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1. Cover Letter

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Retrospective study at a single tertiary hospital in South Africa (Groote Schuur) on the treatment outcome in patients who underwent TransArterial Chemo-Embolization (TACE) for hepatocellular carcinoma.

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ABBREVIATIONS

ABCR- (Alpha feto-protein, BCLC, Child Purgh, Radiological) scoring system

AFP-alpha fetoprotein.

CT- Computed Tomography.

EASL- European Association Society for the study of the Liver

HCC- Hepatocellular Carcinoma.

MR- Magnetic Resonance.

mRECIST- modified Response Evaluation Criteria In Solid Tumours.

NHLS- National Health Laboratory System.

PACS- Picture Archiving and Communication System.

TACE- Transarterial Chemoembolisation.

WHO-World Health Organisation.

Tables:

Figures

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Title: Retrospective study at a single tertiary hospital in South Africa (Groote Schuur) on the treatment outcome in patients who underwent TransArterial Chemo-Embolization (TACE) for hepatocellular carcinoma.

2. Abstract

Background: Hepatocellular carcinoma is amongst the common causes of cancer deaths and has few curative treatment options. Transarterial chemoembolisation (TACE) is an option widely reported and used for palliative care and as a bridge to liver transplantation. Limited South African studies have examined the outcome of this type of therapy, with one comparing survival benefit and hospital stays in TACE using Adriamycin with lipiodol, with no benefit demonstrated. The current study aims to compare the imaging and alpha fetoprotein (AFP) responses with previous international studies on treatment response.

Objectives:.

To elucidate imaging and AFP outcomes after TACE in patients with hepatocellular carcinoma by measuring these in comparison with previous studies.

Methods:

24 patients with hepatocellular carcinoma treated with TACE in the radiology department at Groote Schuur Hospital over a 4-year period were retrospectively reviewed by using an structured protocol. Baseline and post-TACE radiological features were assessed including tumour size and necrosis in conjunction with AFP levels were evaluated to determine tumour response.

Results: During the study period 24 patients (17 males [70.8%] and 7 females[29.2%], with a mean age of 52.9 years) underwent TACE for HCC. 15 patients (62.5%) had documented cirrhosis, 14 patients (54 %) had concomitant hepatitis, with hepatitis B being the commonest in 11 patients (45.8%). The majority of patients were Child Purgh A 21 patients (87.5%) while 3 (12.5%) were Child Pugh B, 20 patients (83.3%) were TACE naïve, while 4 patient's (16.7%) had prior TACE treatment.

4 patient's (16.7%) of the study population had histologically confirmed hepatocellular carcinoma, 5 patients (20%) had HCC metastasis at baseline, 11 patients (45.8%) had AFP levels below 200ug/L and 13 patient's (54.2%) had levels above 200ug/L at baseline.

13 patients had large > 100 mm tumours at baseline, with median tumour size of 115 mm (range 55,50-173 mm). 20 patients (83.3%) had imaging by 6 months (mean of 84 days, range 34- 126 days) post-TACE with a median tumour size of 91.00 mm [range 36.50-168.50 mm]. By both mRECIST criteria and EASL criteria, 10% of the study population had complete responses, 10% demonstrated partial responses by mRECIST criteria alone and none by EASL criteria. 20% had progressive disease by both mRECIST and EASL criteria. Stable disease was evident in 60% by mRECIST and 70% by EASL criteria.15 patients (62.5%) of the study population had AFP results post treatment, with a median of 624.00 micrograms/L (*range* 5.00 – 11548.00 micrograms/L). No patients demonstrated more than 90% reduction or normalisation of alpha-fetoprotein levels. 7 patients (46,67%) had greater than 50% but less than 90% reductions while 8 patients (53.3 %) had increased levels. The study demonstrated a weak correlation between alpha fetoprotein reduction and radiological response post-TACE (r = 0.085).

Conclusion: Our study revealed 60% stable disease following TACE similar to 77% in the previous study by Lewandowski RJ et al ,with our 10% partial response compared to the 35% obtained by Llovet JM et al. The AFP had a 46% response compared to the one shown by Sherman et al which had 65%. TACE in patients with hepatocellular carcinoma has a modest radiological and biochemical response, with the majority of patients having stable disease .

1. Introduction

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer death worldwide, the prevalence has doubled over the past 20 years with incidences increasing from 2.6 to 5.2 per 100 000(1). World-wide in 2020, there were an estimated 905,677 new cases(2). HCC is a significant cause of cancer mortality in South Africa with approximately 46000 new cases diagnosed annually(3). HCC has multivariate causes including Hepatitis B and C. There are an estimate 2 billion cases of past and current hepatitis. Africa has a high prevalence of hepatitis B infection that varies geographically, with an estimated 65 million people infected in Africa and 2.5 million in South Africa (3). Other predisposing factors for HCC include heavy alcohol consumption, aflatoxin ingestion, hereditary hemochromatosis, family history of HCC and other end stage liver diseases from various causes including those of biliary aetiology. Approximately 80% of HCC's develop in patients with cirrhotic livers. In these patients the annual incidence of HCC is 2-8%, with the highest incidence observed in patients with cirrhosis due to hepatitis (4). Cirrhosis is a substrate precursor to HCC formation and develops from the same insults which cause hepatocarcinogenesis (5). HCC develops at a slower rate than does cirrhosis, hence most hepatocellular carcinomas will be diagnosed later.

The molecular and cellular mechanisms underlying the transformation of non-malignant liver cells into HCC are complex and not fully understood. Chronic inflammation with repeated cell injury, death and regeneration of liver cells provides an environment for aberrant cell signalling, epigenetic changes, mutational events and accumulation of genetic damage. The cascade cumulates in de-differentiation and dysplasia of clonal cells with formation of cirrhotic nodules. Early hepatocellular carcinoma can arise from dysplastic nodules and exhibits stromal invasion. Progressed hepatocellular carcinoma has a tumour capsule with internal fibrous septations and malignant features with a propensity for vascular invasion and metastases. Progressed hepatocellular carcinoma usually arises from early hepatocellular carcinoma nodules, but can develop de novo from a high-grade dysplastic nodule.

Hepatocellular carcinoma can be multifocal with synchronous growth of different tumour nodules (multicentric) or from intrahepatic metastases from the primary hepatic malignancy (5).

The prognosis of patient with intrahepatic metastasis is poorer compared to patients with multicentric hepatocellular carcinoma. Hepatocellular carcinoma with intact fibrous capsules has a lower recurrence rate in comparison to those without an intact tumour capsule after ablative treatment or chemoembolization, suggesting that the tumour capsule impedes dissemination(6). Progressed hepatocellular carcinomas have elevated arterial flow and this phenomenon is utilised in embolisation with TACE (7).

Current guidelines recommend multiphasic CT or MR imaging with extracellular intravenous contrast agents for diagnosis and staging of hepatocellular carcinoma. In patients with chronic liver disease, HCC is routinely non-invasively diagnosed on imaging without resorting to tissue biopsy for confirmation as needed for most other tumours. The hallmark imaging features of hepatocellular carcinoma are arterial hyper-enhancement followed by non-peripheral washout on portal venous phase, capsule enhancement and threshold growth, as evaluated by the Liver Reporting & Data System (LI-RADS). In a high-risk populations, imaging features permit diagnosis of hepatocellular carcinoma with a positive predictive value approximating 100%. The per-lesion sensitivity for nodular hepatocellular carcinoma of all sizes on CT is 68-91% and for MR imaging is 77-100%. The per lesion sensitivities stratified by size for both CT and MR imaging approximates 100% (8).

In the majority of patients with hepatocellular carcinoma the prognosis is poor because of advanced liver disease with severe hepatic dysfunction. Many cases are also diagnosed at an advanced stage with poor hepatic reserve, portal vein thrombosis and end-stage cirrhosis.
The Barcelona-Clinic Liver Cancer staging (BCLC) system uses variable independent prognostic factors to stage patients with HCC. The variables relate to the performance status of the patient as determined by the Eastern Co-operative Oncology Group (ECOG), the Child Pugh score which determines the hepatic function as assessed by laboratory markers, and radiologic tumour extent. The BCLC staging is grouped into 4 stages which are linked to different treatment regimens. Patient with very early stage (stage 0) and early stage HCC (stage A) with good underlying synthetic liver function are candidates for surgical resection and percutaneous

ablative techniques. These treatment measures are utilised for localized tumour. Curative options are scarce and transplantation remains the standard of care for patients with limited disease as defined by the Milan criteria with 5-year survival rates of 65-70% (9). Patient's not meeting the Milan criteria can potentially be down-staged with locoregional treatment including TACE.

Few patients are eligible for curative surgery, with hepatic tumour burden being an important determinant. If there are comorbidities, radiofrequency ablation which utilises high frequency alternating currents to produce coagulative necrosis within the tumour is recommended. Microwave ablation is an alternative that involves application of microwaves to induce coagulative necrosis (10).

Transcatheter arterial embolisation is typically offered as palliative treatment and for cytoreductive purposes to patients with Stage B (intermediate stage) disease. Palliative management is reserved for BLCL stage C and D (advanced and end stage respectively)(10). Transcatheter treatments are examples of imaging guided loco-regional therapies that target tumour confined to the liver in patients with primary and metastatic liver malignancy. Transarterial liver therapies include bland particle embolisation, particles with added chemotherapy and with drug-eluting beads (DEB TACE) or radiation emitting yttrium 90 microspheres. Approximately 80% of the blood supply to the HCC is from the hepatic artery while 75% of blood supply to normal liver parenchyma arises from the portal venous system. These arterial embolisation therapies selectively deliver anticancer treatment to the arterial system supplying the tumour. The goal of treatment is terminal arterial blockade which results in avascularity and tumour necrosis thereby decreasing the tumour burden and helping reduce morbidity (11).

Treatment of hepatic malignancies by arterial embolisation with the aim of providing symptomatic relief for local tumours was introduced in the 1970's. Limited South African publications have examined the outcome of this type of therapy. Madden et al (12) compared survival benefit and hospital stay of Adriamycin with lipiodol, with no benefit demonstrated.

Chemoembolisation emerged as a standard of care for irresectable hepatocellular carcinoma after 2 randomised controlled trials (13), (14). Single agent doxorubicin is commonly used worldwide in treating hepatocellular carcinoma with or without lipiodol, particles, beads or contrast. Drug-eluting beads are microspheres that can be pre-loaded with doxorubicin. They have predictable pharmacokinetics and can achieve higher local doses of the chemotherapeutic drug, inducing cytotoxic effects and ischemic necrosis with less systemic adverse effects.

Trans-catheter arterial drug eluting chemoembolization is most effective in nodules under 40 mm in diameter and with thick tumour capsules. Encapsulated hepatocellular carcinomas are mostly fed by hepatic arterial blood and therefore responsive to hepatic arterial embolisation. The development of extra-hepatic arterial blood supply can interfere with the therapeutic efficacy of TACE and result in treatment failure. The table below delineates some of the factors which influence the development of extra-hepatic arterial supply to hepatocellular carcinoma.

Table 1: Factors influencing development of extrahepatic blood supply supplying HCC.

Tumour size greater than 5 cm
Tumour located at the bare area of the liver
Prior TACE
Prior surgery
Exophytic tumour
Extra-hepatic tumour infiltration

Adapted from ***Amr Soliman Moustafa et a l (15) .***

WHO and modified Response Evaluation Criteria In Solid Tumours (mRECIST) (16) is used to evaluate one-dimensional and bi-dimensional tumour measurements to evaluate response to TACE.

Table 2: Disease response according to mRECIST

Complete resolution	Lesion no longer visible
Partial resolution	Decrease of 30% or more in lesion size
Stabilisation	Decrease of less than 30 % or increase of less than 20%
Progression	Increase of 20% or more in lesion size or development of new lesions

The European Association Society for the study of the Liver EASL system incorporates enhancement characteristic and necrosis in the treated target lesion as shown in table 3 below.

Table 3: European Association Society for the study of Liver

Complete response	Absence of any enhancing tissue
Partial response	Greater than 50% reduction in enhancing tissue
Stable disease	Less than 50 % reduction in enhancing tissue
Progressive disease	Any increase in amount of enhancing tissue

The 'partial response' as determined by imaging technique may not always accurately reflect the degree of TACE-induced tumour necrosis as residual necrotic or fibrotic tumour can also be interpreted as tumour and a partial response (17). Thus there is a need to couple laboratory serum tumour markers with imaging response criteria to fully measure the degree of response. The serum biomarkers which include alpha-fetoprotein may be helpful. Alpha fetoprotein (AFP) is a specific marker for hepatocellular carcinoma in the absence of testicular tumour. Other bio-markers in monitoring HCC include des-*γ*-carboxy prothrombin (DCP) and alpha-L-fucosidase (AFU) (18). Sherman (19) showed mean 65% AFP reductions in patients who underwent chemoembolisation and radio-embolisation and therefore supported the use of AFP levels after

loco-regional therapy as an ancillary method to measure hepatocellular carcinoma response to treatment. The best use is in patients with high pre-treatment AFP levels or those in whom it is difficult to use imaging techniques to fully assess tumour response post TACE.

2. Research Methods and Study Design

2.1.1. Study design

Retrospective review of patient laboratory results and CT images.

2.1.2. Setting

All patients who presented for TACE to the Division of Radiology at Groote Schuur Hospital, South Africa with hepatocellular carcinoma during a 4-year period dating from March 2016 to March 2020.

2.1.3. Protocol

Inclusion criteria

The study included only patients with a diagnosis of hepatocellular carcinoma made either histologically or radiologically. The inclusion criteria included patients with laboratory results of alpha fetoprotein done pre and post-TACE during the period. The study was conducted on patients with both AFP results and imaging before treatment and at 6 months post treatment.

Exclusion criteria

The study excluded patients who went underwent TACE for diagnosis other than hepatocellular carcinoma. The study excluded patients who did not have a pre and post TACE CT scans done during the study period.

The study excluded patients with atypical or equivocal diagnostic features of hepatocellular carcinoma on CT scan and no laboratory results.

Materials and methods

The study utilized a 160-slice multi-detector Toshiba computed tomography scanner in spiral mode for acquisition of CT images at 145 KV**,** 10mA-600mA **.** The TACE procedure was conducted and monitored at a single tertiary referral hospital by qualified specialist radiologists with more than 5 years' experience. The procedure was conducted under moderate sedation with intravenous fentanyl and midazolam which was tailored to individual patients in proportion to body habitus and drug tolerance. The transarterial chemo-embolisation protocol involved the use of a 5 French sheath placed in the common femoral artery with selective catherisation of the celiac axis and if needed, superior mesenteric arteries. Baseline angiography of the hepatic arterial system was performed prior to administration of doxorubicin eluting beads. Selective catheterization of the hepatic artery supplying the tumour was performed to maximize the deposition of drug eluting beads into the tumour whilst minimizing the exposure of normal hepatic parenchyma to emboli chemotherapeutic agents. Following the initial arterial assessment, the catheter was advanced into the lobar or segmental hepatic artery supplying the tumour. In cases where the 5 French catheter could not be advanced 2.7 micro-catheter(inner diameter of 0,027 inch) was used for super-selective catheterization. In general, the TACE infusion point was chosen to enable selective tumour embolisation. The microsphere were pre-loaded with doxorubicin shortly before the procedure. The doxorubicin was reconstituted with sterile water and added to the drug eluting beads. Drug loading of the microsphere was monitored by noting the disappearance of the red colour of the solution as the microsphere absorbed the cytotoxic drug. An equal volume of contrast medium was added to the solution before infusion of the solution via the catheter into the hepatic arterial system. The size of the dry microsphere is 100 microns and hydrated size is 200-400microns. The concentration was adjusted according to the tumour volume with doxorubicin doses of either 50 or 100mg being used by different operators. Subsequently the beads were injected under fluoroscopic guidance into the arterial supply of the tumour. Stasis in the tumour feeding artery was used as procedure endpoint for TACE. No more than one package of beads was used.

Afterwards patients were monitored in the post procedure recovery room and transferred to the hospital ward as per established hospital guidelines.

2.1.4. Data collection

The tumour size was measured according to mRECIST criteria using the largest diameters of the tumour in two dimensions and the enhancing tumour component was measured using the EASL criteria. Laboratory results were collected from the National Health Laboratories System (NHLS).

2.1.5. Data analysis

Preliminary data were analysed using univariate and graphical methods to facilitate inspection and interpretation. Results are presented as means and Standard Deviations for normally distributed continuous variables and median Inter Quartile Ratios for non-normally distributed continuous variables. The Shapiro-Wilk test for normal data was used to test for normality. Significance was set at 0.05 and a power calculation of 0.83. A paired sample t-test was used for normally distributed data and the Wilcoxon signed rank test was used for non-normal data during hypothesis testing. A chi-square test was used to analyse the association between categorical variables. All analysis was done with Stata® 13.1 software.

2.1.6. Ethical considerations

Ethical approval was granted by the Human Research Ethics Committee of the of the University of Cape Town.

3. Results

During the study period 25 patients underwent TACE with 24 patients having radiologic or histological proof of HCC. 1 patient had radiological features of HCC but with fibrolamellar carcinoma confirmed on histology and was therefore excluded from the results. Cirrhosis was determined radiologically by a nodular liver outline with atrophy-hypertrophy complex changes. Patients with HCC satellite lesions within the liver, or peri-portal, cardio-phrenic or retroperitoneal lymphadenopathy greater than 20 mm were classified as metastases. Table 4 shows baseline characteristics of the 24 patients included in the study.

Table 4 :Baseline characteristics

Parameter	Number of patients n(%)
Demographics	
Gender Male	17 (70.8%)
Female	7 (29.2%)
$Age_{mean\ (SD)}$	52.92 (15.77%)
Presumed Aetiology	
Hepatitis B	11 (45.8%)
Hepatitis B and C	1 (4.2%)
Hepatitis C	1 (4.2%)
Other aetiologies	11 (45.8%)
Cirrhosis Present	15 (62.5)
Absent	9 (37.5)
Histology	
Hepatocellular Carcinoma	4 (16.7)
Negative	5 (20.8)
No biopsy	15 (62.5)
Imaging findings	
Ascites None	19 (79.17)
Mild	1 (4.17)
Moderate	2 (8.33)
Severe	2 (8.33)
Metastases-Present	5 (20.83)
Absent	19 (79.17)
Tumour size (mm) [median (IQR)]	115.00 (55.50; 173.00)

Tumour size (≤50mm)	4 (16.67)
Tumour size (>50mm &≤100mm)	7 (29.17)
Tumour size (>100mm)	13 (54.17)
Laboratory data	
AFP [ug/L] [median (IQR)]	305.00 (3.00; 4603.00)
AFP (≤200ug/L)	11 (55.00)
AFP (>200ug/L)	9 (45.00)
Albumin [g/L][median (IQR)]	38.00 (36.00; 41.00)
Bilirubin [median (IQR)]	15.00 (8.00; 28.00)
INR [median (IQR)]	1.17 (1.10; 1.28)
Hepatitis B Viral load[median (IQR)]	4083.00 (20.00; 18665.00)
Staging	
Child-Pugh Class A	21 (87.5)
B	3 (12.5)
C	0(0.0)
Prior treatment	
Previous TACE treatment None	20 (83.30)
Once	3 (12.50)
Twice	1 (4.2)

Treatment and follow-up

All patients who underwent TACE had follow-up imaging as well as alpha feto-protein levels post TACE. The median time for follow up CT scan post-TACE was 84 days (Range 34.50 to 126.50 days). Post TACE imaging data for tumour size was available for 20 patients (83.3 %) with median tumour size 91.00 mm [range 36.50 – 168.50 mm]).

Post TACE AFP levels had a median of 624.00 micrograms/L (*range* 5.00 – 11548.00 micrograms/L). There was a weak positive correlation between tumour size reduction and AFP

level drop post TACE (r = 0.085). When the size of the tumour decreased, AFP levels also decreased. If the size of the tumour increased, AFP levels also mostly increased. However, this relationship was also not statistically significant (p = 0.774) at the 95% level of confidence.

Table 5: Post TACE outcomes

Variable	Median (IQR)
Tumour size post TACE(mm)	91.00 (36.50 – 168.50)
AFP(*ug/L)*	624.00 (5.00 – 11548.00)

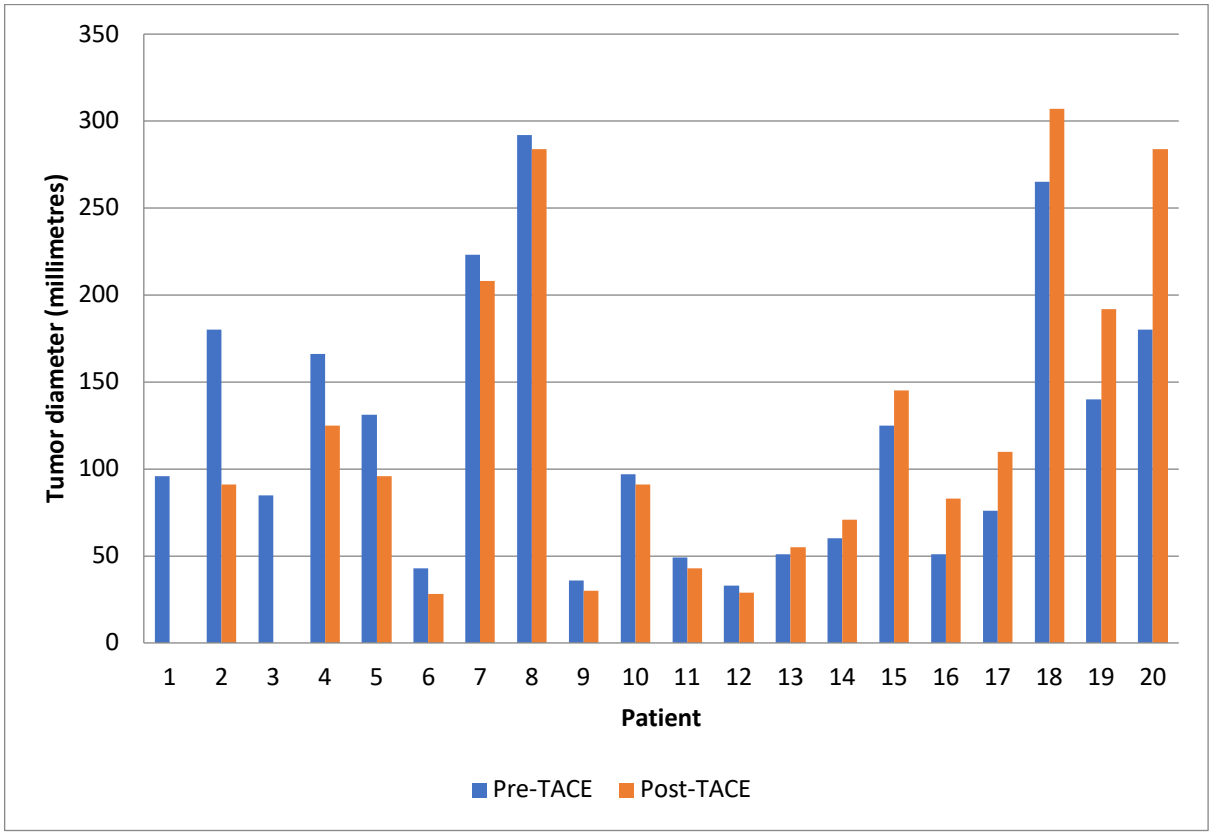
Table below show the WHO mRECIST and EASL methods used to evaluate tumour response. The tumour size was measured according to mRECIST criteria using the largest diameter of the tumour in two orthogonal dimensions.

Table 6: Summary of mRECIST and EASL responses

	mRECIST (n[%])	EASL (n[%])
Complete response	2 [10%]	2 [10%]
Partial response	2 [10%]	0 [0%]
Progressive disease	4 [20%]	4 [20%]
Stable disease	12 [60%]	14 [70%]

Figure 1 below shows the tumour sizes pre TACE and post TACE. On the left are shown the patients in which the size decreased after TACE and on the right are shown those patients in whom the size increased after TACE.

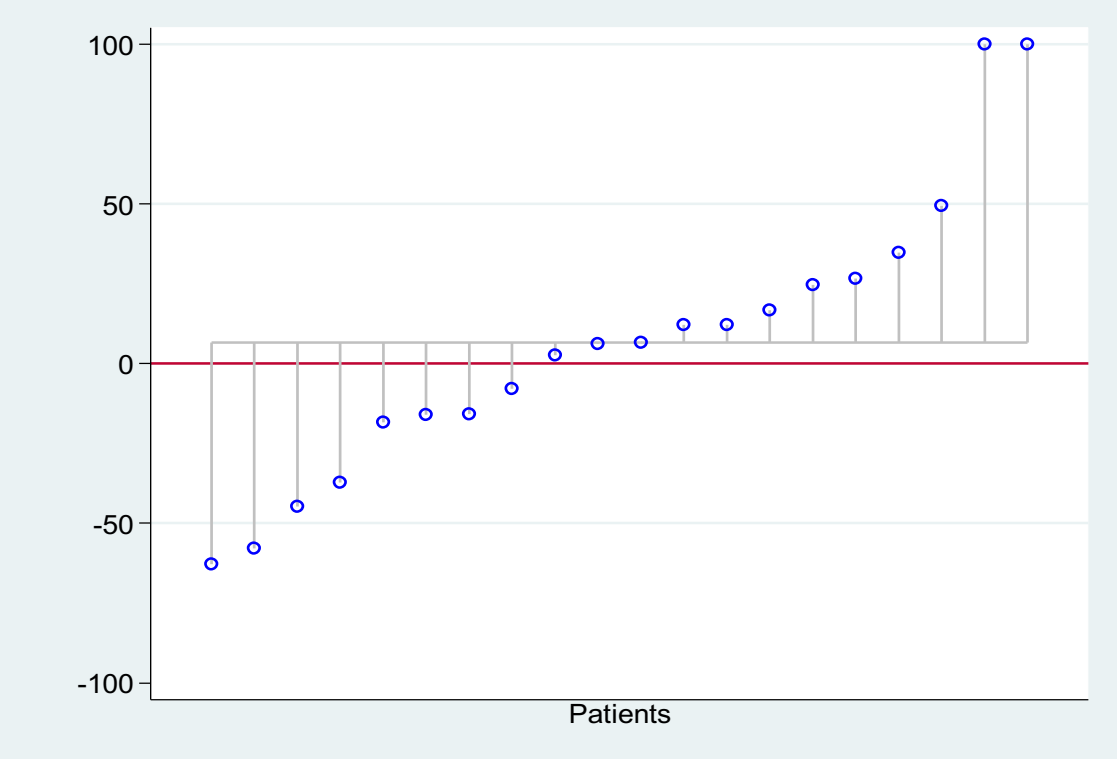
Figure 1: Tumour size pre and post TACE.



20 patients (83.3%) had imaging by 6 months (mean of 84 days, range 34- 126 days) post-TACE with a median tumour size of 91.00 mm [range 36.50-168.50 mm].

The waterfall chart below Figure 2 is a graphical representation of the percentage change in the tumour size post TACE. The values above zero (0%) indicate the tumour that responded positively with reduction in the size of the tumour compared to pre-TACE size, while those values below zero indicate tumours that increased in size. The waterfall chart demonstrates that 12 patients 60% showed a decrease in size whilst 40% (8 patients) had a negative response with increase in the size of the tumour compared to the pre-TACE value. **T**he patients who had an increase in tumour size post-TACE included patient's classified as stable and progressive disease under mRECIST.

Figure 2: Waterfall chart of percentage change in tumour diameter post TACE



The cross product diameter was obtained by measuring the largest tumour sizes in orthogonal planes and obtaining the sum of these diameters.

Data on AFP change post TACE was only available for 15 (62.5%) patients and is shown in Table 7.

Table 7: Summary of AFP change post TACE

AFP change	n(%)
Complete normalization	0(0)
>90% reduction	0 (0)
50 to 90%	7 (46.67)
Increase above pre-treatment	8 (53.33)

Regression analysis

Bivariate analysis was undertaken, with no baseline characteristics shown to be statistically significant to post-TACE tumour size.

No multivariate model was run due to the limited data.

Table 8: Bivariate findings

Variable	Odds Ratio (95% CI)	p-value
Age	0.97 (0.916; 1.032)	0.351
Gender $_{\text{Male}}$	0.583 (0.776, 4.386)	0.601
Cirrhosis $_{\text{Present}}$	1.05 (0.160; 6.924)	0.960
Baseline tumour size	1.00 (0.989, 1.012)	0.936
Baseline AFP	1.000 (0.999; 1.001)	0.289

Chi-square test

A chi-square test was performed to test the null hypothesis that there was no correlation between baseline and post-TACE tumour size. Baseline tumour size data were divided into 2 groups with a cut off size of 60 mm). This chi-square test was performed at the 95% level of significance and failed to reject the null hypothesis. It was concluded that for this sample there was insufficient evidence to suggest a significant effect of baseline tumour size on the post TACE outcome.

4. Discussion

TACE is an accepted loco-regional treatment for hepatocellular carcinoma and is an effective treatment for eligible patients, with overall outcome dependent on tumour burden and severity of liver dysfunction. TACE provides occlusive and chemotherapeutic effects directly to the tumour vascular bed and has reduced side effects compared to systemic treatment. Appropriate follow-up after treatment is important to assess tumour response and to plan for future repeat interventions as recurrence and incomplete response are common. TACE is performed in patients with intermediate stages of HCC as stratified by Child Pugh score. Our study population were all either in Child Pugh class A and B. Hepatitis infection is endemic in South Africa, with 54 % of the study cohort having concomitant infection and with high viral loads.

A mRECIST partial response of 10% was seen in this analysis, although 60% of the tumours demonstrated a decrease in size as shown in the waterfall plot **Fig 1.** In a larger similar study (20) the partial response obtained was 30%,while 77% of lesions demonstrated overall reduction in size post-TACE. In another study, the response rate by size reduction after a standard TACE procedure was 35% at 6 months follow up (14), with another demonstrating a partial response rate of 43 % and that incomplete radiological response after a single TACE was common (21).
The difference in partial response rates could be accounted for by the vigorous follow-up post TACE and multiple repeat TACE's in the study done by Lewandowski et al (20). Due to resource constraints, similar follow-up could not be achieved locally. Additionally, there was a wide variation between time of trans-arterial chemo-embolization and subsequent follow up imaging, with a median of 84 days. Most of the patients in the cohort had large baseline tumour sizes and no prior transarterial chemo-embolization. Prior TACE increases the probability of extra-hepatic collaterals as shown in Table 1 (15). The tumour will recruit extra-hepatic arteries as the blood supply from the hepatic artery will have been occluded. The bivariate analysis did not demonstrate any variable baseline characteristic that was significant in predicting treatment outcome in our cohort. The findings could suggest that tumour response is largely affected by local tumour factors which include adequacy of vascular occlusion and the effects of collateral vessels supplying the tumour.

AFP has an important role in cell proliferation and is produced by HCC. Alpha fetoprotein (AFP) is a specific marker for HCC (in the absence of testicular tumour) thereby making it suitable for follow up and monitoring. Alpha feto protein was previously used as an indicator for diagnosing HCC but has largely been superseded by LI-RADS imaging. The bio-marker alpha feto-protein was used as an ancillary marker to determine tumour response in the current study, with a 46% response compared to that of 65% as demonstrated by Sherman (19). Their study supports transarterial chemo-embolization having a significant effect on the post-treatment alpha fetoprotein levels. Mishra (21) concluded that alpha fetoprotein is a simple and clinically useful prognostic factor for use after TACE. The locoregional embolisation will result in tumour necrosis

with subsequent decrease in tumour burden and alpha fetoprotein levels (21). Favourable response to treatment would be expected to be accompanied by a decrease in levels of alpha fetoprotein levels. We also feel the bio-marker could be used as a complementary adjunct to imaging to determine treatment outcome and for follow-up of patients with HCC. Recent scoring systems have been developed to select cases and monitor treatment outcomes post-TACE, aiding in decisions concerning re-embolisation. These include the HAP, STATE, Munich TACE, ABCR and ART systems (22) and some incorporate measurement of alpha feto-protein. These systems are not widely accepted and used, resulting in variations in disease monitoring. In a recent study by Chen S et al (23), response rate to initial TACE was 35.6%, increased to 46.1% after a second TACE and to 58.3 % after a third TACE. Their study reinforces that belief that repeat TACE has improved response which may be vital for adequate tumour control.

4.1.1. Strengths and limitations:

Data collected from the CT scan of the tumour is reproducible and measurable with minimal inter-observer variability. The laboratory data for the study was also objective and minimised measurement bias. The retrospective nature of the study imposed limitations as there was no standardized timing of imaging and monitoring of alpha feto-protein. Detailed analysis was limited by small number of patients with both imaging and alpha feto-protein and restricted the generalisability of our findings. The patient cohort was largely referred from peripheral institutions and some had advanced disease for palliative treatment only. Further limitations arose due to variability in the dose of doxorubicin by different operators and different beads brands were used which included Hepaspheres and Tandem embospheres. Implications or recommendations

Periodic standardized follow-up with imaging augmented by alpha feto-protein levels is advised to identify tumour response and could facilitate responsive planning for repeat TACE. This may be especially beneficial in large burden tumours that may require multiple TACE treatments. Future prospective studies should also include side-effects and survival analysis.

5. Conclusion

Trans-arterial chemo-embolisation with drug eluting beads has emerged as an effective loco-regional treatment for patient with Child Pugh A and B patients. Our study demonstrated 60% stable disease following TACE similar to 77% in a previous study by Lewandowski RJ et al(20) with our 10% partial response compared to 35% obtained by Llovet JM et al. The AFP with a 46% response compared to that of 65% shown by Sherman et al(19).

TACE in patients with hepatocellular carcinoma has a modest radiological and biochemical response, with the majority of patients having stable disease.

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Western Cape Government
Health

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Dr Qonita Said-Hartley
RADIOLOGY

E-mail: qshartley@gmail.com / irvinesihlahla@yahoo.com

Dear Dr Said-Hartley,

RESEARCH PROJECT: Retrospective Study At A Single Tertiary Hospital In South Africa On Treatment Outcome In Patients Who Underwent Transarterial Chemo-Embolisation For Treatment Of Hepatocellular Carcinoma (MMed Dr Irvine Sihlahla)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **28 February 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form.**
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must always be maintained .
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 17 April 2020

C.C. Mr. L. Naidoo
Dr H. Aziz
Dr S. Moosa

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

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26 February 2020

HREC REF: 068/2020

Dr M Said-Hartley
Radiation Medicine
J-Block D-Floor
GSH

Dear Dr Said-Hartley

PROJECT TITLE: RETROSPECTIVE STUDY AT A SINGLE TERTIARY HOSPITAL IN SOUTH AFRICA ON TREATMENT OUTCOME IN PATIENTS WHO UNDERWENT TRANSARTERIAL CHEMO-EMBOLIZATION FOR TREATMENT OF HEPATOCELLULAR CARCINOMA (MMED DEGREE - DR IRVINE SIHLAHLA)

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.

Approval is granted for one year until the 28 February 2021

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 Irvine Sihlahla also be involved in this study.

Please quote the HREC REF 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, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.