.

In conclusion, this study contributes valuable data and insights into liver resections for HCC and FLC in South Africa. While the challenges and complexities persist, our findings underscore the importance of continued research, refinement of surgical techniques, and personalized care to enhance the outcomes and quality of life for patients facing these complex liver malignancies.

Recommendations for future research

Recommendation 1: In patients with HCC occurring in a non-cirrhotic liver and who undergo liver resection, close follow-up for recurrence is essential. A surveillance program with regular imaging and tumour marker assessment to detect recurrence early should be implemented.

Recommendation 2: Patients with FLC, which typically affects a younger age group without underlying liver disease, should be carefully evaluated for surgical resection when feasible, taking into account factors such as tumour size, lymph node involvement, and vascular invasion.

Recommendation 3: In patients with HCC in cirrhotic livers undergoing liver resection, it is crucial to assess the extent of liver disease and the functional reserve of the liver. The use of pre-operative portal vein embolization (PVE) to increase the size of the future liver remnant (FLR) should be considered and applied when necessary.

Recommendation 4: An institutional protocol for anaesthetic management during liver resection, including monitoring of arterial and central venous pressures, controlled fluid administration, and measures to minimize hepatic venous congestion and blood loss should be implemented.

Recommendation 5: In patients with HCC in non-cirrhotic livers or fibrolamellar carcinoma who undergo liver resection, multidisciplinary management that includes close postoperative follow-up, and surveillance, and individualized adjuvant therapies based on risk factors for recurrence should be considered and used.

Recommendation 6: The development and implementation of strategies to reduce postoperative complications in patients undergoing liver resection for HCC or FLC are necessary, with a focus on minimizing blood loss, preventing bile leaks, and managing intra-abdominal collections.

Recommendation 7: In cases where patients develop recurrence of HCC following initial resection, a comprehensive evaluation should be performed to determine the extent of recurrence and explore

treatment options, which may include repeat resection, ablation, or systemic therapy, depending on the specific clinical scenario.

Recommendation 8: Further studies should investigate the relationship between biological characteristics, epigenetics, and the recurrence of HCC to better understand the factors contributing to recurrence and identify potential targets for prevention.

Recommendation 9: The impact of host gene polymorphisms, virus integration, and host-virus interactions on the development and recurrence of HCC and FLC should be investigated to identify genetic markers that can predict recurrence risk and guide treatment decisions.

Recommendation 10: The effects and prospects of neoadjuvant therapy, such as targeted drugs and immune checkpoint inhibitors, in preventing HCC recurrence after curative treatment, should be investigated as these therapies may have a role in reducing the risk of recurrence.

Recommendation 11: Educational programmes for healthcare professionals, including surgeons, radiologists, and oncologists should be developed and implemented to enhance the early detection, diagnosis, and management of HCC.

Recommendation 12: Research efforts to better understand the factors contributing to HCC recurrence, particularly in patients with different underlying liver conditions (cirrhotic and non-cirrhotic) and HCC histological subtypes should be promoted to tailor prevention and treatment strategies accordingly.

Recommendation 13: Research focused on the development of serological markers with high sensitivity and specificity for the surveillance and early diagnosis of HCC recurrence should be encouraged as early detection is critical for improving outcomes.

Recommendation 14: The role of neoadjuvant anti-tumour antigen vaccines in preventing recurrence after curative treatment of HCC should be investigated with a focus on harnessing the immune system to enhance long-term disease control.

Recommendation 15: Research collaborations between high-incidence and low-incidence regions to better understand the aggressive nature of HCC in regions with a high prevalence of chronic hepatitis B infection, such as SSA should be fostered to explore strategies for early detection and prevention.

Recommendation 16: Research initiatives that focus on improving the quality of life and survivorship outcomes for patients who have undergone liver resection for HCC should be promoted and should include supportive care measures and rehabilitation programs.

CHAPTER 5

PAPER READY FOR PUBLICATION

Abstract

Background: More than 80% of global hepatocellular carcinomas (HCC) occur in sub-Saharan Africa (SSA) and South-East Asia. Compared with the rest of the world, HCC in SSA has the lowest resection and survival rates. This study assessed outcome following liver resection for HCC and fibrolamellar carcinoma (FLC) at a tertiary referral centre in South Africa.

Methods: A retrospective analysis was done of all liver resections for HCC and FLC at Groote Schuur Hospital and the University of Cape Town Private Academic Hospital between January 1990 and December 2021. Three groups were compared, (i) HCC occurring in normal livers, (ii) HCC occurring in cirrhotic livers, and (iii) fibrolamellar carcinoma. Post-operative complications were classified as per the expanded Accordion severity grading system. Median overall survival (OS) and 95% confidence intervals (CI) were calculated.

Results: Forty-eight patients were included in the study, 25 for HCC in non-cirrhotic livers, 15 in cirrhotic livers and eight for FLC. Thirty-six patients (75%) underwent a major resection. No mortality occurred but 16 patients (33%) developed grade 1 to 4 complications post-operatively. Thirty-three patients (69%) developed recurrence of HCC following their initial resection of whom 29 (60%) ultimately died. Median overall survival (OS) for the total cohort after surgery was 57.2 months, 95% CI [29.7 - 84.6], 64.2 months [29.7-84.6], 61.9 months, [28.1-95.6] and 31.7 months, [1.5-61.8] for patients with HCC in non-cirrhotic livers, FLC and HCC in cirrhotic livers respectively.

Conclusions: Liver resection for HCC and FLC was safe with no mortality, but one-third of patients had associated post-operative morbidity. The high long-term recurrence rate remains a major obstacle in achieving better survival results after resection.

Key words: Surgery, liver, HCC, fibrolamellar carcinoma, complications, survival

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy in adults and is the fifth most common solid tumour worldwide with a variable prevalence based on underlying risk factors and geography. [1,2] The incidence has risen over the past several decades and HCC is now the third leading cause of cancer-related deaths globally, after lung and stomach cancers, with a 5-year survival rate less than 20% and recurrence rates as high as 88%. [3,4] More than 80% of global HCCs occur in sub-Saharan Africa (SSA) and Eastern Asia where the incidence ranges from 4.8 to 8.3 per 100,000 per year in different regions of SSA with the highest incidence in western and central Africa compared to less than 3 per 100 000 in Western countries.[5] Hepatocellular carcinoma has become a significant public health concern in SSA and is now the second leading cancer in men and the third for women, occurring in particular in young adults.[3,6] Unfortunately only a small proportion of patients in SSA with HCC are treated with curative intent. Data are scarce, but studies consistently report that curative-intended treatment is pursued in less than 1% of patients in SSA with HCC. [3,6] Fibrolamellar carcinoma (FLC) was until recently regarded as a variant of HCC occurring in young patients with a relatively good prognosis but is now recognized as a distinct clinical entity with consistent chimeric fusion protein (DNAJB1-PRKACA) expression by FLC tumours. [7]

The optimal treatment of HCC and FLC is influenced by the stage of the disease, the degree of liver impairment, and patient performance status. [3,8] Currently, the therapeutic strategy is based on international guidelines and the Barcelona Clinic Liver Cancer (BCLC) staging system in which potentially curative treatment for early-stage HCC includes resection, transplantation and ablation. [3] Surgical resection is the treatment of choice in patients without cirrhosis and in those with cirrhosis and well-preserved liver function. [9] Despite advances in surgical techniques and perioperative care, hepatectomy remains a high-risk surgical procedure with complications occurring in up to 40% of resections. This adds a significant burden to individual patients by adversely affecting quality of life and increasing length of hospital stay, readmission rates, and healthcare costs. Recurrence despite curative-intent treatment occurs more often in patients with tumour multifocality, tumour size ≥5 cm, macroscopic vascular or microscopic lymphovascular invasion, elevated alfa-fetoprotein (AFP) levels and impaired liver function. [4] Previous publications from our unit have reported earlier data on resection for HCC and FLC. [10-12] In this

study, we assessed the peri-operative outcome and survival of patients with HCC and FLC following curative liver resection at a tertiary referral centre in South Africa.

Patients and methods

Patients who underwent a primary liver resection for HCC or FLC in the Surgical Gastroenterology Unit at Groote Schuur Hospital or the University of Cape Town Private Academic Hospital between January 1990 and December 2021 were included in the study. All patients in the study were assessed pre-operatively and treatment recommendations made in a multidisciplinary team meeting. Data were retrieved from an ethics approved prospective database and analysis included patient demographics, imaging results, surgical procedures performed, postoperative morbidity and mortality and histopathology results. Three groups were compared, namely HCC occurring in normal livers, HCC occurring in cirrhotic livers, and FLC. Liver resections were classified as minor (≤ 2 segments) or major (≥ 3 segments) according to definitions of the Brisbane 2000 classification and nomenclature.[13] The expanded Accordion severity grading system of surgical complications was used to assess morbidity.[14] Postoperative bile leaks (BL) and post-hepatectomy liver failure (PHLF) were graded according to the respective International Study Group of Liver Surgery (ISGLS) definitions. [15,16] Details of the surgical technique used have been published.[11,12,17,18] Four-phase contrast-enhanced computed tomography (CE-CT) was used as primary imaging modality for tumour characterization, assessment of biliovascular anatomy and surgical planning. In patients with a marginal future liver remnant (FLR), volumetry was performed. Magnetic resonance imaging (MRI) using gadopentetate dimeglumine (Magnevist®) or Gadoxetate disodium (Primovist®) (Bayer Schering Pharma, Berlin, Germany) was used for further characterization if needed. Patients were followed up at 3 months and then every 6 months post-operatively, which included clinical assessment, screening liver ultrasound, liver biochemistry and tumour marker measurement.

Statistical analysis

Data were analysed using Stata version 11 (StataCorp. 2009. Stata: Release 11. Statistical Software. College Station, TX: StataCorp LP). Months of survival was calculated from the day of

surgery. For bivariate analysis, the Pearson chi square or Kruskal-Wallis tests were used for categorical variables, and the non-parametric Wilcoxon rank-sum test for numerical variables. Univariate and multivariate logistic regression models were used to evaluate the odds ratios (OR) and 95% confidence intervals of clinical variables (while excluding collinearity). All statistical tests were two-tailed and a p-value <0.05 was considered statistically significant. Descriptive statistics as appropriate were used to present clinical and treatment characteristics and outcome of the study subjects. Ethics approval was obtained.

Results

A total of 601 elective liver resections were performed during the inclusion period of which 48 (8%) were the primary operation for HCC or FLC. During the same period 529 patients with a confirmed diagnosis of HCC were assessed in the unit of whom 40 (7.6%) were resected. Twenty-five resections (52%) were performed for HCC in non-cirrhotic livers, 15 (31%) in patients with cirrhotic livers and 8 (17%) for FLC. Patient demographics and operative details are shown in Table 1. The median age of the total cohort was 48 years (range 17-79), the majority of whom were men (62.5%). The viral status was known in 32 patients of whom 13 (27%) had chronic hepatitis B infection, eight in the non-cirrhotic and five in the cirrhotic groups, and one had hepatitis C. Thirty-eight (86.3%) of the 44 patients in whom complete information was available, were outside the BCLC criteria for resection (Stage 0 or A). Seven patients (15%) had pre-operative radiological intervention, of whom six had trans-arterial embolization (TAE) [bland embolization n=4; trans-arterial chemo-embolization (TACE) n=2] and one had a portal vein embolization (PVE). Thirty-six (75%) major resections were performed. The median operating time was 240 min (range 120-570), median blood loss was 725 ml (range 80-2500) and intra-operative blood transfusion was required in 13 patients. Two of the 12 minor resections required a blood transfusion.

Post-operative outcomes are summarized in Table 2. The median post-operative hospital stay for the whole cohort was eight days (range 5-32 days), nine days (range 6-32 days) in patients with complications compared to eight days (range 5-24 days) in patients without complications. Sixteen patients (33%) developed Accordion grade 1 to 4 complications. The highest complication rate (50%) occurred in resections for FLC. The most frequent complications were bile leaks (n=5) and

intra-abdominal collections (n=4), followed by wound infection (n=3), pneumonia (n=2), and acute kidney injury (n=2). Two of the patients with bile leaks were treated conservatively with spontaneous resolution, two underwent ERCP and stenting and one had percutaneous aspiration of a biloma. Two patients required re-exploration, one for bleeding and another for a subphrenic collection which was not amenable to ultrasound-guided percutaneous drainage. There was no in-hospital or 30-day mortality.

Review of the histology showed that 37 patients had R0 resections, two had R1 and four had R2 resections while the margin status was not recorded in six patients. Thirty-three patients (69%) developed recurrence of HCC following their initial resection of whom 29 ultimately died. The most common site of recurrence was the liver which occurred in 29 (60%) patients, five of whom also had extra-hepatic metastatic disease (lung, lymph nodes, omentum, abdominal wall and vertebrae). Four patients (8.3%) had only extra-hepatic metastatic recurrence. One patient had a repeat resection of a segment 4 recurrence one year after the initial right hemi-hepatectomy. A year later, she had percutaneous US guided microwave ablation of a left liver recurrence and remains disease free five years later.

Thirty-three (69%) patients died (29 due to recurrence and four due to other causes) at a median of 952 days (range 51-5740). Median overall survival (OS) for the total cohort after surgery was 57.2 months, 95% CI [29.7 - 84.6]. At three years the OS was 58%, and at 5 years 48% (Figure 1). Patients with a normal liver had a median OS of 64.2 months, 95% CI [29.7 - 84.6], for patients with FL HCC 61.9 months, 95% CI [28.1 - 95.6] and patients with a cirrhotic liver 31.7 months 95% CI [1.5 - 61.8]. There were no statistically significant differences in survival between the three groups, $p = 0.113$ (Figure 1).

Discussion

Hepatic resection is the most widely used method for curative intended treatment of HCC and FLC. [3,6,8] In this retrospective cohort analysis of 40 liver resections performed for HCC and eight for FLC, there was no in-hospital or 30-day mortality, although one-third of patients had one or more post-operative complications. Major resections were performed in 75% of patients, a quarter of whom required an intra-operative blood transfusion. Median OS was best in patients

who had HCC in non-cirrhotic livers, followed by patients with FLC and worst in patients with HCC in cirrhotic livers. Of salient interest in this series was that more than 60% of the resected HCCs were in patients with non-cirrhotic livers, likely due to the oncogenic pathway of chronic HBV infection causing HCC in younger patients, which differs from the predominantly cirrhosis pathway seen in low incidence regions. [19,20] Most patients in SSA present late with advanced disease when cure is not possible and there is evidence that HCC in SSA follows a more aggressive course than elsewhere.[21]

Eight (16%) patients in this study had FLC, a tumour typically affecting a younger age group without underlying liver disease. These tumours display a unique histological pattern distinctly different from HCC and were designated with a unique WHO classification number in 2010.[7, 22] Several factors in FLC are associated with a poor prognosis include lymph node metastases, multiple tumours, metastatic disease at presentation, and vascular invasion.[7]

Despite advances in surgical technique and perioperative management which have reduced mortality and morbidity rates for HCC and FLC resection, one third of patients in our study had postoperative complications. In large published series from high-volume referral centres operative mortality rates of less than 3% are reported, however post-operative complication rates remain substantial and exceed 35%.[23,24] Risk factors for postoperative morbidity include underlying liver dysfunction, a small liver remnant volume, major blood loss, perioperative transfusion and underlying co-morbidities. In most series, a blood transfusion was necessary in less than 10% of resections.[23,24]

The 69% recurrence rate in this study is in line with a previous reports of recurrence rates of up to 80%.[4,8] Fourteen per cent of patients in whom complete data were available had a positive resection margin. Although those patients with positive resection margins are likely to account for disease recurrence, most recurrences were due to new tumours in the remaining liver. The 5-year OS following surgical resection within the Barcelona Clinic Liver Cancer (BCLC) criteria is around 70% compared to the three- and five-year rates in our study of 58% and 48% respectively. The results in terms of long-term survival however vary considerably among series because of variation in resection criteria. Resection outside these criteria result in lower survival rates, but some patients will benefit from 5-year OS rates in excess of 50%. [8,9,26] The majority of patients in this study fell outside the resection criteria of the BCLC staging system. In our cohort OS for FLC and HCC

occurring in non-cirrhotic livers were similar, with a trend of worse survival in HCC occurring in cirrhotic livers. In our study HCC recurred in 33 patients, most commonly involving the liver, but five had associated extra-hepatic metastases. The most powerful predictors of recurrence are the presence of vascular invasion and/or additional tumour sites besides the primary lesion. Risk factors for poor survival after HCC recurrence include histologically poorly differentiated tumours, tumour multifocality, large size (≥5 cm), vascular invasion, high preoperative AFP levels, R1 resection, and the presence of impaired liver function.

Accurate data on outcome after HCC resection in SSA are scant. A literature search for HCC in PubMed, PubMed Central, Scopus Web of Science, AfricaWide and the Cochrane databases up to September 2022 identified only four papers that provided specific outcome after HCC resection apart from the published studies from our unit. [10-12] Of these four, two were from Nigeria, [27,28] and one each from Sudan [29] and Uganda. [30] The Muhammad study from Nigeria included 35 patients all of whom had ruptured HCCs and only 3 had a major liver resection. [27] In the Enwezor study five of 60 HCC patients underwent a resection with a 60% operative mortality and 0% survival at 26 months. [28] The Harrison study from Uganda reported that only ten of 120 patients underwent resection with a 20% operative mortality rate. [30] In the study from Sudan 44 patients with HCC had resections [major (>3 liver segments) n=8; moderate (1-3 segments) n=4; minor<1 segments n=32)] with a major complication rate of 36.4% and a 30-day operative mortality of 9.1%. [29]

This study has several specific limitations. Despite the fact that the data generated are from a high volume tertiary academic centre, patient numbers are small and may reflect an inherent referral, selection and treatment bias. A further limitation is that our study included patients who underwent a liver resection over a period of 30 years, during which time changes in operative techniques and perioperative management may have affected post-operative morbidity rates and data on Child-Pugh score and performance status were not available for all patients. A strength of this study is the prospective documentation of a robust dataset conducted in a single centre using uniform criteria in consecutive patients providing reliable granular data. Although this study may not completely reflect the population of patients treated at all tertiary referral centres, the analysis provided data not typically collected or available in large administrative databases. Because data about resections for HCC in SSA and reports on outcome after surgery are limited, this study provides important and very relevant information.

Conclusion

Hepatic resection is the treatment of choice in patients with resectable HCC. A major concern in this study is the low resection rate of 7.6% of all patients presenting with HCC. Resection was safe with no mortality but despite applying optimal surgical techniques and peri-operative care one-third of patients had associated post-operative morbidity. The high long-term recurrence rate remains a major obstacle in achieving better survival results after liver resection.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209–49.

2. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015; 19: 223–38

3. Jonas E, Bernon M, Robertson B et al. Treatment of hepatocellular carcinoma in sub-Saharan Africa: challenges and solutions. Lancet Gastroenterol Hepatol. 2022;7:1049-1060. doi: 10.1016/S2468-1253(22)00042-5.

4. Papaconstantinou D, Tsilimigras DI, Pawlik TM. Recurrent Hepatocellular Carcinoma: Patterns, Detection, Staging and Treatment. Journal of Hepatocellular Carcinoma 2022:9 947–957.

5. Kedar Mukthinuthalapati V P, Sewram V, Ndlovu N, Kimani S, Abdelaziz A O, Chiao E Y, Abou-Alfa G K. 2021. Hepatocellular carcinoma in sub-Saharan Africa. JCO Global Oncology, 7, 756-766.

6. Spearman CW, Dusheiko G, Jonas E et al. Hepatocellular carcinoma: measures to improve the outlook in sub-Saharan Africa. Lancet Gastroenterol Hepatol. 2022;7:1036-1048. doi: 10.1016/S2468-1253(22)00041-3.

7. Aziz H, Brown ZJ, Madani SP, Kamel IR, Pawlik TM. Fibrolamellar Hepatocellular Carcinoma: Comprehensive Review of Diagnosis, Imaging, and Management. J Am Coll Surg 2023;236:399–410.

8. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022;400:1345-1362. doi: 10.1016/S0140-6736(22)01200-4.

9. Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019; 380:1450–1462. https://doi.org/10.1056/NEJMra1713263.

10. Lemmer ER, Krige JE, Hall PM, Bornman PC, Taylor DA, Terblanche J. Surgical resection for hepatocellular carcinoma in Cape Town--a clinical and histopathological study. S Afr Med J. 1998;88(12):1575-80. [PubMed PMID: 9930254]

11. Bhaijee F, Krige JE, Locketz ML, Kew MC. Liver resection for non-cirrhotic hepatocellular carcinoma in South African patients. S Afr J Surg. 2011;49(2):68-74. [PubMed PMID: 21614976]

12. Bhaijee F, Locketz ML, Krige JE. Fibrolamellar hepatocellular carcinoma at a tertiary centre in South Africa: a case series. S Afr J Surg. 2009;47(4):108-11. [PubMed PMID: 20141066]

13. Terminology Committee of the International Hepato-Pancreato- Biliary Association (2000) The IHPBA Brisbane 2000 terminology of liver anatomy and resections. HPB Surg 2:333-339.

14. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205-213.

15. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680-8. doi: 10.1016/j.surg.2010.12.002.

16. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery 2011;149:713-24.

17. Terblanche J, Krige JE, Bornman PC. Simplified hepatic resection with the use of prolonged vascular inflow occlusion. Arch Surg. 1991;126(3):298-301. [PubMed PMID: 1998469]

18. Krige JE, Thomson SR, Bornman PC. Choosing the optimal tools and techniques for parenchymal liver transection. S Afr J Surg. 2013;51(1):2-4. doi: 10.7196/sajs.1664 [PubMed PMID: 23472644]

19. Spearman CW, Afihene M, Ally R, et al: Hepatitis B in sub-Saharan Africa: Strategies to achieve the 2030 elimination targets. Lancet Gastroenterol Hepatol 2:900-909, 2017

20. Kew MC. Hepatocellular carcinoma in Africa. In: Malignant Liver Tumors: Current and Emerging Therapies, 2nd ed. Clavien PA, ed. Boston: Jones and Bartlett; 2003:439-448.

21. Kew MC: Hepatocellular carcinoma in African Blacks: Recent progress in etiology and pathogenesis. World J Hepatol 2:65-73, 2010

22. Kew MC: Epidemiology of hepatocellular carcinoma in sub-Saharan Africa. Ann Hepatol 12:173-182, 2013

23. Jing Li, Liang Huang, Jianjun Yan, Maixuan Qiu and Yiqun Yan. Liver resection for hepatocellular carcinoma: personal experiences in a series of 1330 consecutive cases in China. ANZ J Surg 88 (2018) E713–E717

24. Capussotti L, Muratore A, Amisano M et al. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival—a European single center experience. EJSO. 2005; 31: 986–993

25.Hassanipour S, Vali M, Gaffari-fam, S. et al. The survival rate of hepatocellular carcinoma in Asian countries: a systematic review and meta-analysis. EXCLI Journal 2020;19:108-130 – ISSN 1611-2156

26. Guglielmi A, Ruzzenente A, Conci, S et al. Hepatocellular carcinoma: Surgical perspectives beyond the Barcelona clinic liver cancer recommendations. World J Gastroenterol 2014 June 28; 20(24): 7525-7533. ISSN 1007-9327

27. Muhammad I, Mabogunje O. Spontaneous rupture of primary hepatocellular carcinoma in Zaria, Nigeria. J R Coll Surg Edinb. 1991 Apr;36(2):117-20.

28. Enwezor CJ. Sixty cases of primary hepatocellular carcinoma in one year. A preliminary appraisal. Int Surg. 1992 Oct-Dec;77(4):277-9.

29 Elsanousi OM, Mohamed MA, Salim FH, Adam EA. Selective devascularization treatment for large hepatocellular carcinoma: Stage 2A IDEAL prospective case series. Int J Surg. 2019 Aug;68:134-141. doi: 10.1016/j.ijsu.2019.06.014.

30 Harrison NW, Dhru D, Primack A, Bhana D, Kyalwazi SK. The surgical management of primary hepatocellular carcinoma in Uganda. Br J Surg. 1973 Jul;60(7):565-9. doi: 10.1002/bjs.1800600719.

Table 1. Patient demography and operative details

	Total n=48	**HCC in non-cirrhotic livers n=25 (52.1%)**	**HCC in cirrhotic livers n=15 (31.2%)**	**Fibrolamellar carcinoma n=8 (16.7%)**
Male **Female**	30 18	13 12	12 3	5 3
Age years: median; range	48; 18-79	49; 21-79	51; 18-74	22; 19-67
No of segments resected median; range	3; 1-5	3; 2-5	3; 1-4	3; 2-5
Surgery duration in minutes. median; range	240; 120-570	245; 120-570	195; 120-480	233; 185-295
Estimated intra-operative blood loss in ml. median; range	725; 80-2500	700; 80-2500	800; 300-1800	850; 300-1500
Intra-operative blood transfusion (patient numbers)	13	7	4	2

Table 2. Post-operative outcome in 48 patients undergoing liver resection

	Total n=48	**HCC in non-cirrhotic livers n=25 (52.1%)**	**HCC in cirrhotic livers n=15 (31.2%)**	**Fibrolamellar carcinoma n=8 (16.7%)**
Days in ICU: median; range	3; 1-6	3; 1-6	2; 1-6	2.5; 1-6
Days in hospital: median; range	8; 5-32	10; 5-32	7; 5-24	8; 6-21
Post-operative complications: n (%)	16 (33%)	8	4	4
Accordion severity grading (n)				
1	5	2	2	1
2	3	1	1	1
3	6	3	1	2
4	2	2	-	-
5	-	-	-	-
6	-	-	-	-

Figure 1. Kaplan-Meier overall survival estimates for patients with hepatocellular carcinoma in non-cirrhotic livers, cirrhotic livers and patients with fibrolamellar carcinoma

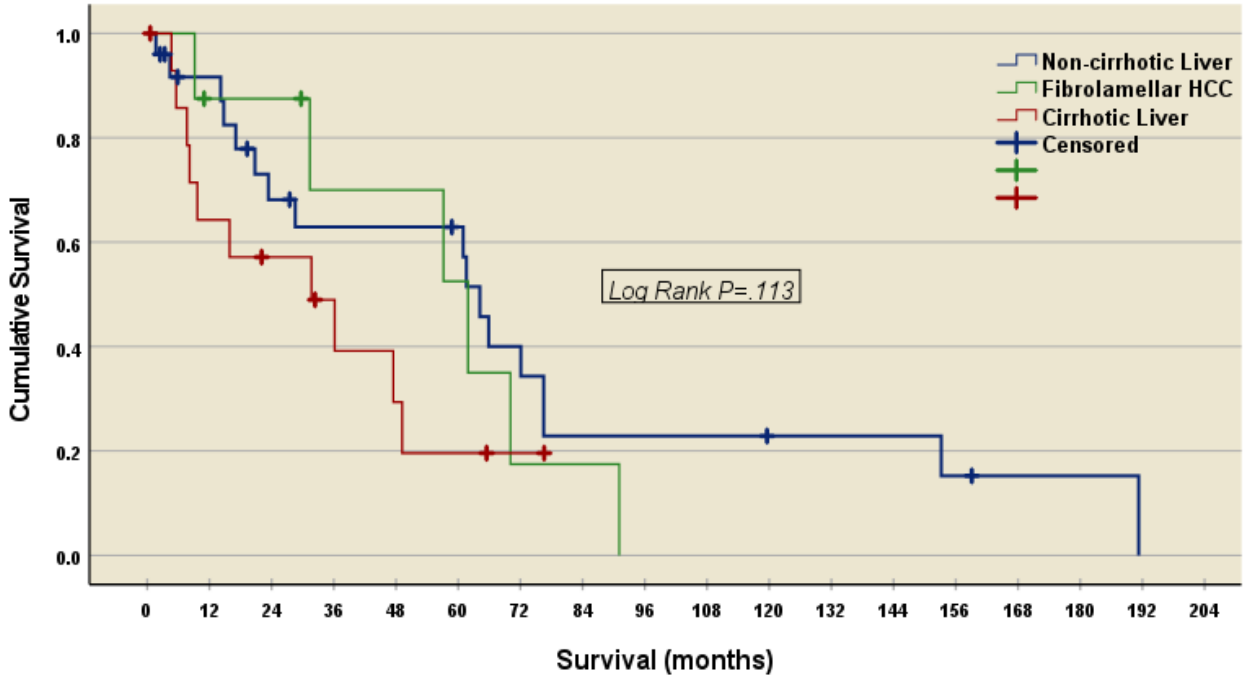
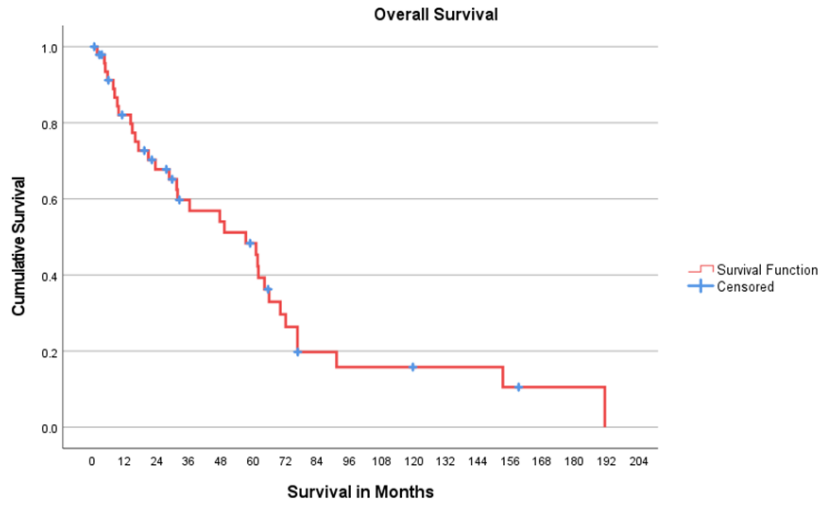


Figure 2. Kaplan-Meier overall survival estimates for the total patient cohort



BIBLIOGRAPHY

1. Zakharia K, Luther C, Alsabbak H, Roberts L. Hepatocellular carcinoma: Epidemiology, pathogenesis and surveillance-implications for sub-Saharan Africa. SAMJ: South African Medical Journal. 2018;108(8):35-40.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108.
3. Hu Y, Zeng S, Li L, Fang Y, He X. Risk factors associated with postoperative complications after liver cancer resection surgery in western China. Cost Eff Resour Alloc. 2021;19(1):64.
4. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022;400(10360):1345-62.
5. Jonas E, Bernon M, Robertson B, Kassianides C, Keli E, Asare KO, et al. Treatment of hepatocellular carcinoma in sub-Saharan Africa: challenges and solutions. The Lancet Gastroenterology & Hepatology. 2022.
6. Kedar Mukthinuthalapati VP, Sewram V, Ndlovu N, Kimani S, Abdelaziz AO, Chiao EY, et al. Hepatocellular carcinoma in sub-Saharan Africa. JCO global oncology. 2021;7:756-66.
7. Spearman CW, Dusheiko G, Jonas E, Abdo A, Afihene M, Cunha L, et al. Hepatocellular carcinoma: measures to improve the outlook in sub-Saharan Africa. The Lancet Gastroenterology & Hepatology. 2022.
8. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nature reviews Gastroenterology & hepatology. 2019;16(10):589-604.
9. Kew MC. Hepatocellular carcinoma in sub-Saharan Africa: Trafford Publishing; 2012.
10. Bhaijee F, Krige JE, Locketz ML, Kew MC. Liver resection for non-cirrhotic hepatocellular carcinoma in South African patients. S Afr J Surg. 2011;49(2):68-74.
11. Bhaijee F, Locketz ML, Krige JE. Fibrolamellar hepatocellular carcinoma at a tertiary centre in South Africa: a case series. S Afr J Surg. 2009;47(4):108-11.
12. Dell A, Krige J, Jonas E, Thomson SR, Beningfield S, Kotze U, et al. Incidence and management of postoperative bile leaks: A prospective cohort analysis of 467 liver resections. South African Journal of Surgery. 2016;54(3):18-23.
13. Lemmer ER, Krige JE, Hall PM, Bornman PC, Taylor DA, Terblanche J. Surgical resection for hepatocellular carcinoma in Cape Town--a clinical and histopathological study. S Afr Med J. 1998;88(12):1575-80.
14. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. Journal of hepatology. 2020;72(2):250-61.
15. Sagnelli E, Macera M, Russo A, Coppola N, Sagnelli C. Epidemiological and etiological variations in hepatocellular carcinoma. Infection. 2020;48(1):7-17.
16. Bialecki ES, Di Bisceglie AM. Clinical presentation and natural course of hepatocellular carcinoma. European journal of gastroenterology & hepatology. 2005;17(5):485-9.
17. Desai A, Sandhu S, Lai J-P, Sandhu DS. Hepatocellular carcinoma in non-cirrhotic liver: A comprehensive review. World journal of hepatology. 2019;11(1):1.
18. Sorrell M. Hepatoeellular carcinoma. Lancet. 1999;353:1253-7.

19. Luo J-C, Hwang S-J, Wu J-C, Lai C-R, Li C-P, Chang F-Y, et al. Clinical characteristics and prognosis of hepatocellular carcinoma patients with paraneoplastic syndromes. Hepato-gastroenterology. 2002;49(47):1315-9.
20. Bruix J, Castells A, Calvet X, Feu F, Bru C, Solé M, et al. Diarrhea as a presenting symptom of hepatocellular carcinoma. Digestive diseases and sciences. 1990;35(6):681-5.
21. Umoh NJ, Lesi OA, Mendy M, Bah E, Akano A, Whittle H, et al. Aetiological differences in demographical, clinical and pathological characteristics of hepatocellular carcinoma in The Gambia. Liver International. 2011;31(2):215-21.
22. O'Neill AF, Church AJ, Perez-Atayde AR, Shaikh R, Marcus KJ, Vakili K. Fibrolamellar carcinoma: An entity all its own. Current Problems in Cancer. 2021;45(4):100770.
23. Raoul J-L, editor Natural history of hepatocellular carcinoma and current treatment options. Seminars in nuclear medicine; 2008: Elsevier.
24. Borzio M, Bruno S, Roncalli M, Mels GC, Ramella G, Borzio F, et al. Liver cell dysplasia is a major risk factor for hepatocellular carcinoma in cirrhosis: a prospective study. Gastroenterology. 1995;108(3):812-7.
25. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment study of 850 patients. Cancer. 1985;56(4):918-28.
26. Investigators CotLIP. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology. 1998;28(3):751-5.
27. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. Journal of hepatology. 2021.
28. Lopez J, Balasegaram M, Thambyrajah V, Timor J. The value of liver function tests in hepatocellular carcinoma. Malaysian Journal of Pathology. 1996;18:95-100.
29. Zhou L, Liu J, Luo F. Serum tumor markers for detection of hepatocellular carcinoma. World journal of gastroenterology: WJG. 2006;12(8):1175.
30. Zhao Y-J, Ju Q, Li G-C. Tumor markers for hepatocellular carcinoma. Molecular and clinical oncology. 2013;1(4):593-8.
31. Lildballe DL, Nguyen K, Poulsen S, Nielsen H, Nexo E. Haptocorrin as marker of disease progression in fibrolamellar hepatocellular carcinoma. European Journal of Surgical Oncology (EJSO). 2011;37(1):72-9.
32. Lafaro KJ, Pawlik TM. Fibrolamellar hepatocellular carcinoma: current clinical perspectives. Journal of hepatocellular carcinoma. 2015;2:151.
33. Inagaki Y, Tang W, Makuuchi M, Hasegawa K, Sugawara Y, Kokudo N. Clinical and molecular insights into the hepatocellular carcinoma tumour marker des-γ-carboxyprothrombin. Liver International. 2011;31(1):22-35.
34. Yamamoto K, Imamura H, Matsuyama Y, Hasegawa K, Beck Y, Sugawara Y, et al. Significance of alpha-fetoprotein and des-γ-carboxy prothrombin in patients with hepatocellular carcinoma undergoing hepatectomy. Annals of surgical oncology. 2009;16:2795-804.
35. Montaser MF, Sakr MA, Khalifa MO. Alpha-L-fucosidase as a tumour marker of hepatocellular carcinoma. Arab Journal of Gastroenterology. 2012;13(1):9-13.
36. Ma J, Gong Q, Lin M, Xi Y, Wang M, Chen Z, et al. Combined five tumor markers in detecting primary hepatic carcinoma. Zhonghua wai ke za zhi [Chinese Journal of Surgery]. 2000;38(1):14-6.

37. Bukofzer S, Stass P, Kew M, De Beer M, Groeneveld H. Alpha-L-fucosidase as a serum marker of hepatocellular carcinoma in southern African blacks. British journal of cancer. 1989;59(3):417-20.
38. Ayuso C, Rimola J, García-Criado Á. Imaging of HCC. Abdominal imaging. 2012;37(2):215-30.
39. Maruyama H, Yamaguchi T, Nagamatsu H, Shiina S. AI-based radiological imaging for HCC: Current status and future of ultrasound. Diagnostics. 2021;11(2):292.
40. Kim TK, Lee KH, Khalili K, Jang H-J. Hepatocellular nodules in liver cirrhosis: contrast-enhanced ultrasound. Abdominal imaging. 2011;36(3):244-63.
41. Eisenbrey JR, Gabriel H, Savsani E, Lyshchik A. Contrast-enhanced ultrasound (CEUS) in HCC diagnosis and assessment of tumor response to locoregional therapies. Abdominal Radiology. 2021;46(8):3579-95.
42. Quaia E. State of the Art: LI-RADS for Contrast-enhanced US. Radiology. 2019;293(1):4-14.
43. Bolog N, Andreisek G, Oancea I, Mangrau A. CT and MR imaging of hepatocellular carcinoma. Journal of Gastrointestinal and Liver Diseases. 2011;20(2):181-9.
44. Aubé C, Oberti F, Lonjon J, Pageaux G, Seror O, N'Kontchou G, et al. EASL and AASLD recommendations for the diagnosis of HCC to the test of daily practice. Liver International. 2017;37(10):1515-25.
45. Vu LN, Morelli JN, Szklaruk J. Basic MRI for the liver oncologists and surgeons. Journal of hepatocellular carcinoma. 2018:37-50.
46. Gluskin JS, Chegai F, Monti S, Squillaci E, Mannelli L. Hepatocellular carcinoma and diffusion-weighted MRI: detection and evaluation of treatment response. Journal of Cancer. 2016;7(11):1565.
47. Rimola J, Forner A, Sapena V, Llarch N, Darnell A, Díaz A, et al. Performance of gadoxetic acid MRI and diffusion-weighted imaging for the diagnosis of early recurrence of hepatocellular carcinoma. European radiology. 2020;30:186-94.
48. Muhi A, Ichikawa T, Motosugi U, Sano K, Fatima Z, Matsuda M, et al. Diffusion-weighted imaging of hepatocellular carcinoma for predicting early recurrence and survival after hepatectomy. Hepatology international. 2013;7:662-8.
49. Bertagna F, Bertoli M, Bosio G, Biasiotto G, Sadeghi R, Giubbini R, et al. Diagnostic role of radiolabelled choline PET or PET/CT in hepatocellular carcinoma: a systematic review and meta-analysis. Hepatology international. 2014;8(4):493-500.
50. Talbot J-N, Gutman F, Fartoux L, Grange J-D, Ganne N, Kerrou K, et al. PET/CT in patients with hepatocellular carcinoma using [18F] fluorocholine: preliminary comparison with [18F] FDG PET/CT. European journal of nuclear medicine and molecular imaging. 2006;33(11):1285-9.
51. Hwang KH, Choi D-J, Lee S-Y, Lee MK, Choe W. Evaluation of patients with hepatocellular carcinomas using [11C] acetate and [18F] FDG PET/CT: A preliminary study. Applied Radiation and Isotopes. 2009;67(7-8):1195-8.
52. Filippi L, Schillaci O, Bagni O. Recent advances in PET probes for hepatocellular carcinoma characterization. Expert Review of Medical Devices. 2019;16(5):341-50.
53. Di Tommaso L, Spadaccini M, Donadon M, Personeni N, Elamin A, Aghemo A, et al. Role of liver biopsy in hepatocellular carcinoma. World journal of gastroenterology. 2019;25(40):6041.

54. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology. 2018;69(1):182-236.
55. Sparchez Z, Mocan T. Contemporary role of liver biopsy in hepatocellular carcinoma. World journal of hepatology. 2018;10(7):452.
56. Wee A, Nilsson B. Highly well differentiated hepatocellular carcinoma and benign hepatocellular lesions. Acta cytologica. 2003;47(1):16-26.
57. Karadag Soylu N. Update on hepatocellular carcinoma: a brief review from pathologist standpoint. Journal of gastrointestinal cancer. 2020;51(4):1176-86.
58. Fowler KJ, Burgoyne A, Fraum TJ, Hosseini M, Ichikawa S, Kim S, et al. Pathologic, molecular, and prognostic radiologic features of hepatocellular carcinoma. Radiographics. 2021;41(6):1611-31.
59. Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut. 2008;57(11):1592-6.
60. Szpakowski JL, Drasin TE, Lyon LL. Rate of seeding with biopsies and ablations of hepatocellular carcinoma: a retrospective cohort study. Hepatology communications. 2017;1(9):841-51.
61. Ahn D-W, Shim JH, Yoon J-H, Kim CY, Lee H-S, Kim YT, et al. Treatment and clinical outcome of needle-track seeding from hepatocellular carcinoma. The Korean journal of hepatology. 2011;17(2):106.
62. Weitz J, D'Angelica M, Jarnagin W, Gonen M, Fong Y, Blumgart L, et al. Selective use of diagnostic laparoscopy prior to planned hepatectomy for patients with hepatocellular carcinoma. Surgery. 2004;135(3):273-81.
63. Lai EC, Tang CN, Ha JP, Tsui DK, Li MK. The evolving influence of laparoscopy and laparoscopic ultrasonography on patients with hepatocellular carcinoma. The American journal of surgery. 2008;196(5):736-40.
64. Klegar EK, Marcus SG, Newman E, Hiotis SP. Diagnostic laparoscopy in the evaluation of the viral hepatitis patient with potentially resectable hepatocellular carcinoma. HPB. 2005;7(3):204-7.
65. Gómez-Rubio M, Moya-Valdés M, García J. Diagnostic laparoscopy and laparoscopic ultrasonography with local anesthesia in hepatocellular carcinoma. World Journal of Gastroenterology: WJG. 2005;11(26):4120.
66. Lo CM, Fan ST, Liu CL, Poon RT, Lam CM, Yuen WK, et al. Determining resectability for hepatocellular carcinoma: the role of laparoscopy and laparoscopic ultrasonography. Journal of Hepato-Biliary-Pancreatic Surgery. 2000;7(3):260-4.
67. Perisetti A, Goyal H, Yendala R, Thandassery RB, Giorgakis E. Non-cirrhotic hepatocellular carcinoma in chronic viral hepatitis: Current insights and advancements. World Journal of Gastroenterology. 2021;27(24):3466.
68. Penzkofer L, Mittler J, Heinrich S, Wachter N, Straub BK, Kloeckner R, et al. Outcome after Resection for Hepatocellular Carcinoma in Noncirrhotic Liver—A Single Centre Study. Journal of Clinical Medicine. 2022;11(19):5802.
69. Xie Q-S, Chen Z-X, Zhao Y-J, Gu H, Geng X-P, Liu F-B. Systematic review of outcomes and meta-analysis of risk factors for prognosis after liver resection for hepatocellular carcinoma without cirrhosis. Asian Journal of Surgery. 2021;44(1):36-45.

70. Beard RE, Hanto DW, Gautam S, Miksad RA. A comparison of surgical outcomes for noncirrhotic and cirrhotic hepatocellular carcinoma patients in a Western institution. Surgery. 2013;154(3):545-55.
71. Sahara K, Paredes AZ, Tsilimigras DI, Hyer J, Merath K, Wu L, et al. Impact of liver cirrhosis on perioperative outcomes among elderly patients undergoing hepatectomy: the effect of minimally invasive surgery. Journal of Gastrointestinal Surgery. 2019;23(12):2346-53.
72. Tarao K, Nozaki A, Ikeda T, Sato A, Komatsu H, Komatsu T, et al. Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases—meta-analytic assessment. Cancer medicine. 2019;8(3):1054-65.
73. Yilma M, Saxena V, Mehta N. Models to Predict Development or Recurence of Hepatocellular Carcinoma (HCC) in Patients with Advanced Hepatic Fibrosis. Current Gastroenterology Reports. 2022:1-9.
74. Chan A, Kow A, Hibi T, Di Benedetto F, Serrablo A. Liver resection in Cirrhotic liver: Are there any limits? : Elsevier; 2020. p. 109-14.
75. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival—a European single center experience. European Journal of Surgical Oncology (EJSO). 2005;31(9):986-93.
76. Sasaki K, Shindoh J, Margonis GA, Nishioka Y, Andreatos N, Sekine A, et al. Effect of background liver cirrhosis on outcomes of hepatectomy for hepatocellular carcinoma. JAMA surgery. 2017;152(3):e165059-e.
77. El Jabbour T, Lagana SM, Lee H. Update on hepatocellular carcinoma: Pathologists' review. World journal of gastroenterology. 2019;25(14):1653.
78. Smith M, Tomboc PJ, Markovich B. Fibrolamellar hepatocellular carcinoma. StatPearls [Internet]: StatPearls Publishing; 2022.
79. Abdelhamed W, El-Kassas M. Fibrolamellar hepatocellular carcinoma: a rare but unpleasant event. World Journal of Gastrointestinal Oncology. 2022;14(6):1103.
80. Chakrabarti S, Tella SH, Kommalapati A, Huffman BM, Yadav S, Riaz IB, et al. Clinicopathological features and outcomes of fibrolamellar hepatocellular carcinoma. Journal of Gastrointestinal Oncology. 2019;10(3):554.
81. Ramai D, Ofosu A, Lai JK, Gao Z-H, Adler DG. Fibrolamellar hepatocellular carcinoma: a population-based observational study. Digestive diseases and sciences. 2021;66(1):308-14.
82. Aziz H, Brown ZJ, Madani SP, Kamel IR, Pawlik TM. Fibrolamellar Hepatocellular Carcinoma: Comprehensive Review of Diagnosis, Imaging, and Management. Journal of the American College of Surgeons.10.1097.
83. Benvegnu L, Noventa F, Bernardinello E, Pontisso P, Gatta A, Alberti A. Evidence for an association between the aetiology of cirrhosis and pattern of hepatocellular carcinoma development. Gut. 2001;48(1):110-5.
84. Trépo C, Chan HL, Lok A. Hepatitis B virus infection. The Lancet. 2014;384(9959):2053-63.
85. Voulgaris T, Papatheodoridi M, Lampertico P, Papatheodoridis GV. Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B. Liver International. 2020;40(3):484-95.
86. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. Journal of hepatology. 2016;64(1):S84-S101.

87. Kim JM, Kwon CHD, Joh JW, Park JB, Lee JH, Kim SJ, et al. Outcomes after curative hepatectomy in patients with non-B non-C hepatocellular carcinoma and hepatitis B virus hepatocellular carcinoma from non-cirrhotic liver. Journal of Surgical Oncology. 2014;110(8):976-81.
88. Manns MP, Buti M, Gane E, Pawlotsky J-M, Razavi H, Terrault N, et al. Hepatitis C virus infection. Nature reviews Disease primers. 2017;3(1):1-19.
89. Ahumada A, Rayón L, Usón C, Bañares R, Lopez SA. Hepatocellular carcinoma risk after viral response in hepatitis C virus-advanced fibrosis: Who to screen and for how long? World Journal of Gastroenterology. 2021;27(40):6737.
90. Sung PS, Shin E-C. Immunological mechanisms for hepatocellular carcinoma risk after direct-acting antiviral treatment of hepatitis C virus infection. Journal of clinical medicine. 2021;10(2):221.
91. Messori A, Badiani B, Trippoli S. Achieving sustained virological response in hepatitis C reduces the long-term risk of hepatocellular carcinoma: an updated meta-analysis employing relative and absolute outcome measures. Clinical drug investigation. 2015;35(12):843-50.
92. Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. Nature Reviews Gastroenterology & Hepatology. 2022:1-13.
93. Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. Journal of hepatology. 2019;70(2):284-93.
94. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology. 2004;127(5):S87-S96.
95. Mandishona E, MacPhail AP, Gordeuk VR, Kedda MA, Paterson AC, Rouault TA, et al. Dietary iron overload as a risk factor for hepatocellular carcinoma in Black Africans. Hepatology. 1998;27(6):1563-6.
96. Kew MC. Hepatic iron overload and hepatocellular carcinoma. Liver cancer. 2014;3(1):31-40.
97. Fan W, Guo J, Zhu B, Wang S, Yu L, Huang W, et al. Drug-eluting beads TACE is safe and non-inferior to conventional TACE in HCC patients with TIPS. European radiology. 2021;31(11):8291-301.
98. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. Liver cancer. 2014;3(3-4):458-68.
99. Chan SL, Mo FK, Johnson PJ, Liem GS, Chan TC, Poon MC, et al. Prospective validation of the Chinese University Prognostic Index and comparison with other staging systems for hepatocellular carcinoma in an Asian population. Journal of gastroenterology and hepatology. 2011;26(2):340-7.
100. Yau T, Tang VY, Yao T-J, Fan S-T, Lo C-M, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology. 2014;146(7):1691-700. e3.
101. Raoul J-L, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer treatment reviews. 2019;72:28-36.
102. Pompili M, Francica G, Ponziani FR, Iezzi R, Avolio AW. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. World Journal of Gastroenterology: WJG. 2013;19(43):7515.

103. Niu Z-J, Ma Y-L, Kang P, Ou S-Q, Meng Z-B, Li Z-K, et al. Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. Medical Oncology. 2012;29(4):2992-7.
104. Luo J, Guo R-P, Lai EC, Zhang Y-J, Lau WY, Chen M-S, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Annals of surgical oncology. 2011;18(2):413-20.
105. Xue T-C, Xie X-Y, Zhang L, Yin X, Zhang B-H, Ren Z-G. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a meta-analysis. BMC gastroenterology. 2013;13(1):1-9.
106. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver International. 2015;35(9):2155-66.
107. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovascular and interventional radiology. 2010;33:41-52.
108. Xie ZB, Wang XB, Peng YC, Zhu SL, Ma L, Xiang BD, et al. Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. Hepatology Research. 2015;45(2):190-200.
109. Tsurusaki M, Murakami T. Surgical and locoregional therapy of HCC: TACE. Liver Cancer. 2015;4(3):165-75.
110. Lo C-M, Ngan H, Tso W-K, Liu C-L, Lam C-M, Poon RT-P, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35(5):1164-71.
111. Takayasu K. Liver Cancer Study Group of Japan: Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology. 2006;131:461-9.
112. Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. Journal of hepatology. 2012;56(6):1330-5.
113. Malagari K, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefaniotou A, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovascular and interventional radiology. 2012;35(5):1119-28.
114. Peng Z-W, Zhang Y-J, Liang H-H, Lin X-J, Guo R-P, Chen M-S. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. Radiology. 2012;262(2):689-700.
115. Peng Z-W, Zhang Y-J, Chen M-S, Xu L, Liang H-H, Lin X-J, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. Journal of clinical oncology. 2013;31(4):426-32.

116. Lencioni R, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. Journal of hepatology. 2016;64(5):1090-8.
117. Meyer T, Fox R, Ma YT, Ross PJ, James MW, Sturgess R, et al. Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial. The lancet Gastroenterology & hepatology. 2017;2(8):565-75.
118. Kudo M, Han G, Finn RS, Poon RT, Blanc JF, Yan L, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. Hepatology. 2014;60(5):1697-707.
119. Kudo M, Cheng A-L, Park J-W, Park JH, Liang P-C, Hidaka H, et al. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. The lancet Gastroenterology & hepatology. 2018;3(1):37-46.
120. Kudo M. Local ablation therapy for hepatocellular carcinoma: current status and future perspectives. Journal of gastroenterology. 2004;39(3):205.
121. Zhu F, Rhim H. Thermal ablation for hepatocellular carcinoma: what's new in 2019. Chin Clin Oncol. 2019;8(6):58.
122. N'Kontchou G, Mahamoudi A, Aout M, Ganne-Carrié N, Grando V, Coderc E, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. Hepatology. 2009;50(5):1475-83.
123. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. Hepatology. 2009;49(2):453-9.
124. Bailey CW, Sydnor Jr MK. Current state of tumor ablation therapies. Digestive diseases and sciences. 2019;64(4):951-8.
125. Lencioni R, Crocetti L. Image-guided ablation for hepatocellular carcinoma. Multidisciplinary Treatment of Hepatocellular Carcinoma. 2013:181-94.
126. Ng K, Chok K, Chan A, Cheung T, Wong T, Fung J, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. Journal of British Surgery. 2017;104(13):1775-84.
127. Chen M-S, Li J-Q, Zheng Y, Guo R-P, Liang H-H, Zhang Y-Q, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. LWW; 2006.
128. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. Journal of hepatology. 2012;57(4):794-802.
129. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Annals of surgery. 2010;252(6):903-12.
130. Liu H, Wang Z, Fu S, Li A, Pan Z, Zhou W, et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Journal of British Surgery. 2016;103(4):348-56.
131. Shin SW, Ahn KS, Kim SW, Kim T-S, Kim YH, Kang KJ. Liver resection versus local ablation therapies for hepatocellular carcinoma within the Milan criteria: a systematic review and meta-analysis. Annals of Surgery. 2021;273(4):656-66.

132. Yin XY, Xie XY, Lu MD, Xu HX, Xu ZF, Kuang M, et al. Percutaneous thermal ablation of medium and large hepatocellular carcinoma: long-term outcome and prognostic factors. Cancer. 2009;115(9):1914-23.
133. Huo YR, Eslick GD. Microwave ablation compared to radiofrequency ablation for hepatic lesions: a meta-analysis. Journal of Vascular and Interventional Radiology. 2015;26(8):1139-46. e2.
134. Yu J, Yu X-l, Han Z-y, Cheng Z-g, Liu F-y, Zhai H-y, et al. Percutaneous cooled-probe microwave versus radiofrequency ablation in early-stage hepatocellular carcinoma: a phase III randomised controlled trial. Gut. 2017;66(6):1172-3.
135. Tan W, Deng Q, Lin S, Wang Y, Xu G. Comparison of microwave ablation and radiofrequency ablation for hepatocellular carcinoma: a systematic review and meta-analysis. International Journal of Hyperthermia. 2019;36(1):263-71.
136. Poulou LS, Botsa E, Thanou I, Ziakas PD, Thanos L. Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World journal of hepatology. 2015;7(8):1054.
137. Liu W, Zheng Y, He W, Zou R, Qiu J, Shen J, et al. Microwave vs radiofrequency ablation for hepatocellular carcinoma within the Milan criteria: a propensity score analysis. Alimentary pharmacology & therapeutics. 2018;48(6):671-81.
138. Liver EAFTSOT. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology. 2012;56(4):908-43.
139. Allaire M, Goumard C, Lim C, Le Cleach A, Wagner M, Scatton O. New frontiers in liver resection for hepatocellular carcinoma. JHEP Reports. 2020;2(4):100134.
140. Bruix J, Takayama T, Mazzaferro V, Chau G-Y, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. The lancet oncology. 2015;16(13):1344-54.
141. Gunasekaran G, Bekki Y, Lourdusamy V, Schwartz M. Surgical treatments of hepatobiliary cancers. Hepatology. 2021;73:128-36.
142. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, S taging, and M anagement of H epatocellular C arcinoma: 2018 P ractice G uidance by the A merican A ssociation for the S tudy of L iver D iseases. Hepatology. 2018;68(2):723-50.
143. Omata M, Cheng A-L, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatology international. 2017;11(4):317-70.
144. Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. Journal of hepatology. 2015;62(3):617-24.
145. Marti J, Giacca M, Alshebeeb K, Bahl S, Hua C, Horn JC, et al. Analysis of preoperative portal vein embolization outcomes in patients with hepatocellular carcinoma: a single-center experience. Journal of Vascular and Interventional Radiology. 2018;29(7):920-6.
146. Terasawa M, Allard M-A, Golse N, Cunha AS, Cherqui D, Adam R, et al. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization alone before major hepatectomy for patients with large hepatocellular carcinoma: an intent-to-treat analysis. Surgery. 2020;167(2):425-31.
147. Ogata S, Belghiti J, Farges O, Varma D, Sibert A, Vilgrain V. Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. Journal of British Surgery. 2006;93(9):1091-8.

148. Chan A, Zhang WY, Chok K, Dai J, Ji R, Kwan C, et al. ALPPS versus portal vein embolization for hepatitis-related hepatocellular carcinoma: a changing paradigm in modulation of future liver remnant before major hepatectomy. Annals of Surgery. 2021;273(5):957-65.
149. Sun Z, Li Z, Shi X-L, He X-W, Chen J, Song J-H. Anatomic versus non-anatomic resection of hepatocellular carcinoma with microvascular invasion: a systematic review and meta-analysis. Asian Journal of Surgery. 2021;44(9):1143-50.
150. Couinaud C. Etudes anatomiques et chirurgicales. vol. 1. Paris: Masson; 1979.
151. Lai P, Lee K, Wong J, Li A. Techniques for liver resection: a review. The Surgeon. 2007;5(3):166-74.
152. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. Journal of hepato-biliary-pancreatic surgery. 2005;12:351-5.
153. Chowdhury MM. Techniques for liver resection. Bangabandhu Sheikh Mujib Medical University Journal. 2010;3(2):112-9.
154. Belghiti J, Guevara OA, Noun R, Saldinger PF, Kianmanesh R. Liver hanging maneuver: a safe approach to right hepatectomy without liver mobilization. Journal of the American College of Surgeons. 2001;193(1):109-11.
155. Mahadevan V. Anatomy of the liver. Surgery (Oxford). 2020;38(8):427-31.
156. van Gulik TM, de Graaf W, Dinant S, Busch OR, Gouma DJ. Vascular occlusion techniques during liver resection. Digestive surgery. 2007;24(4):274-81.
157. Nuzzo G, Giuliante F, Vellone M, De Cosmo G, Ardito F, Murazio M, et al. Pedicle clamping with ischemic preconditioning in liver resection. Liver Transplantation. 2004;10(S2):S53-S7.
158. Clavien P-A, Yadav S, Sindram D, Bentley RC. Protective effects of ischemic preconditioning for liver resection performed under inflow occlusion in humans. Annals of surgery. 2000;232(2):155.
159. Lortat-Jacob J, Robert H, Henry C. Un cas d'hépatectomie droite réglée. 1952. Ref Type: Generic.
160. Heriot A, Karanjia N. A review of techniques for liver resection. Annals of the Royal College of Surgeons of England. 2002;84(6):371.
161. Ekberg H, Tranberg K, Andersson R, Jeppsson B, Bengmark S. Major liver resection: perioperative course and management. Surgery. 1986;100(1):1-8.
162. Aragon RJ, Solomon NL. Techniques of hepatic resection. Journal of gastrointestinal oncology. 2012;3(1):28.
163. Abdalla EK, Noun R, Belghiti J. Hepatic vascular occlusion: which technique? Surgical Clinics. 2004;84(2):563-85.
164. Wang W-D, Liang L-J, Huang X-Q, Yin X-Y. Low central venous pressure reduces blood loss in hepatectomy. World journal of gastroenterology: WJG. 2006;12(6):935.
165. Ronnie T. Current techniques of liver transection. HPB. 2007;9(3):166-73.
166. Lin T. Study on lobectomy of the liver. J Formos Med Assoc. 1958;57:750-69.
167. Lin T-Y. A simplified technique for hepatic resection: the crush method. Annals of surgery. 1974;180(3):285.
168. Kaneko H, Otsuka Y, Takagi S, Tsuchiya M, Tamura A, Shiba T. Hepatic resection using stapling devices. The American journal of surgery. 2004;187(2):280-4.
169. Gurusamy KS, Pamecha V, Sharma D, Davidson BR. Techniques for liver parenchymal transection in liver resection. Cochrane Database of Systematic Reviews. 2009(1).

170. Pamecha V, Gurusamy KS, Sharma D, Davidson BR. Techniques for liver parenchymal transection: a meta-analysis of randomized controlled trials. HPB. 2009;11(4):275-81.
171. Lupo L, Gallerani A, Panzera P, Tandoi F, Di Palma G, Memeo V. Randomized clinical trial of radiofrequency-assisted versus clamp-crushing liver resection. Journal of British Surgery. 2007;94(3):287-91.
172. Buell JF, Cherqui D, Geller DA, O'rourke N, Iannitti D, Dagher I, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Annals of surgery. 2009;250(5):825-30.
173. Wang Z-Y, Chen Q-L, Sun L-L, He S-P, Luo X-F, Huang L-S, et al. Laparoscopic versus open major liver resection for hepatocellular carcinoma: systematic review and meta-analysis of comparative cohort studies. BMC cancer. 2019;19:1-12.
174. Morise Z, Aldrighetti L, Belli G, Ratti F, Belli A, Cherqui D, et al. Laparoscopic repeat liver resection for hepatocellular carcinoma: a multicentre propensity score-based study. Journal of British Surgery. 2020;107(7):889-95.
175. Urade T, Sawa H, Iwatani Y, Abe T, Fujinaka R, Murata K, et al. Laparoscopic anatomical liver resection using indocyanine green fluorescence imaging. Asian Journal of Surgery. 2020;43(1):362-8.
176. Yin Z, Fan X, Ye H, Yin D, Wang J. Short-and long-term outcomes after laparoscopic and open hepatectomy for hepatocellular carcinoma: a global systematic review and meta-analysis. Annals of surgical oncology. 2013;20:1203-15.
177. Di Benedetto F, Petrowsky H, Magistri P, Halazun KJ. Robotic liver resection: Hurdles and beyond. International Journal of Surgery. 2020;82:155-62.
178. Yu Y-D, Kim K-H, Jung D-H, Namkoong J-M, Yoon S-Y, Jung S-W, et al. Robotic versus laparoscopic liver resection: a comparative study from a single center. Langenbeck's archives of surgery. 2014;399:1039-45.
179. Kamarajah SK, Bundred J, Manas D, Jiao L, Hilal MA, White S. Robotic versus conventional laparoscopic liver resections: a systematic review and meta-analysis. Scandinavian Journal of Surgery. 2021;110(3):290-300.
180. Ho C-M, Wakabayashi G, Nitta H, Ito N, Hasegawa Y, Takahara T. Systematic review of robotic liver resection. Surgical endoscopy. 2013;27:732-9.
181. Longchamp G, Labgaa I, Demartines N, Joliat G-R. Predictors of complications after liver surgery: a systematic review of the literature. HPB. 2021;23(5):645-55.
182. Ishii M, Mizuguchi T, Harada K, Ota S, Meguro M, Ueki T, et al. Comprehensive review of post-liver resection surgical complications and a new universal classification and grading system. World journal of hepatology. 2014;6(10):745.
183. Jin S, Fu Q, Wuyun G, Wuyun T. Management of post-hepatectomy complications. World journal of gastroenterology: WJG. 2013;19(44):7983.
184. Kabir T, Syn NL, Tan ZZX, Tan HJ, Yen C, Koh YX, et al. Predictors of post-operative complications after surgical resection of hepatocellular carcinoma and their prognostic effects on outcome and survival: A propensity-score matched and structural equation modelling study. Eur J Surg Oncol. 2020;46(9):1756-65.
185. Clavien PA, Barkun J, De Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Annals of surgery. 2009;250(2):187-96.

186. Kusano T, Sasaki A, Kai S, Endo Y, Iwaki K, Shibata K, et al. Predictors and prognostic significance of operative complications in patients with hepatocellular carcinoma who underwent hepatic resection. European Journal of Surgical Oncology (EJSO). 2009;35(11):1179-85.
187. Kong J, Li G, Chai J, Yu G, Liu Y, Liu J. Impact of postoperative complications on long-term survival after resection of hepatocellular carcinoma: A systematic review and meta-analysis. Annals of Surgical Oncology. 2021;28(13):8221-33.
188. Brooke-Smith M, Figueras J, Ullah S, Rees M, Vauthey J-N, Hugh TJ, et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. Hpb. 2015;17(1):46-51.
189. Mehrabi A, Dezfouli SA, Schlösser F, Ramouz A, Khajeh E, Ali-Hasan-Al-Saegh S, et al. Validation of the ISGLS classification of bile leakage after pancreatic surgery: A rare but severe complication. European Journal of Surgical Oncology. 2022;48(12):2440-7.
190. Sadamori H, Yagi T, Shinoura S, Umeda Y, Yoshida R, Satoh D, et al. Risk factors for major morbidity after liver resection for hepatocellular carcinoma. Journal of British Surgery. 2013;100(1):122-9.
191. Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF)–recent advances in prevention and clinical management. European Journal of Surgical Oncology. 2021;47(2):216-24.
192. Gilg S, Sandström P, Rizell M, Lindell G, Ardnor B, Strömberg C, et al. The impact of post-hepatectomy liver failure on mortality: a population-based study. Scandinavian journal of gastroenterology. 2018;53(10-11):1335-9.
193. Gong W-F, Zhong J-H, Lu Z, Zhang Q-M, Zhang Z-Y, Chen C-Z, et al. Evaluation of liver regeneration and post-hepatectomy liver failure after hemihepatectomy in patients with hepatocellular carcinoma. Bioscience reports. 2019;39(8).
194. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? Digestive surgery. 2012;29(1):6-17.
195. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. American journal of infection control. 2008;36(5):309-32.
196. Chok K, Ng K, Poon R, Lo C, Fan S. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. Journal of British Surgery. 2009;96(1):81-7.
197. Park L, Gilbert R, Baker L, Shorr R, Workneh A, Turcotte S, et al. The safety and efficacy of hypovolemic phlebotomy on blood loss and transfusion in liver surgery: a systematic review and meta-analysis. HPB. 2020;22(3):340-50.
198. Wang F, Sun D, Zhang N, Chen Z. The efficacy and safety of controlled low central venous pressure for liver resection: a systematic review and meta-analysis. Gland Surgery. 2020;9(2):311.
199. Latchana N, Hirpara DH, Hallet J, Karanicolas PJ. Red blood cell transfusion in liver resection. Langenbeck's Archives of Surgery. 2019;404(1):1-9.
200. Hughes MJ, Ventham NT, Harrison EM, Wigmore SJ. Central venous pressure and liver resection: A systematic review and meta analysis. Hpb. 2015;17(10):863-71.
201. Pringle JH. V. Notes on the arrest of hepatic hemorrhage due to trauma. Annals of surgery. 1908;48(4):541.

202. Lee KF, Wong J, Cheung S, Chong CC, Hui JW, Leung VY, et al. Does intermittent Pringle maneuver increase postoperative complications after hepatectomy for hepatocellular carcinoma? A randomized controlled trial. World journal of surgery. 2018;42(10):3302-11.
203. Mobarak S, Stott MC, Tarazi M, Varley RJ, Davé MS, Baltatzis M, et al. Selective Hepatic Vascular Exclusion versus Pringle Maneuver in Major Hepatectomy: A Systematic Review and Meta-Analysis. Frontiers in Surgery. 2022;9:860721.
204. Yamashita Y-i, Hayashi H, Imai K, Okabe H, Nakagawa S, Kitamura F, et al. Perioperative allogeneic blood transfusion does not influence patient survival after hepatectomy for hepatocellular carcinoma: a propensity score matching analysis. World Journal of Surgery. 2019;43(11):2894-901.
205. Martin AN, Kerwin MJ, Turrentine FE, Bauer TW, Adams RB, Stukenborg GJ, et al. Blood transfusion is an independent predictor of morbidity and mortality after hepatectomy. Journal of Surgical Research. 2016;206(1):106-12.
206. Chen G-X, Qi C-Y, Hu W-J, Wang X-H, Hua Y-P, Kuang M, et al. Perioperative blood transfusion has distinct postsurgical oncologic impact on patients with different stage of hepatocellular carcinoma. BMC cancer. 2020;20(1):1-12.
207. Tan LL, Chew VT, Syn N, Tan EK, Koh YX, Teo JY, et al. Intraoperative blood transfusion does not impact overall and recurrence-free survival after curative hepatectomy for hepatocellular carcinoma: A propensity-score-matched and inverse probability of treatment-weighted study. Journal of Surgical Oncology. 2022.
208. Silva MF, Sherman M. Criteria for liver transplantation for HCC: what should the limits be? Journal of Hepatology. 2011;55(5):1137-47.
209. Lingiah VA, Niazi M, Olivo R, Paterno F, Guarrera JV, Pyrsopoulos NT. Liver transplantation beyond Milan criteria. Journal of clinical and translational hepatology. 2020;8(1):69.
210. Peloso A, Oldani G. Enlarged selection criteria for hepatocellular cancer: is the upper limit needed? Translational gastroenterology and hepatology. 2017;2.
211. Menon K, Hakeem A, Heaton N. liver transplantation for hepatocellular carcinoma–a critical appraisal of the current worldwide listing criteria. Alimentary pharmacology & therapeutics. 2014;40(8):893-902.
212. Yao F. Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. American Journal of Transplantation. 2008;8(10):1982-9.
213. Farkas S, Hackl C, Schlitt HJ. Overview of the indications and contraindications for liver transplantation. Cold Spring Harbor Perspectives in Medicine. 2014;4(5):a015602.
214. Parikh ND, Singal AG. Model for end-stage liver disease exception points for treatment-responsive hepatocellular carcinoma. Clinical Liver Disease. 2016;7(5):97.
215. Guerrini GP, Esposito G, Olivieri T, Magistri P, Ballarin R, Di Sandro S, et al. Salvage versus Primary Liver Transplantation for Hepatocellular Carcinoma: A Twenty-Year Experience Meta-Analysis. Cancers. 2022;14(14):3465.
216. Bhangui P, Allard MA, Vibert E, Cherqui D, Pelletier G, Cunha AS, et al. Salvage versus primary liver transplantation for early hepatocellular carcinoma: do both strategies yield similar outcomes? Annals of surgery. 2016;264(1):155-63.
217. Wang H-L, Mo D-C, Zhong J-H, Ma L, Wu F-X, Xiang B-D, et al. Systematic review of treatment strategy for recurrent hepatocellular carcinoma: salvage liver transplantation or curative locoregional therapy. Medicine. 2019;98(8).

218. Krige JE, Jonas E, Thomson SR, Kotze UK, Setshedi M, Navsaria PH, et al. Resection of complex pancreatic injuries: Benchmarking postoperative complications using the Accordion classification. World Journal of Gastrointestinal Surgery. 2017;9(3):82.
219. Strasberg S, Belghiti J, Clavien P-A, Gadzijev E, Garden J, Lau W-Y, et al. The Brisbane 2000 terminology of liver anatomy and resections. Hpb. 2000;2(3):333-9.
220. Spearman CW, Afihene M, Ally R, Apica B, Awuku Y, Cunha L, et al. Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. The lancet gastroenterology & hepatology. 2017;2(12):900-9.
221. Clavien P-A, Fong Y. Malignant liver tumors: current and emerging therapies: Jones & Bartlett Learning; 2004.
222. Cho SJ, Yoon JH, Hwang SS, Lee HS. Do young hepatocellular carcinoma patients with relatively good liver function have poorer outcomes than elderly patients? Journal of gastroenterology and hepatology. 2007;22(8):1226-31.
223. Ha SY, Sohn I, Hwang SH, Yang JW, Park C-K. The prognosis of hepatocellular carcinoma after curative hepatectomy in young patients. Oncotarget. 2015;6(21):18664.
224. Chen CH, Chang TT, Cheng KS, Su WW, Yang SS, Lin HH, et al. Do young hepatocellular carcinoma patients have worse prognosis? The paradox of age as a prognostic factor in the survival of hepatocellular carcinoma patients. Liver international. 2006;26(7):766-73.
225. Su C-W, Lei H-J, Chau G-Y, Hung H-H, Wu J-C, Hsia C-Y, et al. The effect of age on the long-term prognosis of patients with hepatocellular carcinoma after resection surgery: a propensity score matching analysis. Archives of surgery. 2012;147(2):137-44.
226. Zeng J, Lin K, Liu H, Huang Y, Guo P, Zeng Y, et al. Prognosis factors of young patients undergoing curative resection for hepatitis B virus-related hepatocellular carcinoma: a multicenter study. Cancer Management and Research. 2020:6597-606.
227. Bruix J, Llovet JM. Hepatitis B virus and hepatocellular carcinoma. Journal of Hepatology. 2003;39:59-63.
228. Kew MC. Hepatocellular carcinoma in African Blacks: Recent progress in etiology and pathogenesis. World journal of hepatology. 2010;2(2):65.
229. Yang JD, Mohamed EA, Aziz AOA, Shousha HI, Hashem MB, Nabeel MM, et al. Characteristics, management, and outcomes of patients with hepatocellular carcinoma in Africa: a multicountry observational study from the Africa Liver Cancer Consortium. The lancet Gastroenterology & hepatology. 2017;2(2):103-11.
230. Stefan DC. Cancer care in Africa: an overview of resources. Journal of global oncology. 2015;1(1):30-6.
231. Tognarelli J, Ladep NG, Crossey MM, Okeke E, Duguru M, Banwat E, et al. Reasons why West Africa continues to be a hotbed for hepatocellular carcinoma. Nigerian Medical Journal. 2015;56(4):231-5.
232. Olivier J, Tsimpo C, Gemignani R, Shojo M, Coulombe H, Dimmock F, et al. Understanding the roles of faith-based health-care providers in Africa: review of the evidence with a focus on magnitude, reach, cost, and satisfaction. The Lancet. 2015;386(10005):1765-75.
233. Kew MC. Epidemiology of hepatocellular carcinoma in sub-Saharan Africa. Annals of hepatology. 2015;12(2):173-82.
234. Li J, Huang L, Yan J, Qiu M, Yan Y. Liver resection for hepatocellular carcinoma: personal experiences in a series of 1330 consecutive cases in China. ANZ journal of surgery. 2018;88(10):E713-E7.

235. Papaconstantinou D, Tsilimigras DI, Pawlik TM. Recurrent hepatocellular carcinoma: Patterns, detection, staging and treatment. Journal of Hepatocellular Carcinoma. 2022:947-57.
236. Hassanipour S, Vali M, Gaffari-Fam S, Nikbakht H-A, Abdzadeh E, Joukar F, et al. The survival rate of hepatocellular carcinoma in Asian countries: a systematic review and meta-analysis. EXCLI journal. 2020;19:108.
237. Arabsalmani M, Mirzaei M, Ghoncheh M, Soroush A, Towhidi F, Salehiniya H. Incidence and mortality of liver cancer and their relationship with the human development index in the world. Biomedical Research and Therapy. 2016;3:1-8.
238. Shao S-Y, Hu Q-D, Wang M, Zhao X-Y, Wu W-T, Huang J-M, et al. Impact of national Human Development Index on liver cancer outcomes: Transition from 2008 to 2018. World Journal of Gastroenterology. 2019;25(32):4749.
239. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. The lancet oncology. 2012;13(8):790-801.
240. Rafiemanesh H, Mehtarpour M, Khani F, Hesami SM, Shamlou R, Towhidi F, et al. Epidemiology, incidence and mortality of lung cancer and their relationship with the development index in the world. Journal of thoracic disease. 2016;8(6):1094.
241. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Vitali M, Bertuzzo F, et al. Hepatocellular carcinoma: surgical perspectives beyond the barcelona clinic liver cancer recommendations. World Journal of Gastroenterology: WJG. 2014;20(24):7525.
242. Lemmer E, Krige J, de la M Hall P, Bornman P, Taylor D, Terblanche J. Surgical resection for hepatocellular carcinoma in Cape Town-A clinical and histopathological study. South African Medical Journal. 1998;88(12):1575-80.
243. Muhammad I, Mabogunje O. Spontaneous rupture of primary hepatocellular carcinoma in Zaria, Nigeria. Journal of the Royal College of Surgeons of Edinburgh. 1991;36(2):117-20.
244. Enwezor C. Sixty cases of primary hepatocellular carcinoma in one year. A preliminary appraisal. International surgery. 1992;77(4):277-9.
245. Elsanousi OM, Mohamed MA, Salim FH, Adam EA. Selective devascularization treatment for large hepatocellular carcinoma: Stage 2A IDEAL prospective case series. International Journal of Surgery. 2019;68:134-41.
246. Harrison N, Dhru D, Primack A, Bhana D, Kyalwazi S. The surgical management of primary hepatocellular carcinoma in Uganda. Journal of British Surgery. 1973;60(7):565-9.

APPENDICES

Appendix A: Human Research Ethics Committee Letter of Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 March 2022

HREC REF: 131/2022

Prof J Krige
Surgical Gastroenterology
E23 Room 17 NGSH
Email: jej.krige@uct.ac.za
Student: ymy474@gmail.com

Dear Prof Krige

PROJECT TITLE: RESECTION OF HEPATOCELLULAR CARCINOMA AT A SOUTH AFRICAN TERTIARY REFERRAL CENTRE. AN OUTCOMES ANALYSIS OF MORBIDITY, MORTALITY AND SURVIVAL-MPHIL CANDIDATE-DR YALDA ZIAEI

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, our letter dated 02 February 2022 provides guidance found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 March 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Yalda Ziaei will also be involved in this study.

Please quote the HREC REF 131/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix B: Human Research Ethics Committee Letter of Approval – Renewed letter

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30/03/24
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	17/3/2023

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	27 March 2022		
HREC REF Number	131/2022	Current Ethics Approval was granted until	30 March 2023
Protocol title	Resection of hepatocellular carcinoma at a South African tertiary referral centre. An outcomes analysis of morbidity, mortality and survival (MPhil Candidate Dr Yalda Ziaei)		
Principal Investigator	Professor Jake Krige		
Department / Office Internal Mail Address	E23 Room 19, GI Clinic New Groote Schuur Hospital		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
✓	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		48
Total number of records or specimens collected, reviewed or stored since last progress report		48
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	✓ No

4. Signature

Signature of PI		Date	27 March 2023

HUMAN RESEARCH ETHICS COMMITTEE
27 MAR 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN