The profile and outcomes of patients with Hepatocellular Carcinoma treated with curative intent at Groote Schuur Hospital, a Tertiary Referral Centre in South Africa

DR GARETH HARVEY CHILTON

(CHLGAR004)

Submitted to the university of Cape Town

In partial fulfilment of the requirements for the degree of

Master of Medicine in Surgery

Faculty of Health Sciences

University of Cape Town

September 2021

TABLE OF CONTENTS

DECLARATION

I, Gareth Harvey Chilton, hereby declare that the work on which this dissertation/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. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate

Dr Gareth Harvey Chilton

Signed on the 30th day of September 2021

Dr Marc Bernon	Prof Eduard Jonas
SUPERVISOR	CO-SUPERVISOR

ACKNOWLEDGEMENTS

I'd like to thank the following individuals for their unwavering support without which this paper would not have been possible:

Dr Marc Bernon who supported me during this time from inception to fruition, who's passion for research as well as dedication and attention to detail allowed us to complete this Masters dissertation. Thank you for pushing me and inspiring me.

Similarly, I would like extend immense gratitude to my mentor Professor Eduard Jonas whose clinical knowledge and expertise extend far beyond the pages of this paper. You have showed me so much humility and your guidance and professional help with this paper is immeasurable.

To my parents, friends and family – your constant support and dedication to me finishing made this possible.

This paper is dedicated to you, Dad - your humility and constant encouragement are felt daily.

LIST OF TABLES AND FIGURES

ABBREVIATIONS

HCC	Hepatocellular Carcinoma
MELD	Model for End Stage Liver Disease
CPS	Child-Pugh Score
BCLC	Barcelona Clinic Liver Cancer score
TACE	Trans-arterial Chemo-embolization
SSA	Sub-Saharan Africa

LITERATURE REVIEW

Liver cancer is a significant determinant of worldwide morbidity and mortality. At present, liver cancer is the sixth most common malignancy globally, contributing to approximately 9.2% of all new annual cancer diagnoses (1-3). Despite medical advancements over the past decades, prognosis and outcomes remain poor. If we consider the global incidence rate of liver cancer per 100 000 person-years, 2018 yielded a rate of 9.3% with a corresponding mortality rate of 8.5% (1). In developing economies, where resource limitations remain a challenge, the increasing prevalence of liver cancer contributes significantly to the burden on healthcare settings.

At the time of this study, reported incidence rates of liver cancer showed considerable variability. A recent study by Bray *et al.* (1) evaluated the incidence of liver cancer in five continents, concluding that higher rates are seen in Asia and Africa. Although the largest contributor to global liver cancer statistics, distribution across Asia showed great variability (1, 4). Current data on liver cancer in low and middle income continents such as Africa are insufficient to reach accurate conclusions, with only Ugandan data reported on by Bray *et al.* (1).

Of total liver cancer, hepatocellular carcinoma (HCC) contributes an estimated 75% (2, 4) with intrahepatic cholangiocarcinoma (ICC) the second biggest contributor, estimated at 12-15% (4). If we consider the incidence of HCC only, an estimated 80% of global cases occurs in East Asia and Sub-Saharan Africa (SSA) (4, 5). Regional incidences of HCC in SSA exceed those reported in China and other high-prevalence countries (6). Alarmingly, studies suggest an underestimation of 20% of global incidence and mortality of HCC, owing to poor reporting

and lack of definitive diagnosis in resource-constrained countries (7). This is underpinned by the fact that more than 80% of all global cases of HCC occur in resource-constrained countries, primarily in Asia and Africa (5). Furthermore, age-standardised incidence rates in low developing countries have been increasing since 1990, despite decreasing rates globally (6). The incidence of hepatocellular carcinoma is expected to increase over the coming years, reiterating the importance of addressing its effect on health systems.

The demographics of those diagnosed with hepatocellular carcinoma are characterised by repeated disease patterns. Robust epidemiological data suggests a predilection for males, with studies reporting ratios of 1.1 to 3.5:1.0 (8). In SSA, the male predominance is even more substantial, 8:1, compared with 2.5:1 in non-African populations (5). The epidemiology of hepatocellular carcinoma in resource-constrained African populations demonstrates a shift to younger cohorts when compared with non-African populations, with the majority of patients diagnosed at a mean age of 33.4 - 47.5 years as opposed to a 60 - 80 years in non-African cohorts (5). The epidemiological profile of hepatocellular carcinoma underscores the need for increased efforts in furthering both diagnosis and treatment.

The incidence of hepatocellular carcinoma in Africa is grossly underestimated, owing to poor reporting standards and lack of definitive diagnoses. Using histology as the definitive criteria, the official National Cancer Registry places liver and bile duct cancers in South Africa at a very low prevalence (9). When comparing these statistics to other African countries or those classified as low SDI, it becomes evident that these statistics fail to provide an accurate representation of the disease burden.

Hepatocellular carcinoma is associated with an appreciable mortality rate, which is negatively influenced by delayed detection of disease in resource-constrained settings. The cancer carries the highest annual fatality rate of any human tumour, with 93% dying from the effects of the tumour within 12 months of the onset of symptoms (8). The cancer carries a poor prognosis, resulting in incidence and mortality rates that are roughly equivalent. In 2018, the global incidence rate of liver cancer per 100,000 person-years was 9.3 whereas the corresponding mortality rate was 8.5 (1). The significant mortality rate is largely as a result of delayed detection, with patients typically presenting with advanced disease where intervention is no longer possible. This is particularly evident in SSA, where 95% of patients present with advanced or terminal disease (10, 11). In contrast, 40% of patients in developed countries are diagnosed at a stage of disease where curative intended interventions can be considered (5). Alarmingly, even in those that present with potentially curable disease, studies suggest a very small fraction receive intervention with curative intent. In a retrospective observational cohort study that included data from eight SSA countries, a mere 0.6% of patients diagnosed with HCC underwent treatment with curative intent (12). In a similar study conducted in Ghana which comprised a cohort of 206 patients with HCC presenting to a major referral hospital, less than 8% were assessed for curative intended treatment (13). While fortunate to have all curative-intended treatment options for patients with HCC available, few liver transplants were performed in Johannesburg for patients diagnosed with HCC (14). This is significantly low, especially when compared to the higher incidence of liver transplants in low incidence HCC European countries and even higher in Asian countries (15-17). Rising incidence will also result in increased surgical demand, which will need to be met with a resultant increase in capacity. Improved screening and earlier detection may allow for more timeous intervention and improved outcomes.

Substandard curative intervention may highlight the potential benefit of implementation of improved and widely applied screening programmes for Hepatocellular Carcinoma. HCC possesses the ten requirements for a condition in which screening is likely to improve outcome (18). While questions remain surrounding the efficacy of screening programmes for HCC, there is a growing consensus that implementation of screening in the setting of HCC will be of value (5). Two large randomized controlled trials in patients with HBV in China, as well as a number of observational cohort studies in patients with cirrhosis cite the value of HCC surveillance. Earlier-stage HCC was detected, resulting in higher likelihood of curative intended interventions and improved survival in the surveillance group when compared with patients who presented following symptom development or incidental detection (19). The case for its use in SSA is even more apparent, owing to the high incidence and limited aetiological factors in the region. Chronic infections with hepatitis B virus (HBV) in SSA, and hepatitis C virus (HCV) in Northern Africa are responsible for approximately 90% of the total cases (20). Aflatoxin exposure, through contaminated food stables, is also a contributing cause in Sub-Saharan regions (21). The epidemiological profile allows for more targeted screening efforts, providing cost-effective screening in certain cohorts and yielding greater overall benefit.

The risk factors for HCC in SSA differ distinctly from those present in the Western world. An underlying risk factor is typically present in 90% of patients who develop HCC (European Association for the Study of the Liver (EASL), European Organisation for Research and Treatment of Cancer (EORTC) (22). The most common risk factors present in patients that develop HCC are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, with the burden of chronic infection typically mirroring HCC incidence (23, 24). Globally, 54% of cases

are attributed to HBV infection, with HCV infection identified in 31% of cases and 15% comprising other risk factors. In Africa and Asia, chronic HBV infection is responsible for 60% of cases, compared to just 20% in the Western World. Alcoholic cirrhosis, non-alcoholic steatohepatitis (NASH) and consumption of aflatoxin-contaminated foods have also been identified as major risk factors. Additionally, there is a growing body of literature that describes the role of the metabolic syndrome, namely diabetes mellitus and obesity, as a risk factor for HCC. In a study by Welzel *et al.* (25), patients with pre-existing metabolic syndrome were 2.1-fold more likely to develop HCC. Cirrhosis is present in approximately 90% of patients that develop HCC, with 1–8% per year of patients with cirrhosis developing HCC (26). The risk factors that characterise the patient population in Africa should come shape preventative measures, and inform public health policy.

The pathogenesis of HCC is primarily mediated by liver inflammation and fibrosis, resulting in liver cirrhosis. Repeated liver injury, with resultant inflammation and fibrosis, leads to the development of disordered liver architecture that characterises cirrhosis. In 90% of patients, cirrhosis precedes the development of HCC (27). While complex, Dhanasekaran *et al*. (27) describe the natural history as the development of pre-cancerous dysplastic foci, which aggregate into dysplastic nodules. The dysplastic nodules can be classified as either low-grade or high grade, with the distinction informed by the degree of cellular atypia, stromal invasion and trabecular patterns. Both are pre-cancerous lesions and have the potential to progress to HCC. HCC is characterised by stromal invasion, further subclassified in early HCC or progressed HCC. The pathology present at the time of diagnosis is central in guiding the appropriate course of treatment.

Recent years have borne witness to improvements in management of HCC, largely underpinned by advances in diagnostic capabilities, development of improved staging systems and more efficacious treatment strategies. The heterogenous nature of HCC, coupled with the complex nature of the underlying biology, has seen the management of HCC occur at the interfaces of several specialties. Increasingly, multimodal strategies are being used in the management of HCC, with treatment combinations resulting in more favourable outcomes. Briefly, treatment options offered to patients include thermal ablation, trans-arterial chemoembolization, resection with curative intent and ultimately liver transplantation (28). Clinical decision making takes into consideration multiple factors such as tumour stage and patient factors.

This multimodal and multidisciplinary approach, often times combining locoregional techniques and surgical intervention, has resulted from improved understanding of the disease and technical advancements. Staging systems, such as the Barcelona Clinic Liver Cancer (BCLC), use tumour characteristics, liver disease, and patient performance status to inform prognosis and guide treatment (22, 29). While other staging systems have been developed, the BCLC is favoured owing to its ability to provide both prognostic value and aid in treatment decision. Additionally, BCLC has been clinically validated (30) and has been updated several times following the new clinically-related evidence (31, 32). At present, surgery remains the mainstay of treatment in patients diagnosed with HCC, with hepatic resection and transplantation associated with the best oncological outcomes in cases with curative intent (33). Hepatic resection is the first line treatment option in patients with solitary HCC and without clinically relevant portal hypertension, typically employed in non-cirrhotic patients where major resections are better tolerated (22). Unfortunately, most HCC

patients present with advanced disease where transplantation is often not feasible (10). Advances in pre-operative evaluation, surgical advancements and peri-operative care have seen mortality reduced to 1% (34, 35). While associated with good outcomes in well-selected candidates, hepatic resection has a risk 80% recurrence at five years (36) with presence of microsatellites or microvascular invasion on histology conferring increased risk. As such, liver transplantation may be considered in those with a high risk of recurrence.

Thermal ablation has emerged as a suitable and efficacious treatment option in patients with very early solitary tumours (<2cm), regarded as the first line option in those not suitable for transplantation. Its limitations are influenced by tumour characteristics, with efficacy decreasing in parallel to tumour size. In a study by Cho *et al.* (37), a Markov model concluded both hepatic resection and thermal ablation have comparable in outcomes. While similar in outcome, hepatic resection does offer the opportunity to assess for risk of recurrence, assessing the anatomical pathology of the HCC.

The use of liver transplantation as an intervention with curative-intent in HCC is advantageous, removing intrahepatic tumour foci and the underlying oncogenic cirrhotic liver. It outperforms both hepatic resection and ablation when assessed in terms of long-term oncological outcomes (38). The introduction of the Milan criteria, which define the eligibility criteria for transplantation, saw radical improvements in post-transplant outcomes. The 5-year survival rate post-transplant within Milan Criteria is 75% (39). Consequently, there have been calls to expand eligibility criteria as a means of increasing access to potentially curative treatment with limited impact on outcomes (40).

There is a broad spectrum of interventional procedures, used with both curative and palliative-intent. Trans arterial chemoembolization (TACE), relies on the arterial

hypervascularity of HCC and achieves tumour necrosis and delayed tumour progression through embolization of feeding arteries using chemotherapeutic agents (33, 40). Several studies and two meta-analysis have confirmed the benefits of TACE as a palliative treatment (41, 42). Furthermore, TACE has been shown to improve survival in patients with HCC, supported by two meta-analyses that aggregated results from multiple randomized controlled trials (43, 44). Radioembolization has also been employed in the management of HCC, with survival rates comparable to those treated with TACE (43, 44). Locoregional techniques provide utility in both curative and palliative intervention, while also being employed as adjuncts in management of HCC.

Despite the curative intended interventions mentioned, many patients who present with HCC will only be offered palliative care due to disease severity at time of initial presentation (45). A study by Roayaie *et al.* (46) suggests that less than a quarter of patients presenting with HCC worldwide meet preoperative selection criteria for possible curative intervention (46). In low and middle income countries such as South Africa, socio-economic factors remain an important determinant of health seeking behaviour with poor socio-economic status contributing to delayed presentation.

The aim of this study was thus to perform retrospective audit to evaluate the outcomes of patients with HCC who were treated with curative intent at Groote Schuur Hospital over a 5 year period. The primary objective was to review diagnosis, surgical and oncological management of these patients as well as evaluate complications of treatment, disease-free survival and overall survival.

PUBLICATION READY MANUSCRIPT

The Profile of Management of Hepatocellular Carcinoma at Groote Schuur Hospital, a Tertiary Referral Centre in South Africa

Gareth Chilton[1], Wendy Spearman[3], Mark Sonderup[3], Neliswa Gogela[3], Tinus Du Toit[2], Christo Kloppers[1], Chanel Robinson[1], Vuyo Soldati[1] Urda Kotze[1], Eduard Jonas[1], Marc Bernon[1]

[1]Surgical Gastroenterology Unit & [2]Transplant Unit, Department of Surgery, University of Cape Town

[3] Division of Hepatology, Department of Medicine, University of Cape Town

Corresponding author

Dr Marc Bernon

MBChB, MPhil FCS (SA), Cert Gastroenterology (Surg)

Surgical Gastroenterology Unit

Department of Surgery

Groote Schuur Hospital & University of Cape Town

Main Road, Observatory, Cape Town, 7925

Email:mm.bernon@uct.ac.za

Key words: HCC, hepatocellular carcinoma, liver, transplant

ABSTRACT

Introduction: HCC is a common cause of cancer-related death in sub-Saharan Africa (SSA). Whereas several papers have reported on HCC in the South African context, very few studies have evaluated treatment options and subsequent survival data.

Objective: To identify the clinical characteristics of patients with HCC presenting to Groote Schuur Hospital and present survival data on patients treated with curative intent.

Methodology: All patients who presented with HCC from 1 July 2015 to 30 June 2020 were included in the study. Data was extracted from a faculty approved, prospectively maintained registry. Information collected included demographics, clinical characteristics, grading of liver dysfunction according to the Child-Pugh Score (CPS) and Model for end stage liver disease (MELD) score, disease stage according to the Barcelona Clinic Liver Cancer (BCLC) grading system and treatment received. Variables were assessed for the total patient cohort as well as for the palliative and curative intended patient groups. Survival data was collected for the curative intended treatment group up to 31st of August 2021.

Results: A total of 152 patients were included in the study. Chronic hepatitis B infection (60.5 %) was the most common aetiological factor. Twenty-one patients (13.8%) were treated with curative intent. The median survival of the entire curative intended cohort was 45.5 months (range 0.1-72.5). The median survival for the transplantation, resection and local ablation groups were 54.3, 23.0 and 45.5 months respectively.

Conclusion: Only 13.8% of patients were treated with curative intent. Survival data in the patients treated with curative intent is comparable to other reported series. The findings highlight the need for improved screening of high risk patients and appropriate referral of patients for curative intended treatment.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a significant cause of worldwide morbidity and mortality. At present, HCC is the sixth most common malignancy globally, and is the most common cause of cancer-related death in men and the 3rd most common in women in sub-Saharan Africa (SSA) (1-3). An estimated 80 % of global cases occurs in east Asia and SSA (4, 5) with regional incidences of HCC in SSA exceeding those reported in China and other high-prevalence regions (6). Alarmingly, studies suggest an underestimation of 20% of global incidence and mortality of hepatocellular carcinoma, owing to poor reporting and lack of definitive diagnosis in resource-constrained countries (7).

Despite medical advancements over the past decades, prognosis and outcomes remain poor. This is likely a result of delayed presentation and advanced disease not suitable for curative intended intervention (Liver transplant, liver resection, thermal ablation). In reports from high income countries (HICs) an estimated 40% of patients present with very early, early or intermediate stage disease (12, 47). Current targets suggest that 30 to 40% of patients should undergo curative-intended treatment, a goal that has been realised in several, predominantly developed countries (22). In contrast, approximately 95% of patients present with advanced or terminal disease in SSA, where only palliation is possible (12, 47). Worryingly, even in those that present with potentially curable disease, studies suggest only a very small fraction receive intervention with curative intent in SSA.

Despite significant disease burden and associated mortality, data on the profile of HCC presentation in SSA countries are limited. However, while limited, recent papers do speak to the late presentation of hepatocellular carcinoma in an African context, and the lack of

curative-intended intervention performed in these populations. Similarly, there remains a paucity of literature dedicated to the evaluation and validation of the multiple treatment options in the setting of SSA. While several papers have reported on the treatment of HCC in the South African context, none give an overview of the spectrum of treatment performed for a whole patient cohort (19, 48, 49).

The present study seeks to contribute to an improved understanding of hepatocellular carcinoma in a South African context, and form part of the greater global commentary on the disease.

METHODOLOGY

Patient Characteristics and Clinical Parameters

Patients that were referred to the Surgical Gastroenterology Unit at Groote Schuur Hospital with HCC from 1 July 2015 to 30 June 2020, were included in the study. Data were retrieved from prospectively maintained institutional registries. Information collected included demographics, clinical characteristics, grading of liver dysfunction according to the Child-Pugh Score (CPS) and Model for end stage liver disease (MELD) score, disease stage according to the Barcelona Clinic Liver Cancer (BCLC) grading system and treatment received (Table 1). Cirrhosis was diagnosed either on histology from percutaneous biopsy or surgical resection specimens or cross-sectional imaging. Variables were assessed for the total patient cohort as well as for the palliative and curative intended patient groups. In patients treated with curative intent data was analysed separately for the resection, liver transplant and ablation groups. Survival data was collected for the curative intended treatment group up to 31st of August 2021.

Data management

Data were collected and managed using the REDCap electronic data capturing software licensed to the University of Cape Town. Statistical computations were made using IBM SPSS statistics (version 27.0, IBM, USA). Statistical significance was set as $p < .05$. Continuous data were reported as mean ± SD or mean ± SEM and discreet data as percentages.

Ethics

The institutional registries and the study were approved by the Human Research Ethics Committee of the University of Cape Town (approval number: 534/2021).

RESULTS

A total of 152 patients were included in the study. The median age at presentation was 51.4 years (range 12.8-86.6) and 69.7% of patients were male. Forty-nine patients (32.3 %) had confirmed cirrhosis. The predominant cause of cirrhosis was chronic hepatitis B infection (60.5 %). Of the total cohort, 21 patients (13.8%) were treated with curative and 131 (86.2%) with palliative intent. A higher proportion of patients in the curative intended cohort had cirrhosis (p=.03).

The grading of liver disease and HCC staging is shown in Table 1. In the total cohort 92 patients (60.5%) were Child-Pugh Grade A. The median MELD score was 11 (range 6-34) in the total cohort and did not significantly differ between the subgroups. For the total cohort, the Barcelona-Clinic Liver Cancer (BCLC) stage was fairly evenly distributed throughout all stages with stage B as the more predominant stage (n=46, 30.3 %). Comparatively, more patients in the curative intended treatment cohort were BCLC stage A than in the palliative cohort (n=9, 42.9 % and n=22, 16.8 % respectively,(p<.01).

Figure 1 shows the treatment pathways of the patients included in the study The demographics and clinical parameters for the patients in the three curative intended treatment cohorts are shown in Table 2. Six patients underwent transplantation, twelve underwent resection, and three local ablation.. Seven patients were listed for transplant but one progressed on the waiting list and was not transplanted. All transplanted patients had cirrhosis. Six of the 7 patients listed for transplant received TACE as a bridging therapy. The transplant patients were all within the UCSF criteria (Table 3). Five of the twelve resected patients received TACE as neo-adjuvant treatment and 28 of the palliative patients received TACE as a life prolonging palliative treatment modality.

Survival data for individual patients is shown in Table 4. and figure 2 demonstrates Kaplan Meyer survival curves for the three curative treatment patient cohorts. The 60-day perioperative mortality for patients in the curative intended cohort was 4.8% (1/21 patients). One patient in the resection cohort died on post-operative day 4 from post hepatectomy liver failure. Four of the resected patients (23.8%) and one of the thermal ablation patients (33.3%) died in the follow up period whereas all transplant patients were still alive). The median survival of the entire curative intended cohort was 45.5 months (range 0.1-72.5). The median survival for the transplantation, resection and local ablation groups were 54.3, 23.0 and 45.5 months respectively.

DISCUSSION

Of the 152 patients who presented with HCC during the study period, 94 (61.8%) presented with very early, early or intermediate stage disease, which is higher than other series from SSA. This likely represents a selection bias as patients with advanced stage disease are often not referred to tertiary units. The predominate aetiology was hepatitis B which was present in 92 of the patients (60.5%). Hepatitis C and metabolic associated fatty liver disease were not major aetiological factors. This is in keeping with previous publications from SSA (50). Some patients had an overlap of aetiological causes (for instance concurrent chronic HBV infection and alcohol over-consumption).

Cirrhosis was documented in 49 patients (32.3%) which is lower than most series from developed countries. This is probably related to hepatitis B being the predominant aetiological factor in this series. There was a higher proportion of patients with cirrhosis in the curative intended group than in the palliative group (11/21 (52.4%) vs. 38/131 (29.0%)). This may represent a selection bias as cirrhosis may have been diagnosed more frequently on the histology of the resected specimens in the curative intended group. The majority of patients in the palliative group did not have a biopsy and the diagnosis of cirrhosis was based on imaging.

Only 21 patients (13.8%) were treated with curative intent. This is despite the patients being managed in a relatively well-resourced tertiary referral hospital and one of only two centres in SSA where all curative intended treatment options are available. This is due to the advanced stage of disease at presentation and an indication of the lack of adequate screening and

surveillance programs for patients with risk factors such as cirrhosis and chronic hepatis B infection.

CONCLUSION

The survival data of the patients in the curative intended treatment group compares favourably with results from centres outside SSA. Although we did not present survival data of the palliative group, previous studies have highlighted the dismal survival in these patients.

Curative intended treatment offers patients with HCC a chance of long-term survival. These findings highlight the importance of efforts to increase the proportion of patients diagnosed with early-stage disease in SSA. More effort needs to be made to enrol high risk patients into screening programs and once diagnosed with early-stage disease there must be improved access for patients in SSA to centres that offer the appropriate treatment modalities.

Table 1. Demographic and Clinical Characteristics of the entire patient cohort.

*Only significant p values shown

	TOTAL COHORT (n=152)	**CURATIVE* (n=21)**	**PALLIATIVE* (n=131)**	***p=**
Male n (%)	106 (69.7%)	15 (71.4%)	91 (69.5%)	
Age (years) median (range)	51.4 (12.8-86.6)	53.1 (18.7-70.8)	48.9 (12.8-86.6)	
Cirrhosis	49 (32.3%)	11 (52.4%)	38 (29.0%)	.03
Aetiology				
Alcohol	22 (14.4%)	7 (33.3%)	15 (11.5%)	
Hepatitis B	92 (60.5%)	12 (57.1%)	80 (61.1%)	
Hepatitis C	10 (6.6%)	3 (14.3%)	7 (5.3%)	
Child-Pugh Grade				
Grade A	92(60.5%)	16(76.2%)	76(58.0%)	
Grade B	53 (34.9%	5.0 (23.8%)	48(36.6%)	
Grade C	7(4.6%)	0	7(5.3%)	
MELD score median (range)	11 (6-34)	9.5 (6-30)	11 (6-34)	
BCLC stage				
Stage 0	20(13.2%)	4(19.0%)	16 (12.2%)	
Stage A	31(20.4%)	9(42.9%)	22 (16.8%)	<.01
Stage B	46(30.3%)	8(38.1%)	38(29.0%)	
Stage C	20(13.2%)	0	20(15.3%)	
Stage D	35(23.0%)	0	35(26.7%)	

Table 2. Demographic and Clinical Characteristics of participants who underwent Intervention with Curative Intent.

	TOTAL CURATIVE (n=21)	**ABLATION (n=3)**	**RESECTION (n=12)**	**TRANSPLANT* (n=6)**
Male n (%)	15 (71.4%)	3 (100 %)	8 (66.7%)	4 (66. %)
Age (years) median (range)	53.1 (18.7-70.8)	52.7 (52.1-60.9)	52.2 (18.7-70.8)	58.9 (53.1-69.7)
Cirrhosis	11 (52.4%)	2 (66.7 %)	6 (50.0%)	3 (50.0%)
Child- Pugh Grade Grade A Grade B Grade C	 16(76.2%) 5.0 (23.8%) 0	 2 (66.7 %) 1 (35.9 %) 0	 10 (66.7%) 2 (8.3%) 0	 4 (83. %) 2 (15.4%) 0
MELD score median (range)	9.5 (6-30	13 (6-20)	9 (6-21)	10 (6-30)
BCLC Stage 0 A B C D	 4(19.0%) 9(42.9%) 8(38.1%) 0 0	 1 (33.3 %) 2 (66.7 %) 0 0 0	 2 (16.7%) 6 (50.0%) 4(33.3%) 0 0	 0 2 (33.3%) 4 (66.7%) 0 0

Table 3. Details of the transplant patients.

Patient	Aetiology	CPS	Bridging TACE	UCSF Criteria	Days on waiting list	Alive	Survival* (Months)
1	Hepatitis B	B	No	Yes	190 Died on waiting list	No	-
2	Ethanol	B	Yes	Yes	46	Yes	60.6
3	Hepatitis C	A	Yes	Yes	183	Yes	52.5
4	MAFLD	B	Yes	Yes	117	Yes	51.3
5	Hepatitis B	A	Yes	Yes	42	Yes	57.8
6	Ethanol	A	Yes	Yes	64	Yes	56.0
7	AIH/PBC**	A	Yes	Yes	270	Yes	29.2

* From transplant until 31st August 2021

** Autoimmune hepatitis/Primary biliary cirrhosis overlap

Table 4. Survival and follow up in different treatment cohorts

Patient	Intervention	Outcome	Survival* Months	Median Survival Months (range)		
1	Resection	Deceased	3.0	2.7 (0.1-24.1)	23.0 (0.1-71.6)	45.5 (0.1-72.5)
2	Resection	Deceased	0.1			
3	Resection	Deceased	24.1			
4	Resection	Deceased	2.4			
5	Resection	Lost to follow up	9.0	53.8 (9.0-71.6)		
6	Resection	Lost to follow up	58.8			
7	Resection	Alive	20.9			
8	Resection	Alive	71.6			
9	Resection	Alive	21.9			
10	Resection	Alive	53.8			
11	Resection	Alive	28.4			
12	Resection	Alive	54.8			
13	Transplant	Alive	57.8		54.3 (29.2-60.6)	
14	Transplant	Alive	60.6			
15	Transplant	Alive	52.5			
16	Transplant	Alive	51.3			
17	Transplant	Alive	29.2			
18	Transplant	Alive	56.0			
19	Ablation	Dead	32.2		45.5 (32.2-72.5	
20	Ablation	Alive	72.5			
21	Ablation	Alive	45.5			

* From time of intervention until death or date of last follow up

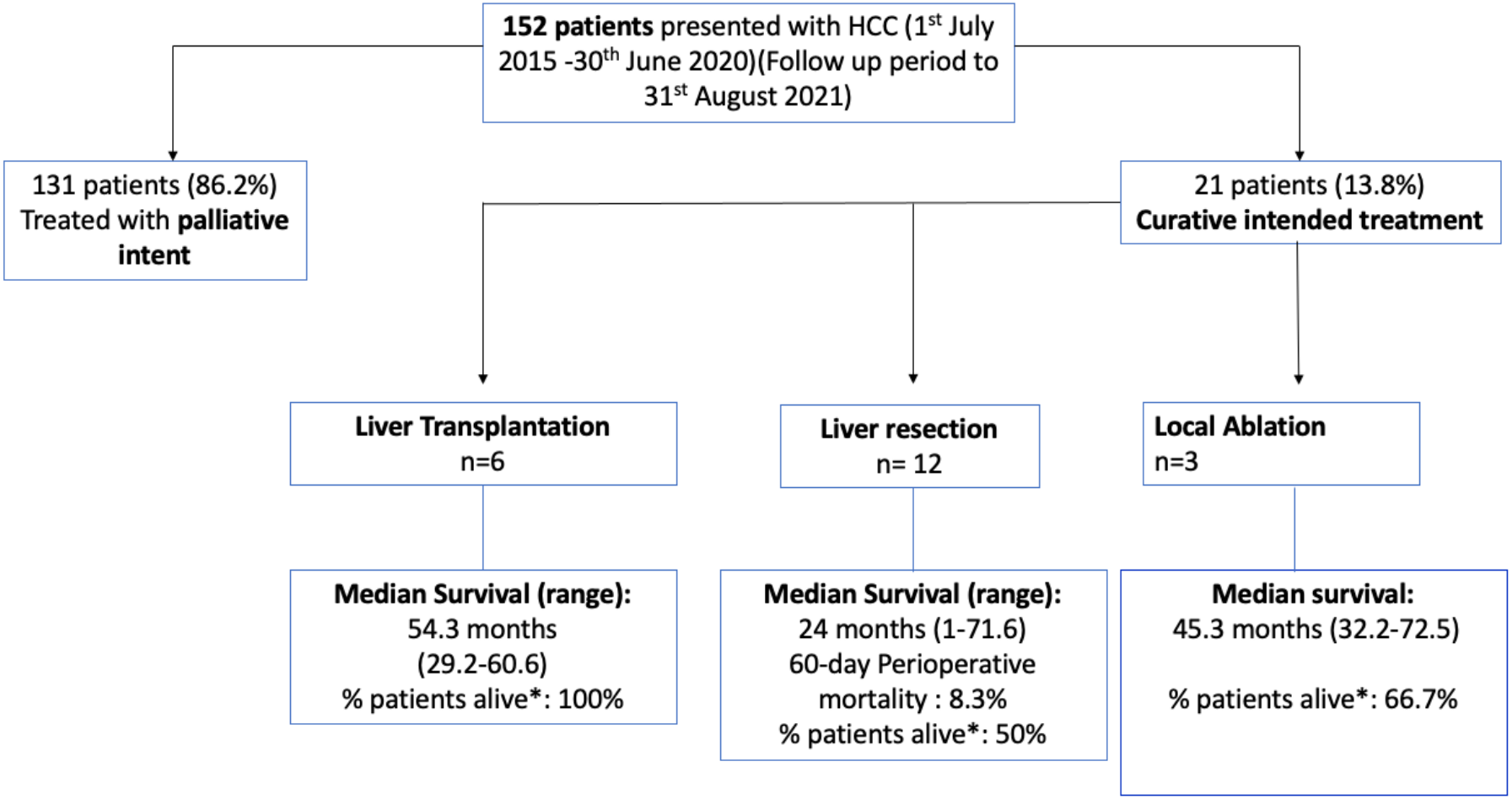

Figure 1. Flow diagram of treatment pathways of HCC patients presenting during the study period

*Percentage of patients alive and not lost to follow up (2 patients in the resection group were lost to follow up)

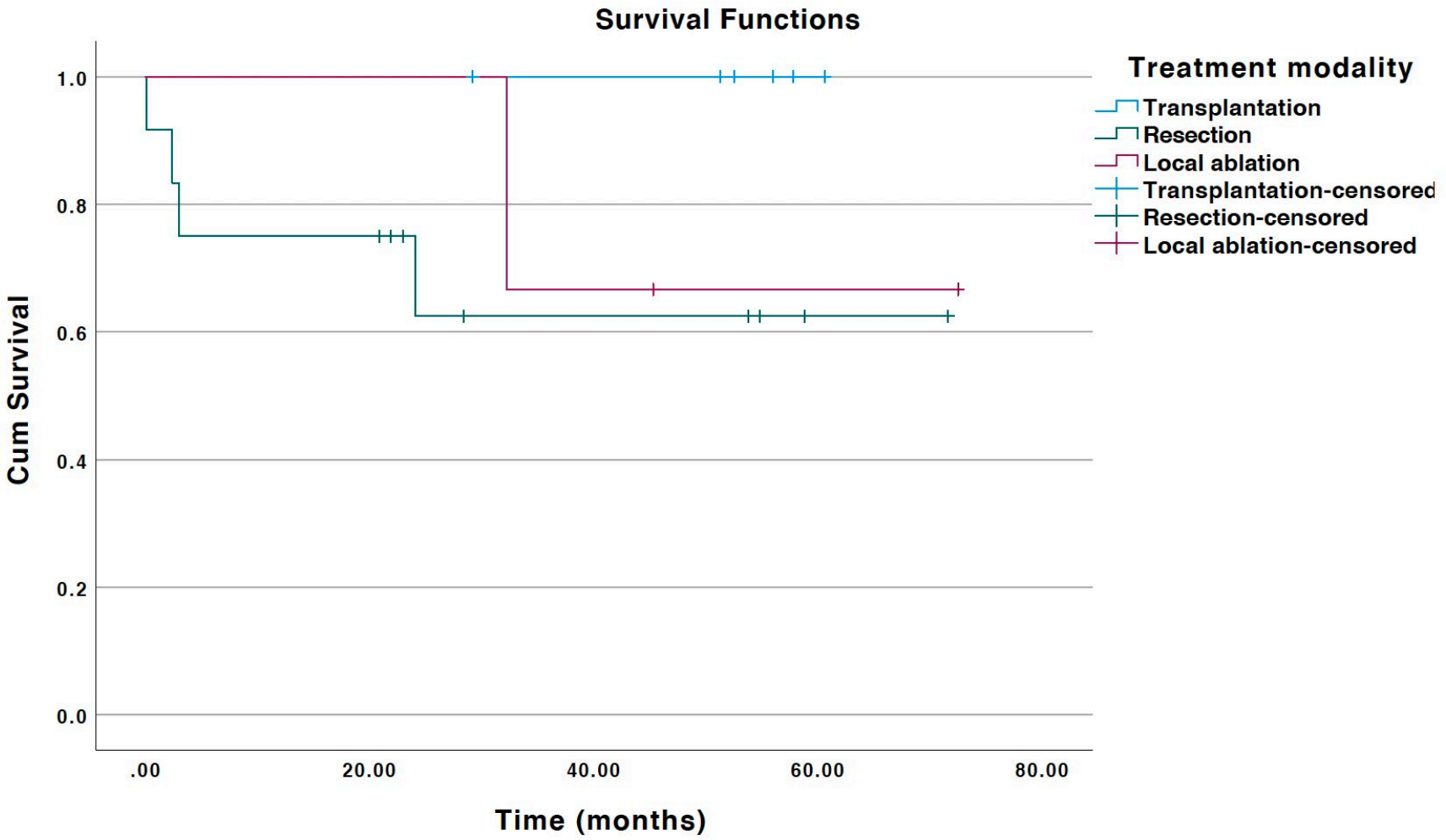

Figure 2. Kaplan-Meyer survival curve for the different curative intended treatment modalities (Censored – time form procedure to last follow up)

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

2. Dasgupta P, Henshaw C, Youlden DR, Clark PJ, Aitken JF, Baade PD. Global Trends in Incidence Rates of Primary Adult Liver Cancers: A Systematic Review and Meta-Analysis. Front Oncol. 2020;10:171.

3. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-48.

4. Petrick JL, McGlynn KA. The changing epidemiology of primary liver cancer. Curr Epidemiol Rep. 2019;6(2):104-11.

5. Jonas E. Hepatocellular carcinoma in sub-Saharan Africa - the way forward. S Afr Med J. 2018;108(8b):12391.

6. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.

7. Zakharia K, Luther CA, Alsabbak H, Roberts LR. Hepatocellular carcinoma: Epidemiology, pathogenesis and surveillance - implications for sub-Saharan Africa. S Afr Med J. 2018;108(8b):35-40.

8. Kew MC. Epidemiology of hepatocellular carcinoma in sub-Saharan Africa. Ann Hepatol. 2013;12(2):173-82.

9. Mak D, Sengayi M, Chen WC, Babb de Villiers C, Singh E, Kramvis A. Liver cancer mortality trends in South Africa: 1999–2015. BMC Cancer. 2018;18(1):798.

10. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379(9822):1245-55.

11. Chang M-H, You S-L, Chen C-J, Liu C-J, Lai M-W, Wu T-C, et al. Long-term Effects of Hepatitis B Immunization of Infants in Preventing Liver Cancer. Gastroenterology. 2016;151(3):472-80.e1.

12. Yang J, Mohammed E, Roberts L, Diseases A, Adeyeye A. Characteristics, outcomes and management of patients with hepatocellular cancer in Africa: a multicountry observational study from the Africa Liver cancer consortium. The Lancet Infectious Diseases. 2017;2:103-11.

13. Gyedu A, Shrauner WR, Kingham TP. No patients to resect or transplant: an analysis of patients with hepatocellular carcinoma admitted to a major African referral hospital. World J Surg. 2015;39(1):231-6.

14. Dempster M, Bouter C, Maher H, Gaylard P, Etheredge H, Fabian J, et al. Adult liver transplant for hepatocellular carcinoma at Wits Donald Gordon Medical Centre in Johannesburg, South Africa. S Afr J Surg. 2019;57(3):6-10.

15. Pommergaard HC, Rostved AA, Adam R, Rasmussen A, Salizzoni M, Bravo MAG, et al. Mortality after Transplantation for Hepatocellular Carcinoma: A Study from the European Liver Transplant Registry. Liver Cancer. 2020;9(4):455-67.

16. Santopaolo F, Lenci I, Milana M, Manzia TM, Baiocchi L. Liver transplantation for hepatocellular carcinoma: Where do we stand? World journal of gastroenterology. 2019;25(21):2591-602.

17. Yoon YI, Lee SG. Living Donor Liver Transplantation for Hepatocellular Carcinoma: An Asian Perspective. Dig Dis Sci. 2019;64(4):993-1000.

18. Croswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: lessons from history and study design issues. Semin Oncol. 2010;37(3):202-15.

19. Kanwal F, Singal AG. Surveillance for Hepatocellular Carcinoma: Current Best Practice and Future Direction. Gastroenterology. 2019;157(1):54-64.

20. Jemal A, Bray F, Forman D, O'Brien M, Ferlay J, Center M, et al. Cancer burden in Africa and opportunities for prevention. Cancer. 2012;118(18):4372-84.

21. Wild CP, Montesano R. A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and prevention. Cancer Lett. 2009;286(1):22-8.

22. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43.

23. Shlomai A, de Jong YP, Rice CM. Virus associated malignancies: the role of viral hepatitis in hepatocellular carcinoma. Semin Cancer Biol. 2014;26:78-88.

24. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol. 2013;47 Suppl(0):S2-6.

25. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. Hepatology. 2011;54(2):463-71.

26. Ioannou GN, Splan MF, Weiss NS, McDonald GB, Beretta L, Lee SP. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol. 2007;5(8):938-45, 45.e1-4.

27. Dhanasekaran R, Bandoh S, Roberts LR. Molecular pathogenesis of hepatocellular carcinoma and impact of therapeutic advances. F1000Res. 2016;5.

28. Raza A, Sood GK. Hepatocellular carcinoma review: current treatment, and evidence-based medicine. World J Gastroenterol. 2014;20(15):4115-27.

29. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Seminars in liver disease. 1999;19(3):329-38.

30. Vitale A, Saracino E, Boccagni P, Brolese A, D'Amico F, Gringeri E, et al. Validation of the BCLC prognostic system in surgical hepatocellular cancer patients. Transplant Proc. 2009;41(4):1260-3.

31. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.

32. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734-9.

33. de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol. 2012;56 Suppl 1:S75-87.

34. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis. 2005;25(2):181-200.

35. Makuuchi M, Sano K. The surgical approach to HCC: our progress and results in Japan. Liver Transpl. 2004;10(2 Suppl 1):S46-52.

36. McMahon BJ, Bulkow L, Harpster A, Snowball M, Lanier A, Sacco F, et al. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology. 2000;32(4 Pt 1):842-6.

37. Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology. 2010;51(4):1284-90.

38. Rahbari N, Mehrabi A, Mollberg N, Müller S, Koch M, Büchler M, et al. Rahbari NN, Mehrabi A, Mollberg NM, Muller SA, Koch M, Buchler MW, Weitz JHepatocellular carcinoma: current management and perspectives for the future. Ann Surg 253(3): 453-469. Ann Surg. 2011;253:453-69.

39. Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. Hepatology. 2016;64(6):2077-88.

40. Lurje I, Czigany Z, Bednarsch J, Roderburg C, Isfort P, Neumann UP, et al. Treatment Strategies for Hepatocellular Carcinoma ‑ a Multidisciplinary Approach. Int J Mol Sci. 2019;20(6).

41. Bruix J, Llovet JM, Castells A, Montañá X, Brú C, Ayuso MC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology. 1998;27(6):1578-83.

42. Pelletier G, Ducreux M, Gay F, Luboinski M, Hagège H, Dao T, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol. 1998;29(1):129-34.

43. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003;37(2):429-42.

44. Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002;224(1):47-54.

45. Makary MS, Khandpur U, Cloyd JM, Mumtaz K, Dowell JD. Locoregional Therapy Approaches for Hepatocellular Carcinoma: Recent Advances and Management Strategies. Cancers (Basel). 2020;12(7):1914.

46. Roayaie S, Jibara G, Tabrizian P, Park JW, Yang J, Yan L, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology. 2015;62(2):440-51.

47. Weinmann A, Koch S, Niederle IM, Schulze-Bergkamen H, König J, Hoppe-Lotichius M, et al. Trends in epidemiology, treatment, and survival of hepatocellular carcinoma patients between 1998 and 2009: an analysis of 1066 cases of a German HCC Registry. J Clin Gastroenterol. 2014;48(3):279-89.

48. Chaple MJ, Freese TE, Rutkowski BA, Krom L, Kurtz AS, Peck JA, et al. Using ECHO Clinics to Promote Capacity Building in Clinical Supervision. Am J Prev Med. 2018;54(6 Suppl 3):S275-s80.

49. Ferenci P, Fried M, Labrecque D, Bruix J, Sherman M, Omata M, et al. World Gastroenterology Organisation Guideline. Hepatocellular carcinoma (HCC): a global perspective. Journal of gastrointestinal and liver diseases : JGLD. 2010;19(3):311-7.

50. Kew MC. Clinical, pathologic, and etiologic heterogeneity in hepatocellular carcinoma: evidence from southern Africa. Hepatology. 1981;1(4):366-9.

APPENDIX 1. HREC APPROVAL

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

23 August 2021

HREC REF: 534/2021

Dr M Bernon
Department of Surgery
OMB
Email: Mm.bernon@uct.ac.za
Student: garethharveychilton@gmail.com

Dear Dr Bernon

PROJECT TITLE RETROSPECTIVE AUDIT OF HEPATOCELLULAR CANCER IN SOUTH AFRICA. FIVE-YEAR EXPERIENCE FROM A TERTIARY HOSPITAL, GROOTE SCHUUR HOSPITAL IN CAPE TOWN-MMED CANDIDATE-DR GARETH CHILTON

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, dated 17 March 2020; 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 August 2022.

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 Gareth Chilton will also be involved in this study.

Please quote the HREC REF 534/2021 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.