TRIPHASIC LIVER CT FINDINGS OF HEPATOCELLULAR CARCINOMA IN COMPARISON TO HISTOPATHOLOGY IN MTRH, ELDORET.

BY

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This Thesis is submitted to the School of Medicine, Moi University in partial fulfillment of the award of the degree of Master of Medicine in Radiology and Imaging of Moi University.

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TRIPHASIC LIVER CT FINDINGS OF HEPATOCELLULAR CARCINOMA IN COMPARISON TO HISTOPATHOLOGY IN MTRH, ELDORET.

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DECLARATION

I declare that this is my original work and has not been presented in any other university or institution for an award of a degree or any academic credit. No part of this work may be reproduced or transmitted in any form without prior permission from the author or Moi University.

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DEDICATION

I would like to dedicate this work to the Almighty God for the gift of life. To my parents my guardians and my siblings for their unwavering support as well as to all the radiology registrars and my classmates for their daily words of encouragement.

To you all, I am truly grateful.

ACKNOWLEDGEMENT

I wish to thank the Almighty God for giving me the chance to undertake this study. I want to thank Moi University and specifically the School of medicine for this opportunity to do this study. I sincerely wish to thank my Supervisors for their guidance and support during writing of this Thesis. To all the lecturers in the Department of radiology and other Departments for their invaluable input during this process, my colleagues and everyone else for their invaluable guidance and support during the development of this research proposal.

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AASLD	American Association for the Study of Liver Disease
EASL	European Association for the Study of Liver
CC	Cranial Caudal
CEO	Chief Executive Officer
CT	Computed Tomography
HCC	Hepatocellular Carcinoma
IREC	Institutional Research and Ethics Committee
MTRH	Moi Teaching and Referral Hospital
USG	Ultrasonography
US	Ultrasound

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a primary malignancy of the liver common with underlying chronic liver disease including cirrhosis. Incidence of HCC is highest in Asia and Africa, due to the endemic high prevalence of hepatitis B and C viruses**.** HCC is increasingly being recognized with the improvement of dynamic imaging such as CT scan. Triphasic liver CT scan is used for diagnosis in a nodule>1cm with arterial enhancement followed by washout and the 2005 diagnostic algorithm has been validated and accuracy demonstrated. All suspected HCC patients are however subjected to biopsy at Moi Teaching and Referral Hospital hence this study will try to establish the value of CT scan in making a diagnosis of HCC.

Objective: To evaluate the use of Triphasic computed tomography findings of hepatocellular carcinoma in comparison to histopathology findings so as to determine if CT imaging findings alone can be used to diagnose HCC without performing a core biopsy.

Methods: This was a descriptive cross-sectional study done at Moi Teaching and Referral Hospital Radiology and Pathology Departments from August 2017 to July 2018. It was a census study where consecutive sampling was done and 61 patients suspected to have HCC were enrolled and subjected to a Triphasic Liver CT scan. All the CT scan images were reported by the principal investigator and reviewed by two consultant radiologists. They were then subjected to image guided core biopsy for the definitive diagnosis. Data was analyzed using STATA version 13MP. Descriptive statistics were summarized using tables and graphs. Comparison of CT scan findings and histopathology was done using Chi square test and Fisher Exact test.

Results: A total of 61 participants were included in the study. The youngest participant was 35 years and the oldest 72 years with a mean age of 52.7 years. On location, 59% of patients had masses in the right lobe, 34.4% in both lobes and 6.6% in the left lobe.

On contrast enhancement, 63.9% of the masses were detected on the non-enhanced phase while the enhanced phases increased the detection to 100%. Of all HCC's, 62.2% demonstrated homogenous enhancement with 32.8% being heterogeneous. Furthermore, 65.5% of HCC had CT features of cirrhosis at diagnosis and HCC was confirmed on histopathology in 88.5% of patients. Features of Cirrhosis was significantly associated with HCC p=0.004, Fisher Exact test, OR=17.1. Hyper-enhancement was significantly associated with HCC, p=0.015, Chi square test. Presence of venous washout was significantly associated with HCC, p<0.00, Chi square test. The association between presence of HCC fibrous capsule and histopathology findings was not statistically significant p=0.190, Fisher Exact test.

Conclusion: Histopathology confirmed 88.5% of all radiologically diagnosed HCC. Majority of the HCC's were in the right lobe and 65.57% of all HCC had CT features of Cirrhosis at diagnosis. Hyper-enhancing masses, venous wash out and presence of CT features of cirrhosis were significantly associated with a diagnosis of HCC.

Recommendation: We should have a high index of suspicion for all hyper-enhancing liver lesions >1cm with a rapid venous washout in the setting of cirrhosis in the absence of a Liver Biopsy.

CHAPTER ONE

1.0 Background Information

Accurate diagnosis of hepatocellular carcinoma is very important because treatment ranges from supportive care for advanced metastatic disease to partial hepatectomy for early primary carcinoma. Radiological imaging is very useful in narrowing the differential diagnosis.(Nasit, Patel, Parikh, Shah, & Davara, 2013). However tissue diagnosis often is required at times to confirm the diagnosis and usually acquired through Fine-needle aspiration cytology (FNAC) or fine-needle aspiration biopsy (FNAB).

The purpose of this study is therefore to evaluate the use of Triphasic computed tomography (CT) findings of suspected hepatocellular carcinoma and to compare these findings to those of histopathological analysis.

1.1 Problem Statement

Hepatic masses are rapidly on the rise and a significant number of them are malignant with the majority of these being hepatocellular carcinoma.

Statistics show that there are approximately 500000 to 1 million individuals who are diagnosed with hepatocellular carcinoma (HCC) worldwide.(D Maxwell Parkin, Pisani, & Ferlay, 1999). These incidence rates have also demonstrated varied geographic variations, ranging from<5 new cases per 100000 persons per year in developed western countries to>100 per 100000 persons per year in parts of south-east Asia and sub-Saharan Africa (Bialecki & Di Bisceglie, 2005; Pal & Pande, 2001; D Maxwell Parkin et al., 1999).

This is a huge burden on the health sector and prompt interventions to help mitigate this would be a welcome boost.

In Moi Teaching and referral hospital all cases of suspected hepatocellular carcinoma are subjected to image guided biopsy which is expensive, invasive and may have dire complications such as hemorrhage, damage to surrounding anatomical structures and tumor seeding upstaging the disease. Furthermore the numbers are growing and booking takes time which delays time taken to institute management. This study will try to address this problem by subjecting patients with suspected Hepatocellular carcinoma to Triphasic liver CT scan and comparing the CT findings with biopsy outcomes so as to try and make a diagnosis based on CT scan features and therefore reduce incidences of all suspected HCC being subjected to image guided biopsy.

1.2 Justification and Significance

Hepatocellular carcinoma is on the rise globally so prompt and accurate diagnosis is becoming increasingly important to be able to manage it adequately.

In addition the 5 year survival rate of patients with advanced HCC is low. Studies have given a mean survival of 6–20 months for these patients and likely reflect the mortality/incidence ratio, which is close to 1. These figures have remained the same despite substantial progress in the diagnostic and treatment of HCC.

Surgical resection offers the best chance for cure. But unfortunately only less than 20% of patients who are diagnosed meet the criteria for resection at time of diagnosis (Capuano, Daniele, Gaeta, Gallo, & Perrone, 1998; Yuen et al., 2000)

This therefore calls for prompt and accurate diagnosis to be taken to reverse this trend. Image guided tissue biopsy is the norm in making a diagnosis for suspected HCC. Tissue biopsy is an invasive procedure, costly and can be associated with a myriad of complications such as bleeding, damage to nearby anatomical structures during the procedure and further worsening the disease stage and therefore the overall prognosis by tumor seeding.

Until 2000, the diagnosis of HCC was based on biopsy. However in 2001, a panel of experts first reported noninvasive criteria for HCC diagnosis based on a combination of imaging and laboratory findings.(Bargellini et al., 2014). Since then, various international guidelines have been updated, confirming the leading role of dynamic cross-sectional imaging as a noninvasive means to diagnose HCC in the setting of liver cirrhosis, thus limiting the diagnostic role of biopsy (Bargellini et al., 2014)

However, all suspected cases of hepatocellular carcinoma in MTRH are always subjected to image guided tissue biopsy regardless of patient characteristics and triphasic liver CT scan characteristics. This has in turn led to delays and loss to follow –up since the booking is long sometimes stretching to a month or two months of waiting. The procedure is also expensive and a lot of patients will spend more time raising funds for the procedure or sometimes not doing it at all then present later with advanced disease.

Less invasively CT scan has improved over time for better identification and characterization of HCC. This needs to be exploited more to determine whether this offers a quicker and cheaper diagnostic solution without having to wait through the

tedious invasive and expensive tissue biopsy that can also take a long time to get results and therefore delaying planning of management.

Furthermore there is paucity of data in this regard and therefore important to create a baseline data for consumption for future use and further studies on the same.

The purpose of this study is therefore to assess the use of triphasic liver CT scan compared to histopathology in the evaluation of hepatocellular carcinoma in MTRH, Eldoret.

1.3 Research Question

What is the association between Triphasic Liver Computed Tomography findings and Histopathological outcome in patients suspected to have hepatocellular carcinoma in MTRH?

1.4 Research Objectives

1.4.1 Main Objective

To evaluate the use of Triphasic Liver Computed Tomography findings in diagnosis of HCC and compare these findings with histopathology.

1.4.2 Specific Objectives

1. To describe the most common Triphasic liver CT scan findings in patients presenting with hepatocellular carcinoma in MTRH.

2. To describe the association between triphasic liver computed tomography findings and histopathology analysis in patients with HCC.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

The burden of cancer is increasing worldwide. According to the European Association for the study of the Liver, each year there are approximately 10.9 million new cases of cancer and 6.7 million cancer-related deaths. Furthermore the most commonly diagnosed cancers are lung, breast, and colorectal while the most common causes of cancer death are lung, stomach, and liver. Liver cancer is the sixth most common cancer (749,000 new cases), the third cause of cancer-related death (692,000 cases), and accounts for 7% of all cancers. HCC represents more than 90% of primary liver cancers and is a major global health problem. (European Association for the Study of the, European Organisation for, & Treatment of, 2012)

2.2 Epidemiology

According to the International Agency for Research on Cancer the most widely diagnosed cancers worldwide are lung (1.61 million, 12.7% of the total), breast (1.38 million, 10.9%) and colorectal cancers (1.23 million, 9.7%). Furthermore, cancer death is increasing rapidly with the most common causes of cancer death are lung cancer (1.38 million, 18.2% of the total), stomach cancer (738,000 deaths, 9.7%) and liver cancer (696,000 deaths, 9.2%). (Ferlay et al., 2010)

Studies in France, demonstrate rising number with between 5000 and 6000 cases are diagnosed each year. The studies further associate Hepatocellular carcinoma to liver cirrhosis, which is considered a true precancerous state. However hepatocarcinogenesis is a long and heterogeneous process, and much more remains to be understood.

Epidemiological data states that the incidence of HCC increases progressively with advancing age regardless of population characteristics, reaching a peak at 70 years. This age is considered younger however in Chinese and in black African populations. However in Japan, the incidence of HCC is highest in the age group of men aged 70–79 years. HCC has a strong male predominance with a male to female ratio estimated to be approximately 2.4 (European Association for the Study of the et al., 2012)

In Asia and Africa, largely Sub-Saharan regions, hepatitis B virus is the most common cause for the chronically diseased liver while, in the West, Europe and Japan, hepatitis C virus is more prevalent. These differences in liver disease may lead to different results in HCC imaging.

Other etiologies, such as alcohol abuse, hemochromatosis, and primary biliary cirrhosis, also contribute to chronically diseased liver and HCC. There is in addition rising early evidence about the present problem of obesity leading to non-alcoholic steato-hepatitis and, subsequently leading to cirrhosis with HCC occurrence (Niendorf, Spilseth, Wang, & Taylor, 2015)

Chronic liver disease causes the development of regenerative nodules where proliferating hepatic cells are cordoned off by several thickened strands of fibrous tissue. A substantial fraction of these nodules usually differentiate into premalignant lesions and ultimately malignant lesions (Niendorf et al., 2015)

Numerous studies have demonstrated that the pattern of HCC occurrence has a varied geographical distribution, with the highest incidence rates being reported in East Asia,

sub-Saharan Africa, and Melanesia, where approximately 85% of cases occur(European Association for the Study of the et al., 2012)

Locally its estimated that Hepatocellular carcinoma is the third most common malignancy in Kenyan males occurring with a peak incidence at 40 years of age according to a study by Mwangi et al in KNH(Mwangi & Gatei, 1993)

2.3 Risk Factors

According to a study by the European association for the study of Liver disease, approximately 90% of HCCs are associated with a known underlying risk factor. Some of these are well studied with the most frequent factors being chronic viral hepatitis (types B and C), alcohol intake and aflatoxin exposure. Further studies in Africa and East Asia have shown the largest attributable fraction being due to hepatitis B (60%) while in the developed Western world only approximately 20% of cases can be attributed to HBV infection, whereas chronic hepatitis C appears to be the major risk factor.

Worldwide, about 54% of cases are attributed to HBV infection (which affects 400 million people globally) while 31% are attributed to HCV infection (which affects 170 million people), with approximately 15% being associated with other causes. (European Association for the Study of the et al., 2012)

The most important risk factor for HCC is liver cirrhosis, and this may be caused by chronic viral hepatitis, alcohol, inherited metabolic diseases such as hemohromatosis or alpha-1-antitrypsin deficiency, and non-alcoholic fatty liver disease. All the different forms of cirrhosis can be complicated by HCC occurrence, but the risk is higher in

patients who have hepatitis infection. Overall, studies have demonstrated that one-third of all cirrhotic patients will go on to develop HCC at a time during their lifetime (European Association for the Study of the et al., 2012)

Primary liver cancers are increasingly becoming very common worldwide. It has a wide geographic distribution and the incidence is increasing with a higher prevalence in developing countries. Early diagnosis remains an obstacle and results in poor outcomes for hepatocellular carcinoma (HCC), the most prevalent primary liver cancer, and cholangiocarcinoma(Ananthakrishnan, Gogineni, & Saeian, 2006)

Hepatocellular carcinoma (HCC) has been reported to be the fifth most common malignancy in the world and has been estimated to cause approximately half a million deaths annually. Because of these high fatality rates, the incidence and mortality rates are reported to be almost equal. The major risk factors for HCC are chronic hepatitis B virus infection, chronic hepatitis C virus (HCV) infection, and alcoholic cirrhosis with hepatitis B virus infection, being responsible for most cases in developing countries.

The male gender is the more commonly affected gender with men being two to three times more often affected than women. Furthermore with the rising rates of HCC, there has been a reported shift of incidence from the typically elderly age group to relatively younger age group between ages of 40 to 60 years. Hepatocellular carcinoma continues to harbor an overall very poor survival rate (close to 5%); very few patients qualify for and receive potentially curative therapy (El-Serag, 2002).

Liver cancer has been ranked as the fifth most common cancer worldwide by the number of cases recorded (626,000 or 5.7% of new cancer cases). However the number of deaths

is almost the same due to the very poor prognosis, (598,000). It is therefore ranked as the third most common cause of cancer related deaths. Survival rates are reported as 3% to 5% in cancer registries for the United States and developing countries.(D Max Parkin, Bray, Ferlay, & Pisani, 2005)

Approximately 82% of all cases (and deaths) are recorded in developing countries with china alone accounting for approximately 55%. The areas with the highest incidence are sub-Saharan Africa, eastern and southeastern Asia. The reported incidence is low in developed areas. The overall sex predilection (male:female) is around 2.4, and much higher in the high-risk areas and much lower in low-risk areas. (D Max Parkin et al., 2005)

Worldwide, the major risk factors reported to be associated with liver cancer are infection with the hepatitis B and C viruses, hereby increasing the risk of liver cancer by about 20-fold. Moreover, more than 75% of cases worldwide, and 85% of cases in developing countries, are caused by these two viruses.

There is documented poor prognosis related to HCC development that is illustrated by the fact that in most countries the mortality rate almost equals the incidence rate. This disease is associated with chronic disease and cirrhosis in >90% of cases (Niendorf et al., 2015)

Cholangiocarcinoma, which is a tumor of the epithelium of the intra-hepatic bile ducts, comprises 10% to 25% of liver cancers in men in Europe and North America, and a much larger proportion in women (D Max Parkin et al., 2005). The incidence shows very little international variation, with rates reported in males ranging between 0.5 and 2.0, and slightly lower in females.(D Max Parkin et al., 2005)

Primary liver cancer carries a very poor prognosis and is ranked as the third leading cause of cancer death worldwide. Data from the Surveillance, Epidemiology, and End results (SEER) study and Euro care study show that primary liver cancer has the lowest overall survival rate worldwide among the 11 most common cancers with a less than 10% 5-year survival (Ananthakrishnan et al., 2006; D Max Parkin et al., 2005)

Primary liver cancer has shown an average increase in incidence and mortality over the past 10 years, with annual percentage increament of 3.3 and 1.9, respectively compared to some of the other common cancers like breast, colorectal, lung and gastric, which have shown either significant decreases or no change in these two parameters. Liver cancer has the second highest APC in the time period 1992 to 2002 after thyroid cancer and the highest APC (1.9) in mortality during the same time period. A majority of these cancers are diagnosed in older patients, with the highest incidence (26.4%) in the age group 65 to 74. The median age of diagnosis is 64 years with a lifetime risk of being diagnosed with liver cancer of 0.89%. The mean 5-year survival rates even in the United States is less than 10% with an average of 16.4 years of life lost per person dying of liver cancer (CASES, 2016)

The hepatocellular carcinoma (HCC) is the most common malignant primary liver cancer with a poor survival rate and statistics show that it has an increasing incidence worldwide. In most cases and especially in developing nations, HCC is diagnosed at a late stage hence the prognosis of patients with HCC is generally poor and has a less than 5% 5-year survival rate (Bertino et al., 2011; Spangenberg, Thimme, & Blum, 2006).

Accurate diagnosis of HCC very important because treatment ranges from supportive care for advanced metastatic lesions to partial hepatectomy for early carcinoma. Radiological imaging is very useful in narrowing the differential diagnosis (Nasit et al., 2013).

However tissue diagnosis often is required at times to confirm the diagnosis and usually acquired through Fine-needle aspiration cytology (FNAC) or fine-needle aspiration biopsy (FNAB). These procedures are increasingly being done under image guidance either by ultrasound guidance or CT guidance.

At risk Surveillance for Hepatocellular Carcinoma

Population surveillance for HCC has been recommended for the following Groups of Patients. All hepatitis B carriers, Asian males age group ⩾ 40 years Asian females age group ⩾ 50 years, all confirmed cirrhotic hepatitis B carriers, those with family history of HCC as well as Africans over age 20 years.

Other that are considered as non-hepatitis B cirrhosis include hepatitis C, people with alcoholic cirrhosis, metabolic diseases such as genetic hemochromatosis and Alpha1-antitrypsin deficiency, autoimmune diseases such as Autoimmune hepatitis as well as primary biliary cirrhosis. (Jordi & Morris, 2011)(AASLD, 2011)

2.4 Liver Biopsy

Although the imaging diagnosis of HCC using Triphasic Liver CT/MDCT/MRI is not without some concerns, the complications, complexities, ambiguity of diagnosis, and cost of biopsy confirmation are considered too great (Niendorf et al., 2015)

Liver biopsy is a diagnostic procedure used to obtain a small amount of liver tissue, which can be examined under a microscope to determine the histological pattern of liver disease and the degree of fibrosis (scarring) of the liver. Liver biopsy can be either done blindly or under image guidance either ultrasound guided or less commonly CT scan guided.

Other forms of biopsy are laparoscopic biopsy and trans-venous or trans-jugular liver biopsy. The primary risk of liver biopsy is bleeding from the site of liver biopsy, although this event occurs in less than 1% of all patients. Other possible complications include injury to other organs, such as the kidney, lung or colon. Another complication of liver biopsy is tumor seeding which can occur during the procedure of carrying out a liver biopsy.

Damage to the gallbladder may lead to leakage of bile into the abdominal cavity, causing peritonitis. However, the risk of death from liver biopsy is extremely low, with a mortality of 1 in 5,000.Liver biopsies may not be routinely recommended to diagnose hepatic masses except on occasions when a diagnosis is not clear. Typically, hepatic masses are diagnosed by using a CT scan or an MRI (Bortolasi, Marchiori, Dal Dosso, Colombari, & Nicoli, 1995).

In a systematic review of the complications that arose after 68,276 percutaneous liver biopsies performed from 1973 to 1983, the complications are analyzed in relation to the underlying liver disease and to the type of needle used. Death was infrequent (9/100 000) and was always due to haemoperitoneum and occurred only in patients with malignant diseases or cirrhosis. Approximately 61% percent of complications occurred within two

hours of biopsy and 96% within one day. The data indicate a post biopsy observation period of at least 24 hours. The day-case procedure should be reserved for patients not presenting with liver tumor or cirrhosis. (Piccinino et al., 1986)

In another study by Janes et al, 405 outpatients underwent biopsy. They found that of the 405 patients, 13 (3.2%) were admitted with complications after biopsy. Five patients (38%) were admitted with persistent localized pain, five (38%) with orthostatic hypotension, one (8%) with both pain and hypotension, one (8%) with peritoneal signs, and one (8%) with lightheadedness but no orthostatic changes. All complications were noted within 3 hours after the biopsy. Bleeding, potentially the most serious complication, was radiographically defined in 5 of the 13 patients (38%) admitted. (Janes & Lindor, 1993)

In a study by Stigliano et al in 2007 to evaluate the risk of seeding, which was defined as new neoplastic cells occurring outside the liver capsule, either in the subcutaneous tissue or peritoneal cavity after performing a needle biopsy they concluded that the risk of seeding with HCC is substantial and is more with using diagnostic biopsy alone as compared to other therapeutic percutaneous procedures.(Stigliano et al., 2007)

Ewe in a study in 1981 concluded that indices of coagulation in the peripheral blood used are unreliable guides of the risk of bleeding after liver biopsy and, hence, are of limited value in determining contraindications to this procedure(Ewe, 1981).

According to Garcia-Tsao et al in 1993, liver biopsy complication rates have ranged from 0.9% to 3.7%; most complications have become manifest within the first 3 hours after biopsy, and none has resulted in death. (Garcia-Tsao & Boyer, 1993).

Terjung et al retrospectively analyzed 629 procedures with in patients with an increased a prior bleeding risk. In their results, biopsy-related bleeding events defined as clinically overt complication (n = 10; 1.6%), an otherwise unexplained drop in serum hemoglobin concentration of greater than 2 g/dl (n = 45; 7.1%) or intra- or extra hepatic hematoma assessed by ultrasound (n = 17; 2.7%) were identified in 72 patients. 58% of the bleeding events occurred in patients with particular risk factors for bleeding. Biopsy-related mortality in the study cohort was 0.48% (Terjung et al., 2003)

Cohen et al reviewed percutaneous liver biopsy at Children's Hospital over a 6-year period (1981–1986). In data collected from 469 (97%) of 483 eligible charts, 21 patients (4.5%) developed major complications including bile leak (n = 3, 0.6%), prolonged drainage of ascitic fluid (n = 1, 0.2%), pneumothorax (n = 1, 0.2%), bleeding requiring transfusion (n = 13, 2.8%), and death (n = 3, 0.6%)(Cohen, A-Kader, Lambers, & Heubi, 1992)

A systematic review and meta-analysis of observational studies by Silva et al reported needle tract seeding following biopsy of suspicious liver masses. Lesions suspected of being hepatocellular cancer (HCC) were considered. They concluded that the incidence of needle tract tumor seeding following biopsy of a HCC is 2.7% overall, or 0.9% per year.(Silva et al., 2008)

Takamori et al retrospectively reviewed 91 cases of hepatocellular cancer during a 4-year period from 1994 to 1997. In their study of 91 patients with hepatocellular cancer, 59 patients underwent percutaneous needle biopsy as part of diagnostic workup. They found that 3 patients (5.1%) were identified with needle-tract implantation of tumor. Two

patients required en bloc chest wall resections for implantation of hepatocellular cancer in the soft tissues and rib area. The third patient, who also received percutaneous ethanol injection of his tumor, required a thoracotomy and lung resection for implanted hepatocellular cancer. They therefore concluded that percutaneous needle biopsy of suspicious hepatic lesions should not be performed indiscriminately because there is a significant risk for needle-tract implantation and therefore should be reserved for those lesions in which no definitive surgical intervention is planned and pathological confirmation is necessary for a nonsurgical therapy (Takamori, Wong, Dang, & Wong, 2000)

Therefore tumor seeding, whereby malignant cells are deposited along the tract of a biopsy needle, can have fatal consequences. Available data shows that more than 90% of cancer-associated mortality may be attributed to metastasis and it is a great challenge to treat as it is difficult for one to discern the extent of systemic involvement even though the primary tumors can be removed by surgical resection, chemotherapy or radiotherapy. Therefore once in the circulation these metastatic seeds or the circulating tumor cells (CTCs) bring about dissemination to anatomically distant organs from a primary tumor (Shyamala, Girish, & Murgod, 2014)

2.5 Imaging techniques

2.5.1 Ultrasound

Ultrasound (US) imaging has in the recent past been largely replaced in diagnosis by CT scan and MRI as a diagnostic method of choice due to low sensitivity and positive predictive value with cirrhosis as a co-morbidity. However recent introduction of sonographic contrast agents such as intra-arterial carbon dioxide and helium has brought gains in accuracy. (Bialecki & Di Bisceglie, 2005).

However its use cannot be dismissed since duplex and colour Doppler ultrasound are very useful in assessment of intrahepatic vascular flow. Liver masses that are HCC usually display fine branching patterns with increased vascularity. They also display greater flow velocity than metastatic lesions or hemangiomas(Bialecki & Di Bisceglie, 2005).It's also still employed as an initial screening tool in suspected HCC.

2.5.2 CT Scan Findings

An initial screening patient suspected to have or at risk for HCC is usually done with the use of ultrasound. Confirmation is however then be obtained by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), due to the fact that both have a relatively high specificity.(Niendorf et al., 2015)

Imaging by CT/MRI plays an important role in HCC screening and diagnosis. Ultrasound is now the first and only screening exam for HCC in this patient population as the previously used serum alpha-fetoprotein is now not being used. If a mass is suspected on screening ultrasound, a further follow up imaging study is obtained. Currently, both Triphasic CT/MDCT and MRI are the recommended for further characterizing suspected

lesions found on ultrasound. More recently, strong recommendations in the scientific community suggest that multiphase MRI, obtained with standard techniques is the exam of choice for HCC diagnosis. Unlike most malignancies, that usually require tissue biopsy for diagnosis, HCC can be adequately diagnosed based on CT or MRI characteristics alone since they have relatively high specificity (Niendorf et al., 2015)

However sometimes not all tumors demonstrate the described typical pattern of tumour vascularity and some HCCs, including the poorer grades, can only be visualized in the post arterial phases. (Niendorf et al., 2015)

Usually in Triphasic liver CT rapid intravenous infusion of contrast media are done and imaging conducted during various time intervals that correspond to the phase of contrast enhancement. Triphasic scanning denotes hepatic imaging performed before contrast, during arterial and venous phases. HCC tumors derive blood flow predominantly from the hepatic artery and tend to enhance during the arterial phase or 2–40 seconds after contrast infusion. The surrounding hepatic parenchyma obtains 75–80% of its blood flow through the portal vein and is best demonstrated 50–90 seconds after infusion of contrast during the portal phase. Arterial phase enhancement can increase HCC tumor detection by 10% (Oliver 3rd, Baron, Federle, & Rockette Jr, 1996)

Blood flow in HCCs usually passes through the lesion and into the venous circulation more rapidly than normal hepatic parenchyma which leads to a characteristic “washout” appearance of relative low enhancement of the tumor as compared to the liver on these phases 88% of the time. Furthermore, 97% of moderately and poorly differentiated cancers are appreciated in this phase.(Niendorf et al., 2015)

Van Leeuwen in a study of 94 patients, 375 liver lesions concluded that Triphasic liver CT enables characterization of a wide range of focal liver lesions, including the benign liver lesions that occur most frequently (van Leeuwen, Noordzij, Feldberg, Hennipman, & Doornewaard, 1996)

The characteristic pattern of enhancement of a regenerative nodule to HCC progression has allowed for the development of specific diagnostic criteria for HCC. "Hyperenhancement" of the lesion in the late arterial phase is one of the most important characteristic for the diagnosis of HCC. This "hyperenhancement" is defined as a pattern of increased enhancement of the tumour relative to the surrounding liver. There are however other conditions that can have hyperenhancement in the arterial phase, atypical cholangiocarcinoma, which is also present in chronically diseased liver, hepatic adenomas or a hemangioma or focal nodular hyperplasia. In addition, some dysplastic nodules, which are yet progressed to HCC, can also demonstrate hyperenhancement. The addition of "washout" on the portal venous phase and/or equilibrium phase however is used to distinguish these causes from the true HCC hyperenhancement(Niendorf et al., 2015)

According to AASLD, the combination of arterial hyperenhancement and venous or delayed washout has a sensitivity of 64%–89%; specificity of 96%; as well as a positive predictive value of 93% in the diagnosis of HCC.

At present, both the American Association for the Study of Liver Diseases (AASLD) and the United Network for Organ Sharing (UNOS) systems use the standard dimension of a

nodule >1 cm having arterial hyperenhancement followed by washout to qualify for the diagnosis of HCC (Jordi & Morris, 2011).

There is also the potential but not always present development of an enhancing rim surrounding the HCC on delayed or equilibrium phase called a capsule or pseudo capsule. This additional finding is very important as it adds to the strength of diagnosis for HCC. The appearance of this capsule is very critical as it allows the diagnosis of HCC to be made to an otherwise suspicious nodule measuring ≥1 cm and <2 cm in diameter according to the Organ Procurement and Transplantation Network (OPTN) Classification(Niendorf et al., 2015)

Ichikawa et al in their study on the detection rate of adenomas per type of examination concluded that hepatic adenomas often have characteristic features at multiphase CT that may allow their distinction from other hepatic masses. (Ichikawa, Federle, Grazioli, & Nalesnik, 2000)

In a study by Monzawa et al in 2007, the mean sensitivity for the use of arterial and portal venous phase phases was 86.8%, for the use of arterial and delayed phases was 90.3%, whereas that for the combination of all the three phase imaging was 93.8%. They concluded that delayed phase imaging is very useful for detecting small HCCs and should be routinely included in dynamic CT examinations of patients with liver cirrhosis. (Monzawa et al., 2007)

Miller et al in a study to determine the value of triphasic helical CT (unenhanced, hepatic arterial, and portal venous phases) in the detection of malignancies concluded that patients with hypovascular malignancies had more lesions detected on the portal venous

phase with increased conspicuity than on the other phases. More over Patients with hypervascular malignancies had their lesions best detected on the hepatic arterial phase, which revealed small lesions that were not seen on the other phases in seven (21%) of the 33 patients with hypervascular malignancies. No lesions were detected on the unenhanced phases that were not seen on the other phases.

Further they concluded that unenhanced phase is not routinely necessary for the detection of metastases whereas hypovascular malignancies are best evaluated using the portal venous phase. Hypervascular metastases are best evaluated with hepatic arterial phase, and should therefore be used routinely in these patients. The hepatic arterial phase was also found to be of limited value in diagnosing hypovascular malignancies (Miller et al., 1998)

Hwang et al in 1997 evaluated the effectiveness of three-phase spiral computed tomography (CT) for the evaluation of nodular hepatocellular carcinoma (HCC). They found that arterial phase images demonstrated a statistically significantly larger number of lesions (n = 67), although the differences in the number of lesions depicted between the portovenous phase and delayed images were not statistically significant. The most clearly visualized lesions were mostly depicted on the Arterial Phase images compared than the Porto venous Phase images or the Delayed Phase (23 images). They therefore concluded that lesion detection and conspicuity were best with the Arterial Phase images but maximum lesion visualization is well achieved by using all three phases. (Hwang, Kim, Yoo, & Lee, 1997)

Diagnosis of HCC should usually be based on imaging techniques characteristics and/or biopsy. According to AASLD, the 2005 diagnostic algorithm for HCC has been validated in many centres and the diagnostic accuracy of a single dynamic or multiphase imaging technique showing avid arterial uptake followed by “washout” of contrast in the venous-delayed phases has been well demonstrated.

The diagnostic algorithm is shown in the Figure below. However the application of these dynamic imaging criteria can and should only be applied to patients with cirrhosis or Imaging features of cirrhosis of any etiology and to patients with a known risk factor such as chronic hepatitis B who may not have fully developed cirrhosis but could be in the process or have regressed cirrhosis(Jordi & Morris, 2011)(AASLD, 2011).

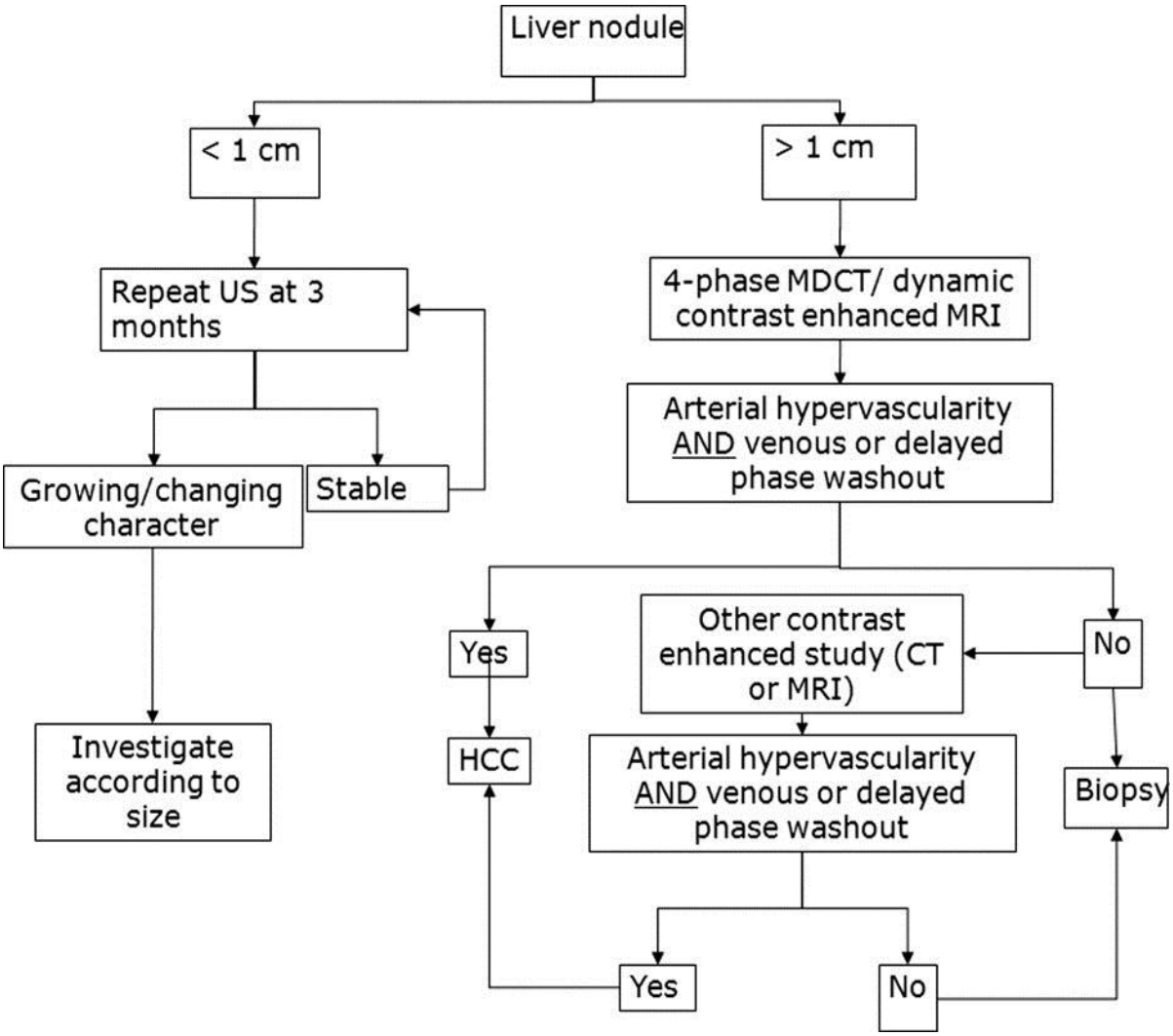


Figure 1: Diagnostic algorithm for suspected HCC. CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound (European Association for the Study of the et al., 2012)

2.6 Cholangiocarcinoma

Cholangiocarcinoma is the second most common primary liver cancer, accounting for up to 15% of the cases. Cholangiocarcinomas are of two types, intrahepatic (ICC) and extra hepatic. Some risk factors are well recognized like hepatolithiasis, liver fluke infection, primary sclerosing cholangitis (PSC), and thorotrast,(Ananthakrishnan et al., 2006; Donato et al., 2001)

2.7 Other Primary Liver Cancers

2.7.1 Fibrolamellar Carcinoma

Fibro-lamellar carcinoma (FLC) is an uncommon tumor usually occurring in younger patients with non-cirrhotic livers. It accounts for 0.5 to 1% of all cases of liver cancer (El-Serag & Davila, 2004)

2.7.2 Hepatoblastoma

Hepatoblastoma (HB) is the most common primary hepatic tumor of childhood arising from incompletely differentiated hepatocyte precursors. It accounts for between 0.2 and 5.8% of all childhood malignant tumors and occurs at an incidence of ~1 in 100,000.It is also two to three times more common in boys. It is almost exclusively seen in children younger than 3 years, though rare cases have been reported in adults (Benson III et al., 2009; Bortolasi et al., 1995)

2.8 Differential diagnosis of Hepatic Masses.

2.8.1 Malignant Masses

HCC is classified as the most common primary malignant hepatic masses. Commonest associated comorbidities include cirrhosis from alcoholism, hepatitis (B and C), as well as toxin exposure. Standard liver function tests are of no use in making a diagnosis of HCC, especially in patients with cirrhosis (Matsumoto et al., 1982). The serum α-fetoprotein levels are elevated.

Tumours of the colon, lung, prostate, gastric, and transitional cell carcinomas show hypovascular metastasis and are the most common primary tumors metastasizing to the liver and showing this pattern (Elsayes et al., 2005; Pedro, Semelka, & Braga, 2002).

Lymphomas are also known to involve the liver. This involvement of the liver can be classified as either primary or secondary involvement. Primary lymphoma of the liver is rare. Secondary involvement occurs in up to approximately 50% of patients with non-Hodgkin lymphoma and also in about 20% of patients with Hodgkin lymphoma (Elsayes et al., 2005; A. D. Levy, 2002)

2.8.2 Benign Masses

Hepatic Cysts

Hepatic cysts are among the most common liver lesions. They are usually thin walled, have well defined margins and are usually oval in shape.

Simple Hepatic Cyst – These are benign developmental lesions that have no communication with the biliary tree. They are thought to originate from hamartomatous tissue. Simple hepatic cysts are found in approximately 2.5% of the population (Mortelé & Ros, 2001; vanSonnenberg et al., 1994)

Caroli Disease - This is a rare condition characterized by congenital cystic dilatation of the intrahepatic bile ducts. It is thought to generally involve the entire liver, however it may be segmental. It is autosomal recessive (Duvnjak, Supanc, Virović, Tomasić, & Dojcinović, 2002)

Regenerating and Dysplastic Nodules - Accurate and timely characterization of various nodular lesions especially those that occur with cirrhosis is important for appropriate patient treatment. This is due to the fact that majority of HCCs are postulated to arise as a regenerating nodule and progressively develop into a low-grade dysplastic nodule, and finally progress to a high-grade dysplastic nodule, which eventually becomes HCC (Elsayes et al., 2005).

Other benign nodules include Lipomas and Bile Duct Hamartoma.

2.8.3 Inflammatory Lesions

Inflammatory lesions of the liver are rare and include the following.

Sarcoidosis - This is a granulomatous systemic disease whose etiology is not known and can involve numerous sites, including the liver. Liver involvement by sarcoidosis is estimated to be about 24%–94% of patients by biopsy (Warshauer & Lee, 2004).

Histoplasmosis is rare and mostly seen in immunocompromised patient although it can be seen in patients with competent immune systems.

Other rare lesions are Focal Fat and Confluent Hepatic Fibrosis.

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Study Setting

This study was set at MTRH in Eldoret, Kenya. It was conducted in the Radiology and Pathology departments of MTRH between August 2017 and July 2018. Moi Teaching and Referral Hospital is a level 6 hospital located on Nandi road East of Eldoret town in UasinGishu County in the North Rift region of Kenya. It is approximately 320 kilometers northwest of the capital city Nairobi. It has a bed capacity of approximately 800 beds. The radiology unit has the Digital General X-ray unit, The Digital Mammography unit, The Fluoroscopy unit, the X-ray reporting unit, The CT scan unit and CT scan reporting unit, the Ultrasound unit, and the Magnetic Resonance Imaging unit. The Ultrasound unit has four machines whereas the CT scan unit has three machines, a 32 slice multi-detector Siemens scanner, a 64 slice multi-detector Phillips scanner and a 128 slice multidetector Neuviz scanner. This study was specifically based in the Ultrasound guided biopsy and CT scan room. It has a catchment population of approximately 18 million people mainly from the North Rift and Western regions of Kenya.

3.2 Study Design

The study was a hospital based cross sectional study evaluating the use of Triphasic liver CT scan findings in assessing suspected hepatocellular carcinoma in MTRH.

3.3 Study Population

All patients presenting at MTRH radiology department with suspected hepatocellular carcinoma were recruited for the study. These clients were then subsequently sent for image guided liver biopsy.

3.4 Sample Size Determination

In order to be 95% sure that the proportion of patients with liver masses was within plus or minus 5% of the population, a census study was used to recruit all patients presenting with suspected hepatocellular carcinoma for Triphasic liver CT at the radiology department of MTRH. This was reached upon owing to the small number of patients who presented with suspected HCC and had a liver biopsy subsequently done in the year 2016. According to MTRH records 51 liver biopsies were performed in MTRH in 2016 and so based on these numbers we set out to recruit all patients that presented with suspected HCC and the number of patients was limited by the study period of 1 year.

3.5 Sampling Technique

Purposive sampling technique was used to select the study area to MTRH since patients were more likely to present at MTRH for image guided liver biopsies as it is the only main centre carrying out biopsies in this region. Consecutive patients were sampled for this study.

3.6 Eligibility Criteria

3.6.1 Inclusion criteria

All patients presenting at MTRH radiology department for CT scan examination who had Hepatocellular carcinoma and who consented to undergo an image guided biopsy were recruited into this study.

3.6.2 Exclusion criteria

Referrals in with a known diagnosis and those on follow-up for a known diagnosis were excluded.

3.7 Data Collection

All consenting patients were awarded special numbers. A data sheet was used for data collection. The principle author was the main data collector. Data regarding age at presentation and the reasons for abdominal CT scan examination, time taken before presentation, and any cormobidities were recorded in the data sheet. Liver CT scan findings were recorded. The patient was then followed up and the Image guided biopsy findings were then recorded. All data was then stored in flash drives and computer for analysis.

3.8 Study Procedure

All patients presenting with HCC for Triphasic Liver CT scan examination and who met the inclusion criteria were explained to in a language they well understood about the purpose, risks and benefits of the study and were given a chance to consent to be part of this study. All their demographics details were retrieved from their records and recorded. All this data was then recorded in a data abstraction sheet. A Triphasic liver CT scan was

then performed and those who had suspicion of HCC and consented for an image guided liver biopsy were then recruited into the study.

Clinical and radiological data was then obtained from patient and case files and the CT scan console. Bleeding time, clotting time and prothrombin time were then evaluated in all cases. Ultrasound guided liver biopsy was then performed when all the parameters allowed and histopathological diagnosis was sought. Histological data was then captured in the form of soft and hard copies. Images were also saved in the CT machine computer memory and compact disks. Image interpretation was done by the principal investigator and later corroborated by at least two senior consultant radiologists. The abnormalities detected were described and a diagnosis of HCC was made on the basis of characteristic Triphasic Liver CT scan findings.

3.8.1 Image Acquisition

A total of 61 patients underwent a liver protocol, triphasic CT scan, non-enhanced, arterial phase, portal venous phase and equilibrium phase.

Helical scanning was performed with a Siemens, Somatom Perspective, Germany 32 Slice CT scanner in the CT room of MTRH. Scan parameters were identical for each phase.

CT scans were obtained in the cranio-caudal direction. The following CT parameters were used: slice thickness, 5.0 mm; reconstruction interval, 1.5mm, 80-100 mAs; tube potential 110-130 kVp; Pitch 1.5; scan time 14 seconds and matrix size, 512×512.

CT images were obtained after an injection of 1.5 mls/kg of Iodine (Iohexol® 350; GE Health care, Ireland, Cork , Ireland) at a rate of 4.0 ml s^{-1} and titrated depending on the

weight of the patient using 18 gauge IV catheter placed in an antecubital vein, using a dual pump automatic power injector pump. (Medtron, Dual Pump, Germany)

Arterial phase imaging was performed 8-10 seconds for early arterial, 12-15 seconds for late arterial after achieving of 100 HU attenuation of the descending aorta measured using a bolus tracking method. A time of 20-25 seconds was used for portal venous phase acquisition and 180 seconds for the delayed phase imaging following administration of a contrast medium.

The scan time and number of slices were varied with the volume required to cover and the patient's ability to hold his or her breath. Multiple slices covering 14.5 cm were obtained with a breath-hold of 16sec.

Our triphasic helical CT examinations consisted of obtaining images during the unenhanced hepatic arterial and portal venous phases. Initial images were obtained without IV contrast material.

3.8.2 Image Evaluation

CT Images were reviewed by the principal investigator and corroborated by two consultant radiologists and consensus was reached and images stored using a picture archiving and communications system (PACS) workstation. The scans were assessed using both soft-tissue (width, 400 HU; level, 70–100 HU) and narrow (width, 150 HU; level, 60–90 HU) window settings.

3.8.3 Enhancement pattern

To evaluate the characteristic enhancement pattern of suspected HCC, the HCC attenuation in each phase was classified as hyperattenuation or hypo attenuation compared to the surrounding normal liver parenchyma. On portal venous phase and delayed or equilibrium phase observation, each mass was evaluated for the presence of washout, which was defined as when any part of the lesion showing hyperattenuation on arterial phase images becomes hypoattenuated relative to the adjacent liver parenchyma on portal or delayed/equilibrium phase.

An area of hypo-attenuation with no change in the degree of attenuation during the dynamic phase was defined as necrosis. If it was difficult to determine the degree of mass attenuation through direct visual inspection of each image phase, quantitative analysis of the HCC was done as a reference. Using the regions of interest (ROIs) or pixels, tumour to liver attenuation was evaluated. Attenuation values were performed in a 0.2 to 2.0 cm^2 circular ROIs.

To assess tumour attenuation, ROI cursors were well placed so as to contain as much of the most enhancing portions of the suspected HCC's as possible in order to avoid areas of intralesional necrosis or adjacent liver parenchyma. Measurement of normal liver parenchyma attenuation excluded visualized portal or hepatic vessels, bile ducts, suspected calcifications and artifacts. At least two measurements were performed for each lesion and liver parenchyma, and the results were then averaged. Tumors with heterogeneous enhancement were regarded as hyperattenuation when most of the lesion was enhancing during the arterial phase compared to the pre-contrast phase.

3.8.4 Comparison with histological examination

The radiologic diagnosis was compared with the histological classification (benign, malignant and the exact type of histological classification). Histological classification was obtained prospectively from the pathologic reports given by the pathologist.

3.8.5 Analysis of the imaging findings

In order to determine the most useful CT findings for diagnosing HCC's in MTRH, the following CT characteristics were analyzed: (a) tumour size; (b) lesion attenuation on the non-contrast phase; (c) tumour margins; (d) the presence of a capsule; (e) heterogeneity of enhancement; and (f) presence of a tumour washout. Pre-contrast tumour attenuation was evaluated in the same way as used in the enhancement pattern above.

The shape of the tumour margin was then qualitatively evaluated and classified as having either a smooth or irregular margin according to the CT characteristics for each lesion.

Furthermore, a thin (1–3 mm), hypo attenuating rim around a nodular HCC seen on the arterial phase and later a hyper attenuating rim on delayed-phase images were considered as capsules. Tumor heterogeneity of enhancement pattern was considered present when the attenuation of the enhancing portion of the lesion was not equal.

3.8.6 Biopsy Procedure.

The biopsy procedure was explained to the patient and informed consent sought to carry out the procedure. The skin of the area to be biopsied was washed with antiseptic and draped. A fine needle was used to give local anaesthetic to numb the area for biopsy.

Then a small cut was made on the skin and under aseptic precautions. During suspended respiration the biopsy needle gauge 20 was gently inserted into the liver to reach the mass and tissues taken. Three to six cores were done. Several samples between 3 and 6 were taken. After the samples were taken, the biopsy area was compressed for a few minutes to reduce bleeding, and then dressed. The samples were processed and sent for histopathology analysis. Findings were recorded for analysis. The results of biopsy were evaluated and categorized into benign, malignant groups. The evaluation of abdominal CT scan findings compared to histopathology as the gold standard was done.

3.9 Data Collection and Management

3.9.1 Data Collection

Data was collected between August 2017 and July 2018. Entry was made in the data sheet and later transferred to a computer database. Double entry was used to ensure accuracy of the data. All patient details were kept confidential and data was only available to the investigator and the supervisors via password access. Patients were given a copy of their results and had autonomy over who else had access to their scan results. Serial numbers were used in order to protect patients' identity. At the end of each day data collection forms were verified for completeness and coded.

3.9.2 Quality control

All abdominal CT scans and Ultrasound guided biopsies were done at MTRH, US room that has internal quality controls. The scans were done by the Principal Investigator conducting the study plus two other trained assistants based on a standard MTRH protocol. Images were then reviewed by two consultant radiologists.

3.9.3 Data Analysis and presentation

To evaluate the differences in demographic data, the χ^2 test was used. To determine the statistically significant CT features in evaluation of suspected HCC, statistical analysis was performed using the χ^2 test and Fisher's exact test for categorical variables The sensitivity and specificity of each significant CT features and a combination of the significant CT features to diagnose HCC were also calculated. In addition, the CT and pathology findings were compared for patients with HCC. All statistical analyses were performed using commercial software (STATA® v. 13.0; for Windows, v. 8.0.). A *p*-value <0.05 was considered to indicate statistical significance.

Data was then entered in a computerized data base designed in STATA version 13 MP. Descriptive statistics were summarized for patient socio-demographics. Frequency tables were generated for categorical variables. Inferential statistics were done using Chi-square test to test for significance of socio-demographic characteristics in patients presenting with liver masses. The significance of the variable was calculated using adjusted or non-adjusted odd ratio backed with confidence intervals. Significance level was set at 0.05.

Data was then presented in terms of graphs and tables and disseminated in reputable journals and conferences.

3.10 Ethical Considerations

Approval to carry out the study was sought and granted from the Institutional Research and Ethics Committee (IREC), Director of Moi Teaching and Referral Hospital. All patients/guardians were informed about the study and the procedures involved in the study and the possible benefits and harm to them and that the procedure was generally safe but had potential risks. Regarding the necessity of the investigation for management of the patient, consent was sought from the hospital management and IREC to allow studying of CT scans of the patients who had undergone evaluation. All patients received medical attention as necessary regardless of their willingness/unwillingness to participate in the study. No incentives or inducements were used to convince patients to participate in the study. The cost of CT scan and ultrasound guided biopsy was solely met by the participant.

Patients were informed of their results and appropriate standard treatment given. Confidentiality was maintained throughout the study. The data collection forms used neither contained the names of the patients nor their personal identification numbers. Data collecting material were kept in a locked cabinet during the study period. The results of the research were presented to the Hospital's management and the university's department of Radiology and Imaging for use as necessary. It will also make available for academic reference in the College of Health Sciences Resource Centre. The results of this research shall be availed for publication in a reputable journal of medicine for use by the wider population in the general improvement of patient management and as a reference for future studies.

CHAPTER FOUR

RESULTS

4.1 Socio-demographic Characteristics of Study Participants

There were 25(40.98%) females in this sample giving a female to male ratio of 1.4**:**1. The youngest participant was 35 years and the oldest 72 years with an average age of 52.7 (SD 9.3) years. There was no significant difference in average age between males ($\bar{x}$=53.2, SD=1.4) and females ($\bar{x}$==51.9, SD=2.1) (p=0.613). Most 16(26.2%) of the patients were residence of UasinGishu County followed by Nandi 11(18.0%), Elgeyo-Marakwet 9(14.7%), and Trans Nzoia 7(11.5%). These four counties contributed to 70.1% of the entire sample. All the study participants were from Kenya.

Most participants (49.2%) were between 43 and 55 years (n=30). (Figure 4.1)

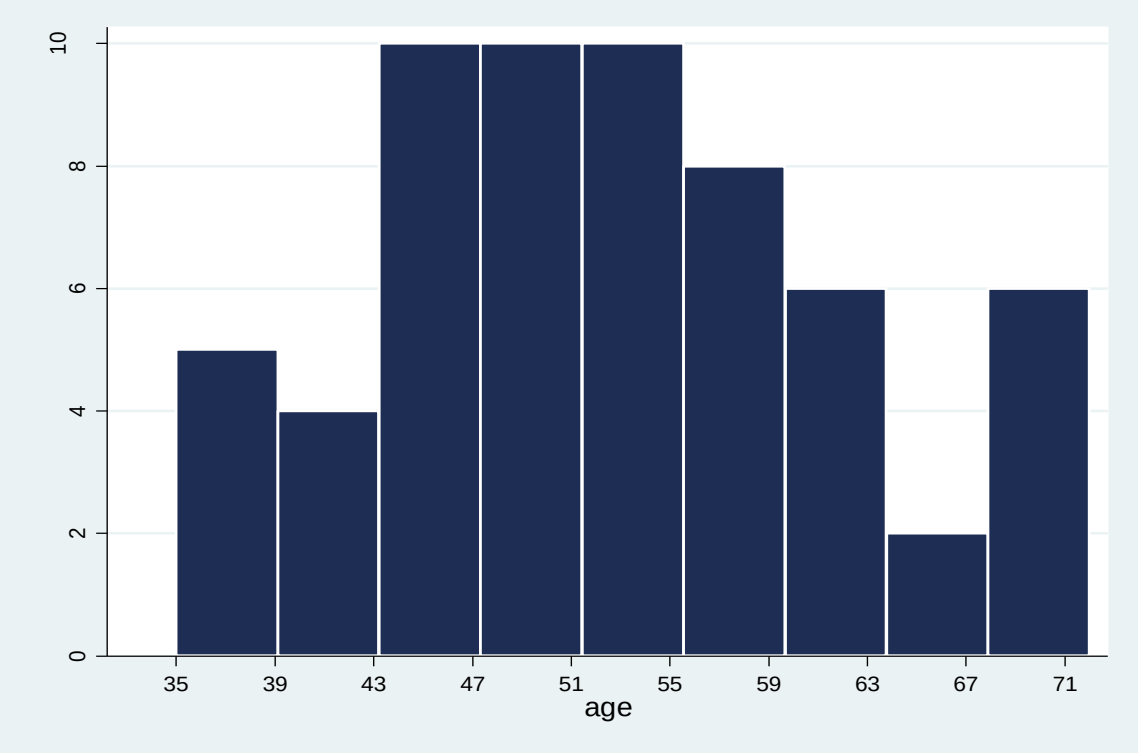


Figure 2: Distribution of Study Participants by Age Group in Years.

4.2 Distribution of CT Examination Characteristics

4.3.1 Clinical presentation

Table 1: Presenting symptoms

Variable	Category	Frequency	Percent
Symptoms	Pain	27	44.26
	Abdominal swelling	27	44.26
	Jaundice	16	26.23
	Weight loss	12	19.67

Study participants presented with the following complaints: 44.26% (n=27) had abdominal pain, 44.26% (n=27) abdominal swelling, 26.23% (n=16) jaundice and 19.67% (n=12) weight loss. 44.26 % (n=27) were referrals from other facilities.

Most 27(44.3%) of the patient presented with pain and abdominal swelling. Eight (8) patients had a history of previous CT scan although only one showed an abnormality (cirrhosis).

4.3 Triphasic CT Characteristics of HCC

A total of 59.0% of patients (n=36) had a mass or masses in the right lobe 34.4% (n=21) in both lobes and 6.6% (n=4) occurred in the left lobe.

Most masses; 78.7% had masses of more than 2cm in diameter whereas the rest were found to be between 1-2 cm in diameter.

On the multiplicity of masses; 75.4 (n=46) had one mass, 13.1 (n=8) had 2 masses and 11.5% (n=7) being multiple.

Table 2: Lesion characteristics

Variable	Category	Frequency	Percent
Site	Right lobe	36	59.02
	Left lobe	21	34.43
	Both lobes	4	6.56
Size	1-2 cm	13	21.31
	>2 cm	48	78.69
Masses number	One	46	75.41
	Two	8	13.11
	Multiple	7	11.48
Mean diameter	Mean(SD), Min-Max	3.7(1.4)	1.4 – 7.3

On conspicuity 63.9% of the masses (n=39) were detected on the non-enhanced CT scan and the addition of Arterial Phase increased the detection to 100% (n=61).27.9% (n=17) had cystic components within them while 47.5% (n=29) predominantly showed a peripheral pattern of enhancement. 62.2% (=n=41) of all the HCC's demonstrated homogenous enhancement pattern whereas 32.8% (n=20) showed heterogeneous enhancement pattern. On Tumor margins 67.2% (n=41) whereas 32.8% 9n=20) had ill defined margins. Only 13.1% (n=8) of the masses had calcifications (Figure 4.4).

4.4 Triphasic CT Enhancement Pattern of Suspected HCC

Table 3: CT enhancement patterns.

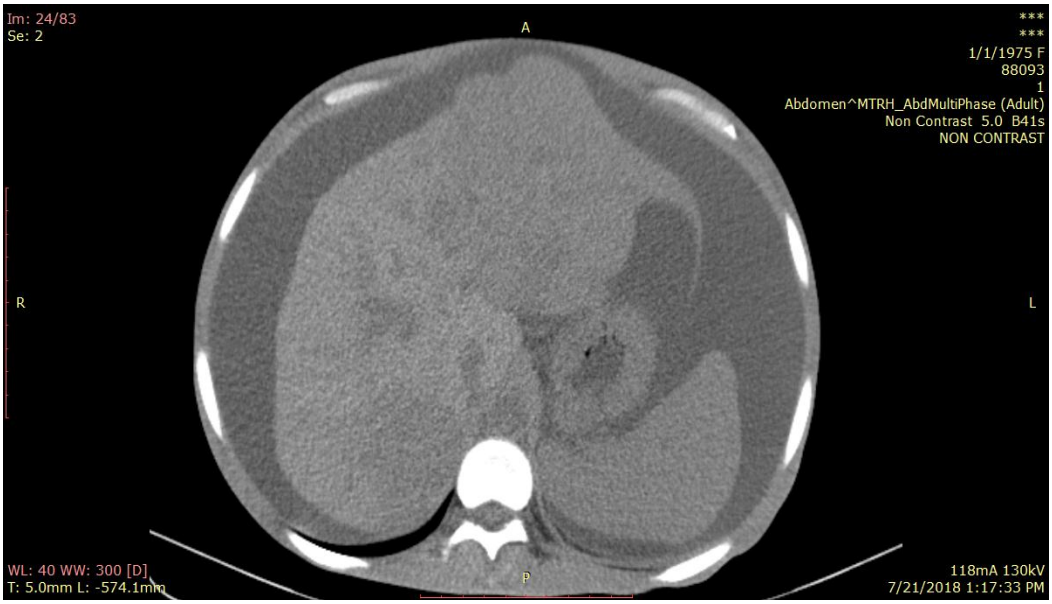
Variable	Category	Frequency	Percent
Hepatic arterial phase	Hypervascular	44	72.13
	Hypovascular	17	27.87
Enhancement pattern	Homogenous	41	67.21
	Heterogeneous	20	32.79
	Washout (n=54)	48	78.69

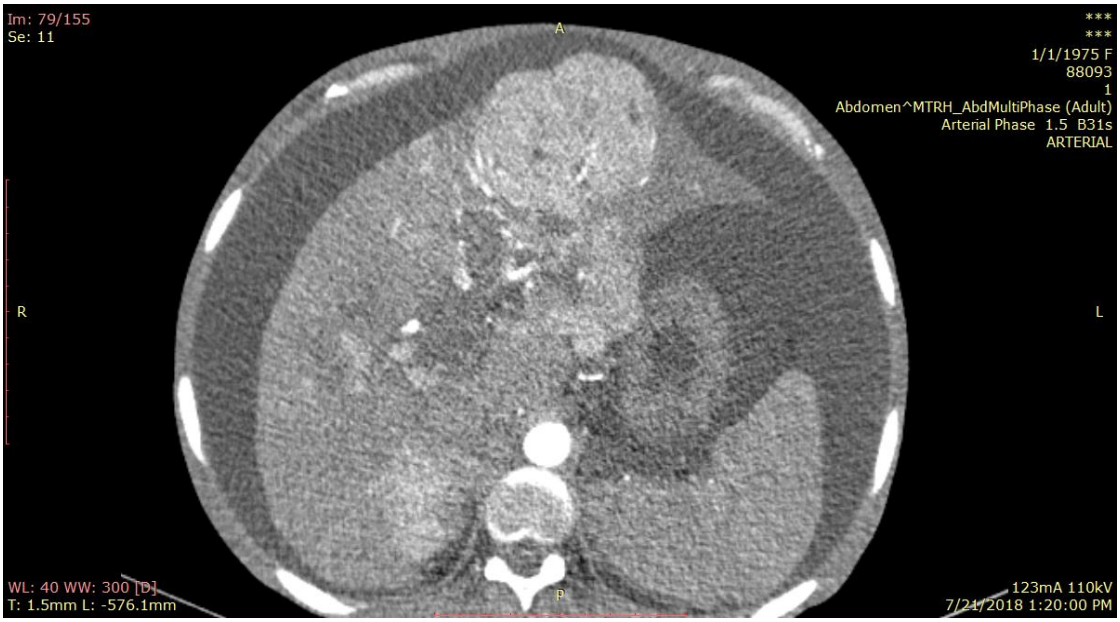
Table 4: CT enhancement patterns continued…

Variable	Category	Frequency	Percent
	Central scar (n=54)	21	34.43
Tumour margins	Smooth	41	67.21
	Ill defined	20	32.79
Others	Washout (n=54)	48	78.69
	Peripheral enhancement (n=61)	29	47.54
	Cystic components (n=61)	17	27.87
	Calcification (n=61)	8	13.11

4.5 Sample images of HCC on Triphasic CT based on image Characteristics.

Figures 3 to 9 below present selected CT scan images of hepatic masses included in the study





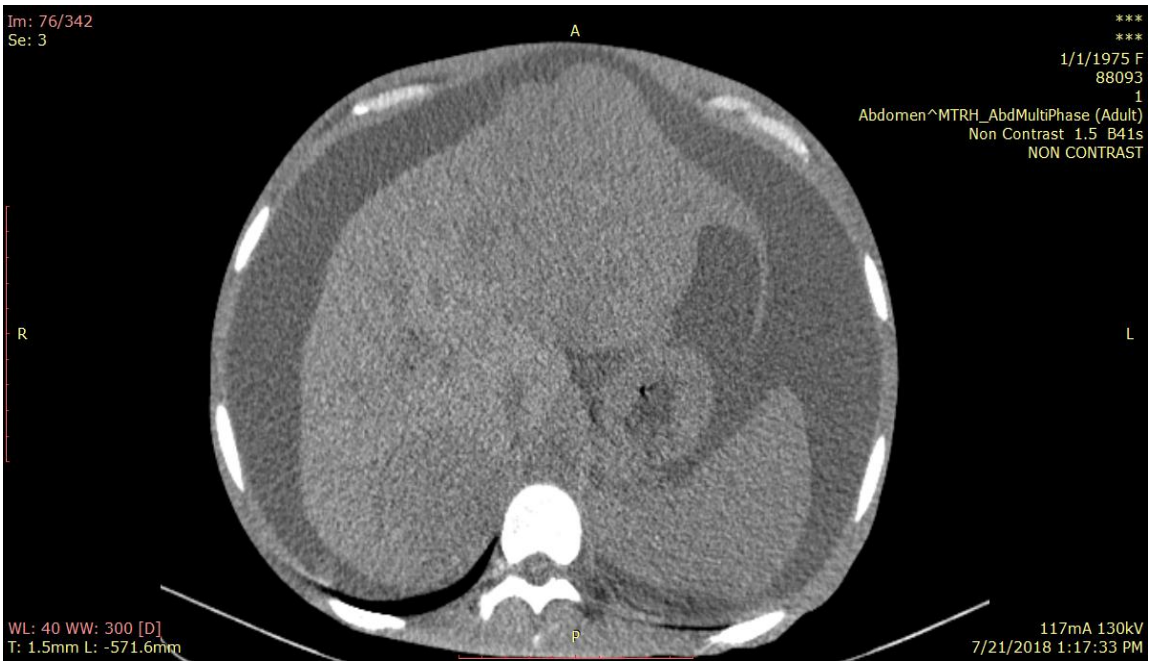
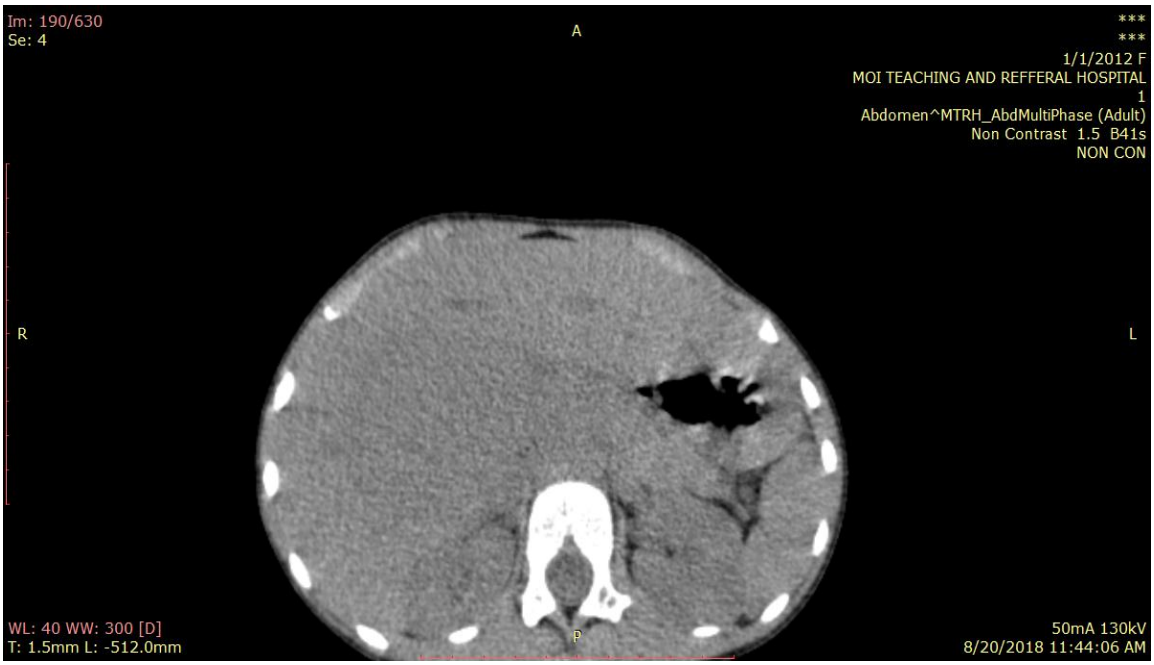


Figure 3: Triphasic scan of a 43 year old male with a left hepatic (seg 4b) mass which had enhancement and washout and a nodular shrunken liver with ascitis confirmed to be HCC.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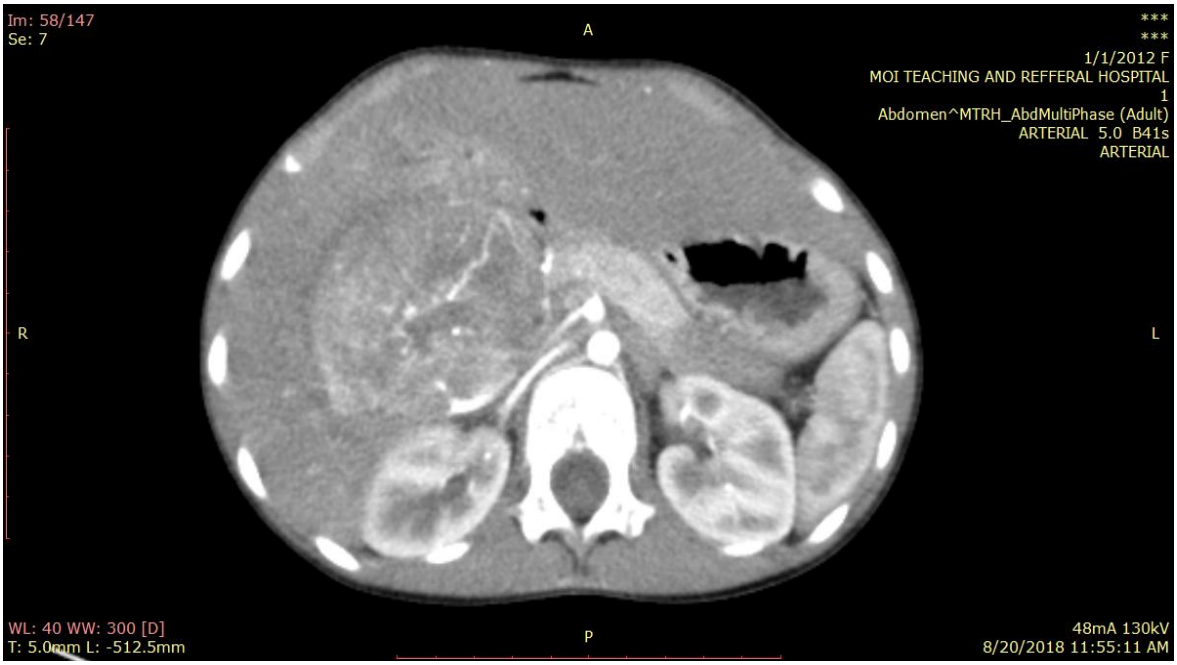
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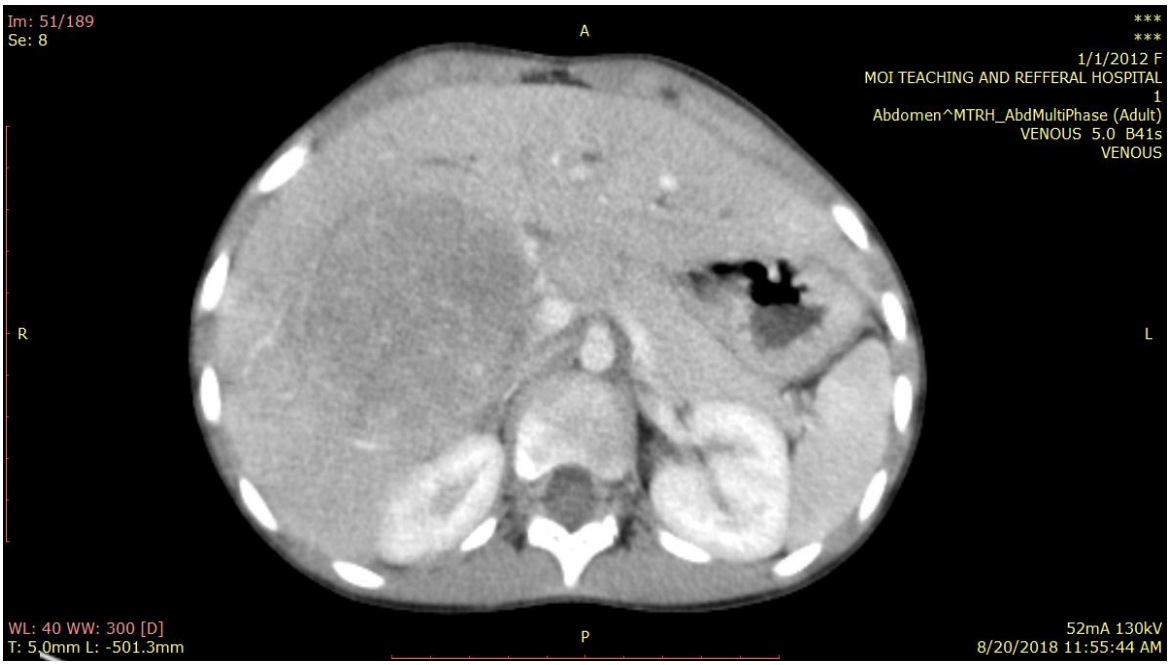

Figure 4: Triphasic scan of a 56 year old female with a right hepatic (Seg 5) mass which had enhancement and washout confirmed to be HCC.

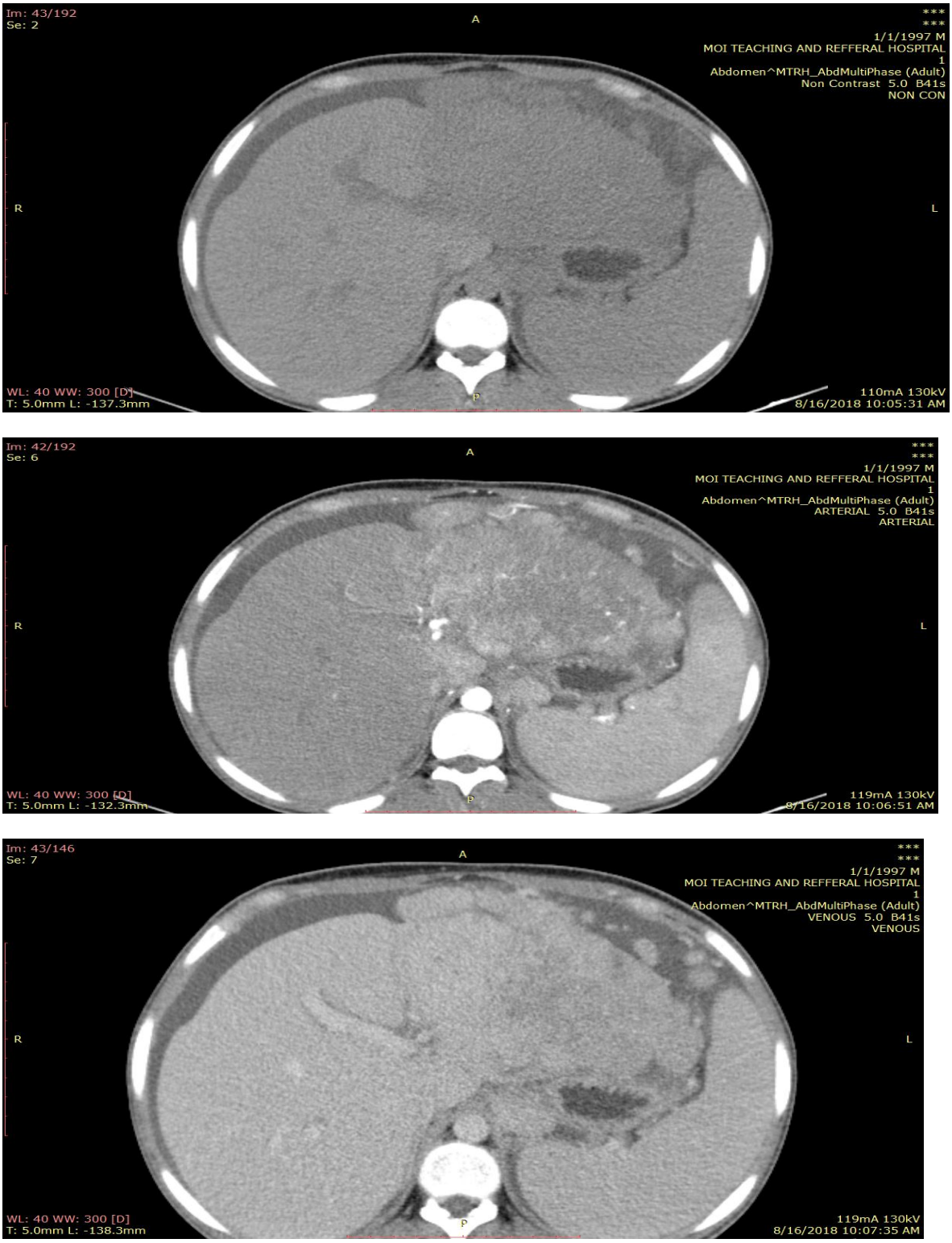

Figure 5: Triphasic scan of a 60 year old male with a left hepatic mass (Seg 3, 4b) which had enhancement and washout and a nodular liver with ascitis confirmed to be HCC.

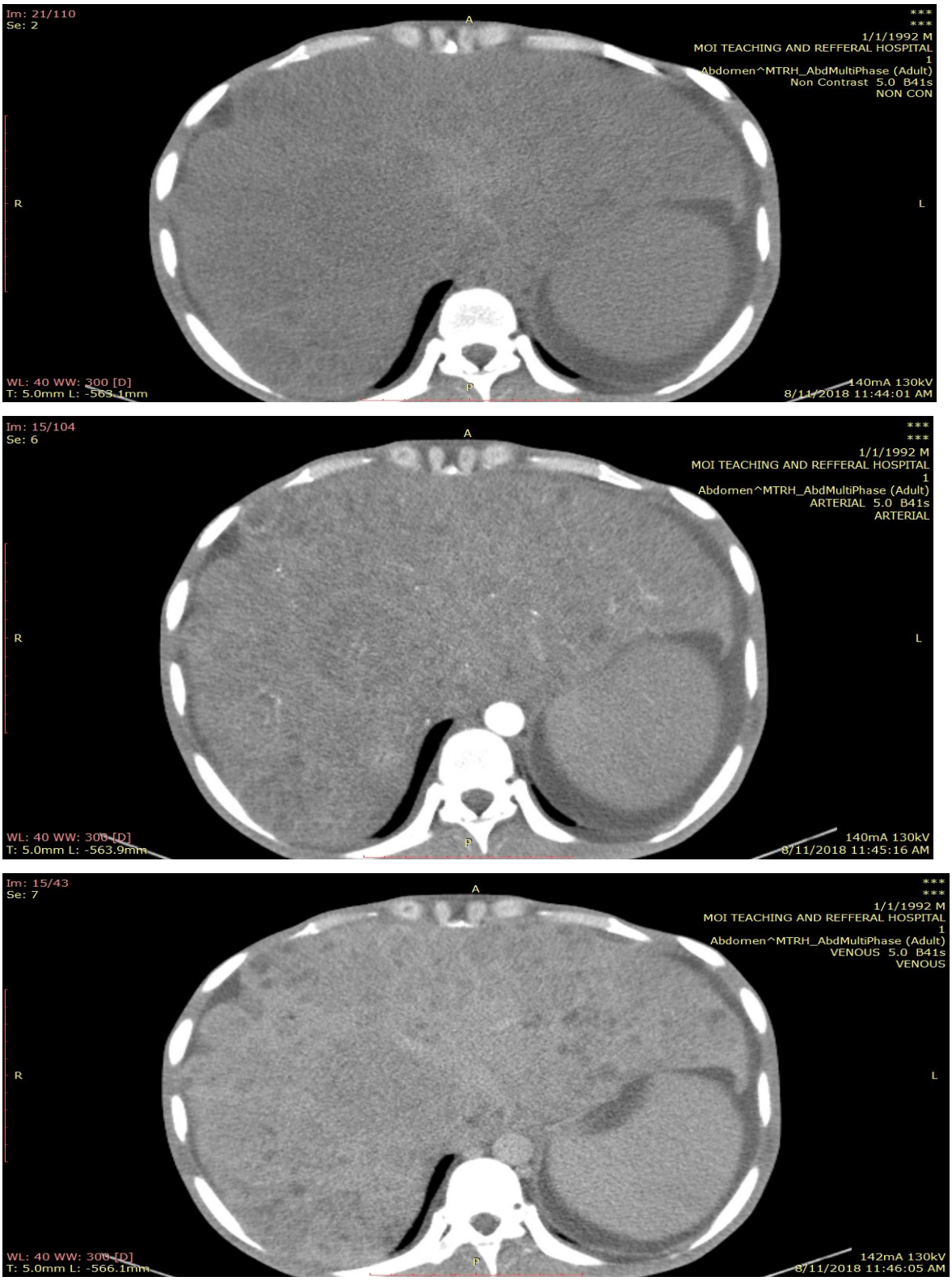

Figure 6: Triphasic scan of a 49 year old male with a multifocal enhancement of the liver and washout and a nodular liver confirmed to be infiltrative HCC.

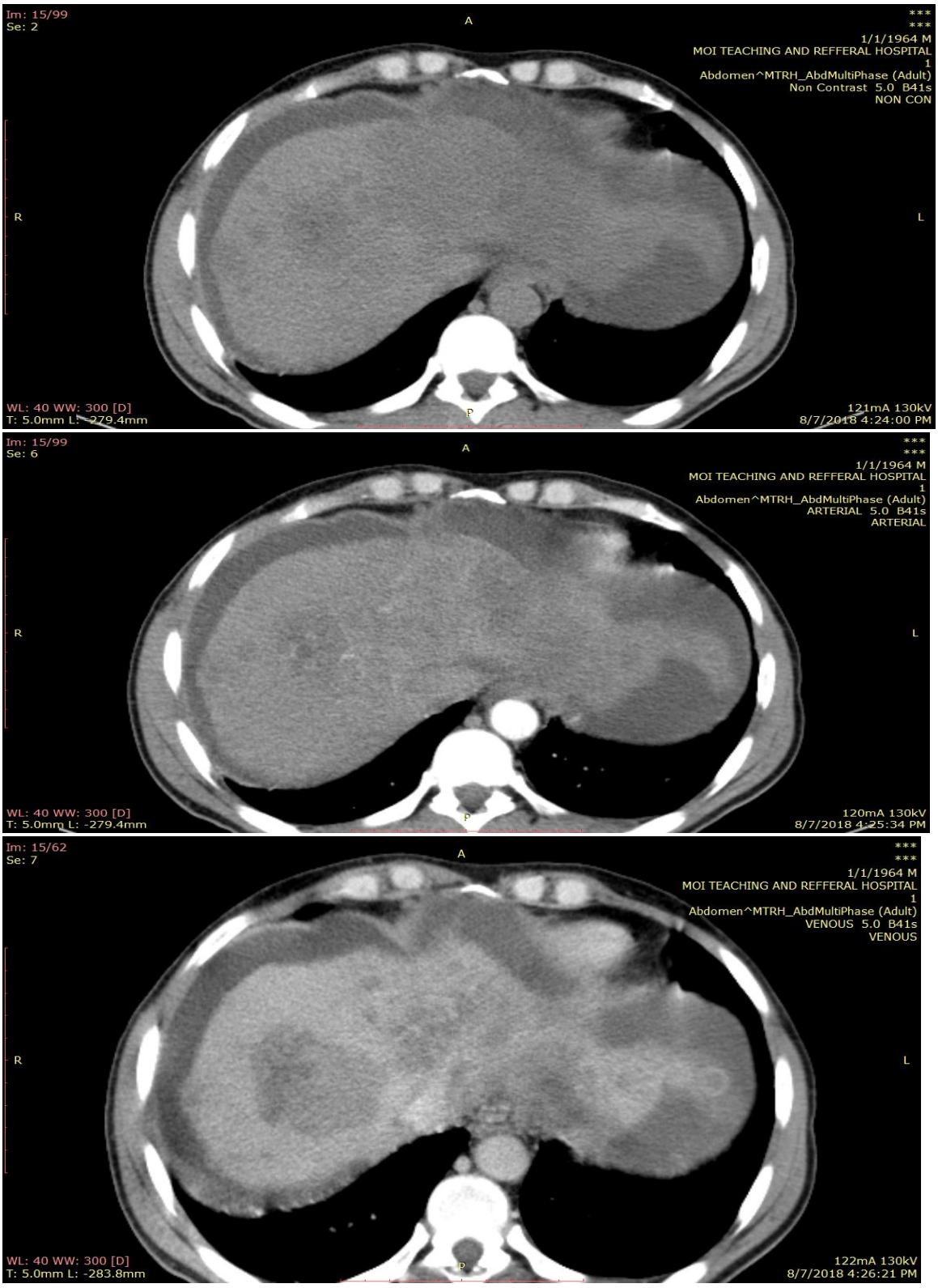

Figure 7: Triphasic scan of a 41 year old male with an ill left hepatic mass (Seg 4a) which had mild enhancement and wash out confirmed to be metastasis.

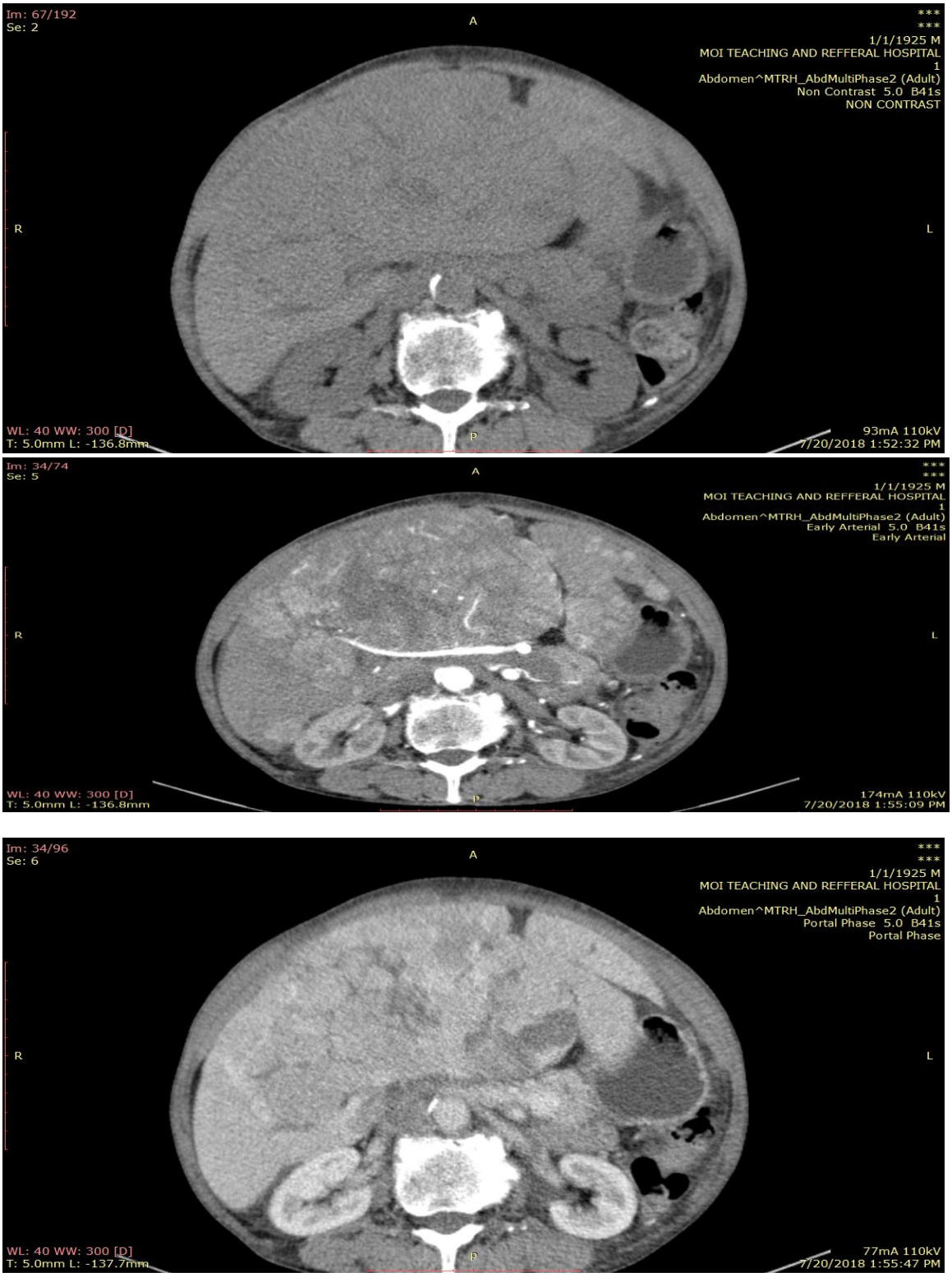

Figure 8: Triphasic scan of a 57 year old male with a left hepatic mass (Seg 4b, 5) which had enhancement and washout and a nodular liver confirmed to be HCC.

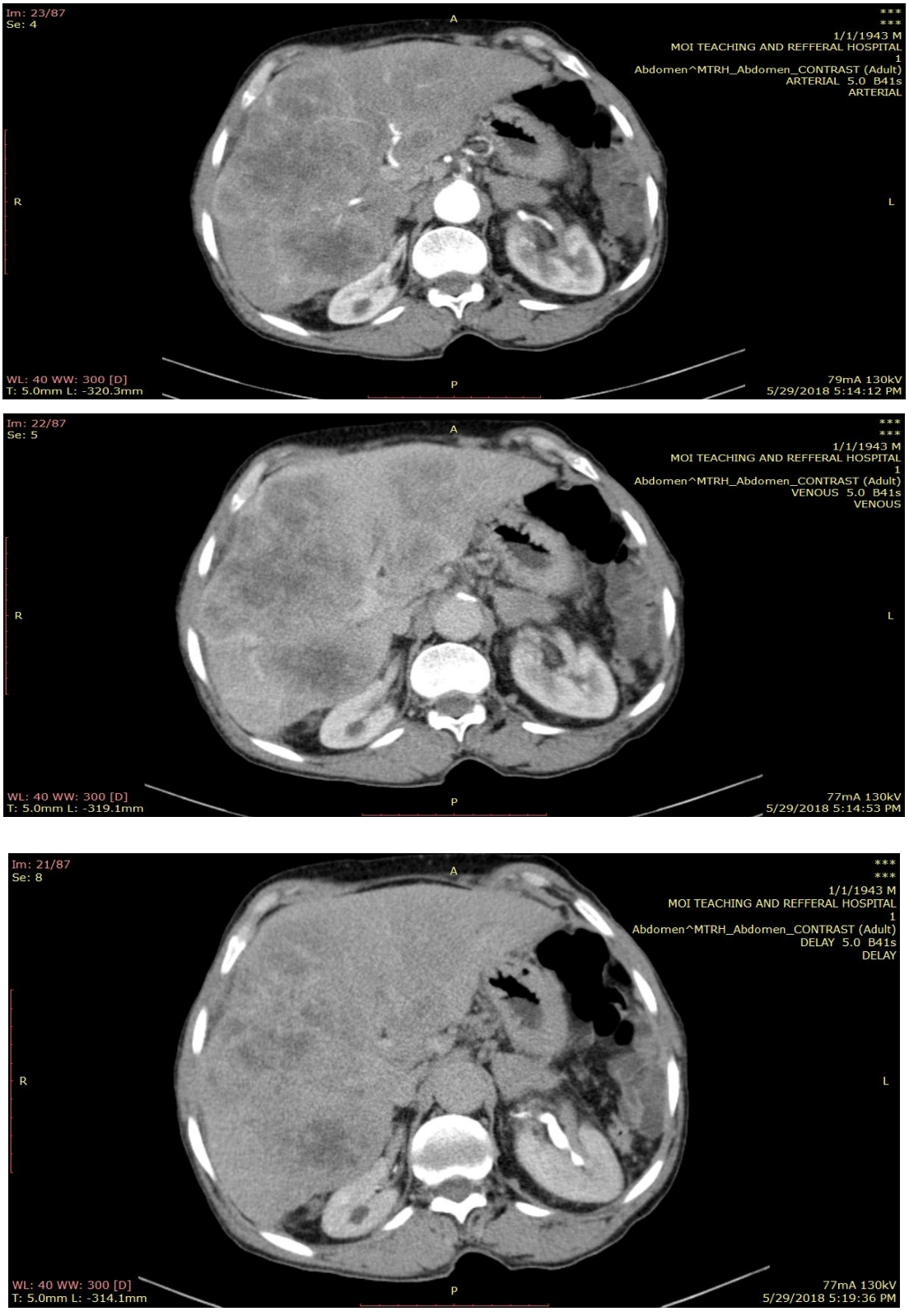

Figure 9: Triphasic scan of a 54 year old female with a right hepatic mass (Seg 5, 6) which had enhancement and washout confirmed to be Cholangiocarcinoma.

4.7 Features of Liver Cirrhosis on CT scan

Table 5: Signs of liver cirrhosis (n=54)

Signs	Frequency	Percent
Surface and parenchymal nodularity	24	58.54
Fatty changes	10	24.39
Atrophy of right lobe	6	14.63
Others	1	2.44
Total	41	100

Table 6: Signs of liver cirrhosis and histopathology findings

	Histopathology findings	
Signs	**No HCC**	**HCC**
Surface and parenchymal nodularity	0	24
Fatty changes	0	10
Atrophy of right lobe	0	6
Others	1	0
Total	1	41

4.8 Histological Diagnosis of HCC

Tissue specimen of the HCC were subjected to histological examination, 88.5%% (n=54) were found to be HCC, 4.9% (n=2) were focal nodular hyperplasia (FNH), 3.3% (n=2) and 3.3% (n=2) were found to be hypervascular metastasis and Cholangiocarcinoma respectively. (Figure 4.13)

All the masses were reported as HCC on triphasic liver CT however the histological diagnosis differed in 7 of the 61 cases studied.

Table 7: Biopsy findings

Variable	Category	Frequency	Percent
Benign	FNH	3	4.92
Malignant	HCC	54	88.52
	Metastatasis	2	3.28
	Cholangiocarcinoma	2	3.28

4.9Association between histopathology findings and CT findings

Table 8: Association between histopathology findings and Enhancement Pattern

Variables	Category	No HCC	HCC	P-value
Hypervascular	No	4	13	0.087
	Yes	3	41	
Washout	No	6	7	
	Yes	**1**	**47**	**<0.001**

Table 9: Association between histopathology findings and presence of a Capsule

Variables	Category	No HCC	HCC	P-value
Capsule	No	4	15	0.190
	Yes	3	39	

The association between capsule and histopathology findings was not statistically significant (p=0.190). (OR 3.4, p=0.13, 95% CI 0.69-17.36)

Table 10: Association between histopathology findings and Signs of Cirrhosis

Variables	Category	No HCC	HCC	P-value
Liver cirrhosis signs	No	6	14	0.004*
	Yes	1	40	

There was significant association between signs of cirrhosis and histopathology findings (p=0.004).

The association between washout and histopathology findings was statistically significant (p<0.001). (OR 40.2, p=0.001, 95% CI 4.19 - 386.45)

The association between hypervascular and histopathology findings was not statistically significant (p=0.087). (OR 4.2, p=0.083, 95% CI 0.83-21.28).

100% of those who had all the 4 features combined were diagnosed of HCC

CHAPTER FIVE

DISCUSSION

5.1 Socio-demographic Characteristics

Majority of study participants, 26.2 %, were from UasinGishu County followed by the neighboring counties of Nandi (18.0%), ElgeyoMarakwet (14.7%), and Trans Nzoia (11.5%). These four counties contributed to 70.1% of the entire study population. The rest (29.9%) were spread over several counties in Western, Nyanza and Rift Valley regions. This distribution reflects the importance and the utilization of MTRH as a regional referral centre for the greater north rift region.

The mean age of participants was 52.7 years with a standard deviation of 9.3 and 59% of them were above the age of 35 years. 59% of all participants were male with a mean age of 53.2 and a standard deviation of 1.4. The mean age for the female participants was 51.9 with a standard deviation of 2.1.

The male to Female ratio was 1.4:1.

This compares well with Mwangi et al who found a peak incidence of 40years in their study in KNH (Mwangi & Gatei, 1993)

This compares well to a study by El-Serag in 2002 which found a male predominance of 2-3 times. (El-Serag, 2002)

This compares well with findings by Kumar in a study in India who found a ratio of2:1(Kumar, Saraswat, Sharma, Sakhuja, & Sarin, 2008).This can be explained by the

fact that Hepatocellular carcinoma is recognized to occur more in men compared to women. (Borgfeldt & Andolf, 1999; Modesitt et al., 2003)

This differed to as study by El-Zayadi in Egypt(El-Zayadi et al., 2005). This can be explained by the geographical differences between the study populations.

Age is a strong determinant in the development of HCC. However more disease is being seen in slightly younger people.

5.2 Objective 1: Triphasic liver CT scan Findings of HCC.

5.2.1 Tumour location

From our study the commonest location of tumours was the right lobe accounting for 59% of all the tumours, This was followed closely by both lobes with 34.4%,and the left lobe was the least with 6.6%.This is consistent with a study by Kumar et al in India who found frequencies of 48%, 34% and 18% respectively.(Kumar et al., 2008)

This however contrasts with a study by El-Zayadi in Egypt in 2005 who found frequencies of 65%,21.6% and 13.4%respectively(El-Zayadi et al., 2005; Kumar et al., 2008). This can be explained by geographical differences in the study population.

The most common symptoms were abdominal pain at 44.3% and abdominal swelling 44.3%. Jaundice at 26.2% and weight loss at 19.7% Triphasic Liver CT and MRI where available are the modalities of choice in evaluating and diagnosing hepatocellular carcinoma. These two are instrumental in confirming the presence of HCC, the consistency, contour, size, and vascularity and also in staging of the disease (Munir, Sultana, & Amin, 2010; Wani & Hammad, 2002). These CT characteristics are crucial in

determining the diagnosis and may be relied upon to start treatment without a tissue biopsy. In this study, all liver masses with suggestive CT features were diagnosed as HCC by the radiologist. Fifty nine percent (39) of them were found in the right lobe. 78.7% of the masses measured more than 2 centimeters in their widest diameter. All the masses enhanced post contrast in the late arterial phase, with 78.7% washing out in the Porto venous phase. 68.8% of them had a capsule in the delayed phase and approximately 67.2% had features of Cirrhosis on CT scan. These findings reflect the common CT characteristics of Hepatocellular carcinoma. A majority of these masses turned out to be HCC on histopathology. Any enhancing mass on late arterial phase with a rapid wash out, in a cirrhotic patient and whose size is greater than 1 centimeter among other factors like presence of a capsule, or risk factors for chronic liver disease are usually considered as HCC (McDonald et al., 2010). In this case, the sizes below 1 centimeter were too small for characterization and follow up with triphasic CT in 3 months was recommended.

5.2.2 Features of Cirrhosis on CT

From our study, of the 54 patients with cirrhosis 67.2% had CT features of cirrhosis at the time of diagnosis. This finding compares well with Kumar study in India who found 59% ((Kumar et al., 2008). This can be explained by the fact that scientifically>1/3 of all cirrhotic patients go on to develop cirrhosis in their lifetime (European Association for the Study of the et al., 2012)

However this differs from a study by Walker et al in the USA who found a much higher percentage(80.1%)(Walker et al., 2016).

This difference can be explained by the fact that in their study, the presence cirrhosis was confirmed based on several modalities which included review of the clinical, biochemical, radiological or histological criteria for diagnosis of HCC.

Another reason for this could be that many clinicians in our setting fail to disclose the diagnosis of cirrhosis before a triphasic CT scan is performed and we only picked the features of Cirrhosis on CT during the diagnosis of HCC.

5.3 Objective 2: Findings of Histopathological Diagnosis

In seven instances, histological diagnoses were not indicative of HCC diagnosed by Triphasic liver CT. Three cases turned out to be focal nodular hyperplasia (FNH) accounting for 4.9%, two cases accounting for 3.3% were Cholangiocarcinomas whereas 2 cases were metastatic (3.3%) on histopathology.

This compares to a study by Sherman et al who found out that most lesions that were larger than 2 cm turned out to be HCC. The majority (84%) displayed typical radiology features and were confirmed by biopsy (Sherman, 2005)

This also compares well with a study by Levy et all who were studying HCC's larger than 3cm and in their findings HCC was confirmed histologically in the 63 of the 65 cases (96.9%) (I. Levy, Greig, Gallinger, Langer, & Sherman, 2001)

This can be explained by the fact that larger HCC's tend to display the EASL radiological criteria hence confirms the EASL recommendations for liver lesions larger than 2 cm (European Association for the Study of the et al., 2012)

5.4 Objective 3: Association between histopathology findings and CT findings

Presence of Cirrhosis was significantly associated with HCC with a p value of 0.004.

This compares well with Mwangi et al in KNH who found a background cirrhosis in 52% of biopsies showing HCC. They concluded that it is clear that a causal association exists between hepatitis B virus (HBV) and both liver cirrhosis and hepatocellular carcinoma. (Mwangi & Gatei, 1993)

This compares well with a study by Kalaitzakis who found similar p values for development of hepatocellular carcinoma in cirrhotic patients (Kalaitzakis et al., 2011)

A study by Zhang et al in China who stratified his risks into various groups found p values of 0.014 for history of hepatitis B, 0.037 for history of hepatitis C and 0.018 for presence of a fatty liver. (Zhang et al., 2015)

Our study however contrasts to Walker et al study in Texas who found odds of 5.0 of developing HCC in cirrhotic patients. This could be explained by the fact that he looked at cirrhosis caused by other things besides HCV and HBV (Walker et al., 2016).

5.4.1 Association between Histopathological diagnosis and Enhancement Pattern.

In our study 72.13% of all HCC's were hypervascular.

This compares to a study by O. I. Karahan who also found that a majority of HCC's were hypervascular at 57% and hypoattenuated in 43% (O. I. Karahan et al., 2003). This can be explained by the fact that by dynamic imaging, HCC diagnosis is established by the detection of contrast hyperattenuation in the arterial phase followed by washout in the portal venous and/or delayed phases. (Bargellini et al., 2014) This pattern is today

defined as “HCC radiological hallmark” and its presence in the setting of liver cirrhosis, it demonstrates HCC diagnosis with almost 100% specificity and positive predictive value for nodules more than least 1 cm in diameter.(Bargellini et al., 2014)

The slight differences in the respective percentages can be explained by the fact that a non-negligible number of HCCs can be hypovascular and thereby lead to a false-negative diagnosis using the imaging criteria(Hennedige & Venkatesh, 2012). It therefore may be useful to further investigate atypical or hypovascular nodules >1 cm with a different imaging technique or subject them to biopsy in order to rule out HCC. (Hennedige & Venkatesh, 2012)

5.4.2 Association between Histopathological diagnosis and Presence of a capsule

The association between capsule and histopathology findings was not statistically significant with a p value of 0.190).

This compares well with a study by Kim et al who found similar findings.(Kim et al., 2018).

This can be explained by the fact that a fibrous capsule is not entirely specific to HCC, however the presence of capsule adds to the strength of diagnosis.

5.4.2 Association between Histopathological diagnosis and Features of Cirrhosis

In our study, 67.2% of our participants had features of cirrhosis at diagnosis.

This compare**s** well with a study by Kumar in India who found 59% of participants with signs of cirrhosis(Kumar et al., 2008).

This can be explained by the fact that >1/3 of all cirrhotic patients go on to develop cirrhosis in their lifetime (European Association for the Study of the et al., 2012).

This however contrasts to Walker et al in the US who found a higher % (80.1%).(Walker et al., 2016) and Sahil Mittal in Texas who found 80.1% (Sahil Mittal et al.,2016)

This can be explained by the fact that cirrhosis confirmed based on clinical, biochemical, radiological or histological criteria in their study whereas in our study we only looked at radiological diagnosis.

Furthermore many clinicians in our setting fail to disclose diagnosis of cirrhosis at time of CT scan.

5.5 Study limitations

1. High cost of CT scans and Biopsy and some patients could not afford.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

1. Mean age of HCC was 52.7 years, with a M:F ratio of 1.4**:**1.
2. Majority of the masses were in the right lobe.
3. 74.1% of all HCC outcome had signs of Cirrhosis.
4. Histology confirmed 88.5% to be HCC.
5. Hypervascular masses, Venous wash out and presence of cirrhosis were significantly associated with HCC.

6.2 Recommendations

1. In the setting of liver cirrhosis, there should be a high index of suspicion for HCC for nodules>1cm by the characteristic “HCC radiological hallmarks”, shown by the detection of arterial phase hyperenhancement and portal or delayed phase wash-out on triphasic liver CT.
2. Larger longitudinal study with more data is needed to verify the usefulness of these newer technologies in the diagnosis of HCC to further look at all the risk factors and to translate them into clinical practice.

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APPENDICES

Appendix I: Consent Form

English Version

Investigator: My name is Dr. NYAGA Kenneth Gitonga. I am a qualified doctor, registered by the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a Masters degree in Radiology and Imaging at Moi University. I would like to recruit you into my research which is Evaluating the Use of Triphasic Liver CT in Correlation to Histopathology in Evaluating Suspected Hepatocellular Carcinoma in MTRH, Eldoret, Kenya.

Purpose: This study will seek to describe the findings of abdominal CT scan examination for hepatocellular carcinoma and to establish whether liver biopsy is important for all the cases.

Procedure: All adult clients presenting with liver masses will be subjected to an abdominal CT scan. These patients will then be interviewed for age and presenting symptoms. Data will be collected on data collection forms. Data collecting material will be kept in a locked cabinet in the office of the principal investigator during the study period.

Benefits: There will be no direct benefits of participating in this study. Study subjects will be accorded same quality of management as non-study subjects. The feedback from my findings will be shared with you and the institution and this will help in management of patients with liver masses in the future.

Risks: There are minimal risks anticipated during the procedure of taking a liver biopsy to the participants attributable to this study but will be well mitigated.

Confidentiality: All information obtained in this study will be treated with utmost confidentiality and shall not be divulged to any unauthorized person

Rights to Refuse: Participation in this study is voluntary, there is freedom to decline to take part or withdraw at any time. This study has been approved by the Institutional Research and Ethics Committee (IREC) of Moi University/Moi Teaching and Referral Hospital.

Sign or make a mark if you agree to take part in the study

Parent/Guardian: …… Investigator: …….. Date:

Kiswahili Version

Mpelelezi: jina langu ni Dr. NYAGA Kenneth Gitonga.Mimi nidaktarialiohitimu,kusajiliwa na bodi ya Kenyaya Madaktari naMadaktari wa meno.Mimi sasanatafutashahada ya uzamili katikaRadiologyna ImagingkatikaChuo Kikuu cha Moi. Ningependakukusajiliwewe katikautafiti wanguambao ni wa kujifunzaumuhimu wa wa kupiga picha ya CT scan kwa kushirikiana na biopsy kwa wagonjwa wenye uvimbe kwenye ini katika eneo la Eldoret.

Kusudi: Utafiti huu utajaribu kueleza umuhimu wa kutumia picha ya CT kugundua uvimbe wa ini bila kufanya utafiti wa biopsy.

Utaratibu: Watu wote ambao watakuwa wanafanyiwa picha ya CT na kupatikana na uvimbe watafanyiwa utafiti wa biopsy kuchunguza zaidi. Kisha wataulizwa maswali madogo kuhusu umri wao na shida walizonazo. Data zitakusanywa kwenye fomu za kukusanya data. Hifadhi zitakazo tumika katika ukusanyaji wa data zitawekwa katika kabati iliyofungwa katika nyumba ya mpelelezi mkuu kwa kipindi cha utafiti.

Faida: Kutakuwa hakuna faida moja kwa moja ya kushiriki katika utafiti huu. Wanaofanyiwa utafiti watakuwa na haki ya kupewa ubora sawa na wale ambao hawatofanyiwa utafiti huo. Matokeo ya utafiti huu yatasambazwa kwa hospitali zinazoshiriki na kwako wewe binafsi na yatasaidia kushughulikia wagonjwa wenye uvimbe kwa ini katika siku za usoni.

Hatari: Kuna hatari kidogo inayotarajiwa kwa washiriki itakayotokana na utafiti huu lakini itashughulikiwa vilivyo ikitokea.

Usiri: Habari zote zilizopatikana katika utafiti huu wa kutibiwa zitawekwa kwa usiri mkubwa na wala haitatolewa kwa mtu yeyote asiye husika kwenye utafiti.

Haki ya kukataa: Kushiriki katika utafiti huu ni kwa hiari yako, kuna uhuru wa kukataa kuchukua sehemu au kutoka wakati wowote. Utafiti huu umeidhinishwa na kamati ya Utafiti wa Taasisi na Kamati ya Maadili (IREC) ya Chuo Kikuu cha Moi na Hospitali ya Rufaa ya Moi.

Kusaini au kufanya alama kama unakubali kushiriki katika utafiti.

Mzazi / Mlezi: ..... Mpelelezi: .....

Tarehe: .....

Appendix II: Data Collection Form

DEMOGRAPHICS

Date: ……. Medical Record Number: ……

Sex…….

Age: …… Serial Number…….

Referred…….Yes ☐ No ☐

County of residence.....

Presenting symptoms……...

Have you had an abdominal CT scan done before in your life? Yes No

If yes was there any abnormality noted? Yes No

If yes specify the abnormality…….

…….

…….

Are you on follow-up or treatment for any Liver disorder? Yes.....No…….

If yes specify……. …….

……

ABDOMINAL CT SCAN EXAMINATION FINDINGS

Reason for Examination

Swelling……..

Pain…….

Yellowness of eyes……

Any other; Specify…….....

……

2. Hepatomegally:

Yes……...No……

3. Presence of a Mass:

Yes……..….No……...

Mass effect; Yes…….. No……

5. Site:

Right lobe…… Left Lobe…… Both……

6. Size

<1cm…….. 1-2cm…… >2cm……

Any other……..

Mean Diameter…….

No. of Masses……..

Detection Phase:

Plain…… Hepatic arterial……. Portal Venous…….

Other……

Unenhanced Phase:

Hypodense…….

Hyperdense……

Enhancement Pattern:

Conspicuity; Yes…… No……..

Hepatic Arterial Phase;

Hypervascular……..Hypovascular……Isoattenuating……

Porto Venous Phase;

Hypervascular……..Hypovascular……Isoattenuating……

Homogenous…….Heterogeneous……

Washout; Yes……..No…….

Peripheral Enhancements; Yes…….. No…….

Tumour Margins:

Smooth……Ill defined……..

Cystic components;

Yes……..No……

Calcifications:

Yes……..…. No…….....

Other Findings……

…….

…….

ULTRASOUND GUIDED BIOPSY FINDINGS

Benign……

Malignant……

Inflammatory……..

Other Findings…….

…….

…….

…….

Appendix III: Assent Form
English version

Information

This informed assent form is for children above 7 years of age who have liver masses suspected to be HCC and subjected to triphasic liver CT and liver biopsy.

What is medical research?

Medical research is when doctors collect information to get new knowledge about disease or illness. This helps doctors find better ways of treating diseases and helping children or people who are sick.

What is this research study about?

This research study is on patients who have liver masses suspected to be HCC and subjected to triphasic liver CT and liver biopsy.

CT scan is used by doctors to see the presence of abdominal masses including the liver. In this study, liver CT findings will be compared to the histopathology findings to decide whether they were helpful in diagnosing the patient. This will help the patients who have suspected liver cancer.

Who is doing this research?

My name is Dr. Nyaga k. Gitonga and I'm a medical doctor. I'm currently studying for my second degree (Masters in Medicine) in Radiology & Imaging at Moi University.

What will happen to me in this study?

I will invite you to be part of this study. If you agree to participate in this study liver CT scan findings will be reviewed, and compared with histopathology findings.

There are no risks or benefits of participating in this study and you will be given the same medical care as the children who are not in the study. You can choose whether or not you

would like to participate in the study. I have discussed this with your parent(s)/ guardian(s) and they know we are asking for your permission to be part of the study. In case you refuse to be part of the study you will not be forced to even if your parents agreed for you to participate.

In case of any questions, feel free to ask, I will be happy to assist.

Certificate of assent

Do you understand this research study and are willing to take part in it?

Yes: …….. No: ……..

Has the researcher answered all your questions?

Yes: ……... No: ……..

Do you understand that you can pull out of the study at any time?

Yes: ……. No: …….

I agree to take part in the study _____

OR

I do not wish to take part in the study, and I have not signed the assent below_____.

Only if child assents:

Name of child _____

Child's thumb print: 

Date: _____

Kiswahili version

Fomu hii ya idhini ni ya watoto walio umri wa zaidi ya miaka saba ambao walio na uvimbe kwenye ini lao.

Utafiti wa matibabu ni nini?

Utafiti wa matibabu ni wakati madaktari wanapopata taarifa ili kupata ujuzi mpya kuhusu magonjwa. Hii husaidia madaktari kupata njia bora za kutibu magonjwa na kusaidia watoto au watu ambao ni wagonjwa.

Utafiti huu unahusu nini?

Utafiti huu unahusishawagonjwawalio na uvimbe kwenye ini. CT scan hutumiwa na madaktari kuona uvimbe ndani ya tumbo na uvimbe kwa ini. Katika utafiti huu, picha ya CT scan itafanywa na matokeo yake kulinganishwa na yale ya biopsy. Hii itakuwa ya manufaa kwa watoto wenye uvimbe kwa ini.

Nanianafanyautafitihuu?

Jina langu ni Dkt.Nyaga K. Gitonga na mimi ni daktari aliyehitimu. Kwa sasa ninajifunza kwa shahada yangu ya pili (Masters in Medicine) katika Radiologia & Imaging katika Chuo Kikuu cha Moi.

Nini kitatokea kwangu katika utafiti huu?

Nitakualika kushiriki katika utafiti huu. Iwapo utakubali, matokeo yako ya picha CT scan ya ini yataangaliwa tena na matokeo ya biopsy kurekodiwa. Baadaya biopsy, ainayauvimbeitarekodiwanakulinganishwanayaleyapichaya CT scan

Hakuna hatari au faida za kushiriki katika utafiti huu na utapewa huduma sawa ya matibabu kama watoto ambao hawatashiriki kwenye utafiti.Unaweza kuchagua kama ungependa kushiriki katika utafiti huu. Nimezungumza na mzazi na/au mlezi wako na anajua tunaomba ruhusa yako kushiriki katika utafiti. Ikiwa unakataa kuwa sehemu ya utafiti huwezi kulazimishwa hata kama wazazi wako walikubali kushiriki.

Ikiwa kuna maswali yoyote, jisikie huru kuuliza, nitafurahia kusaidia.

Hati ya kukubali

Je unaelewa utafiti huu na uko tayari kushiriki?

Ndio: ..... La: .....

Je, mtafiti alijibu maswali yako yote?

Ndio: ..... La: .....

Je unaelewa kwamba unaweza kuondoka kwa utafiti huu wakati wowote?

Ndio: ……. La: ……

Nakubalikushirikikatikautafitihuu _____

AU

Sitaki kushiriki katika utafiti huu na sijasaini idhini hii _____

Ikiwatumtotoataidhinisha:

Jina la mtoto: ……..

Alama ya kidole cha mtoto:

Tarehe: ……

Appendix IV: Procedure for Doing an Abdominal CT scan.

Helical scanning was performed with a CT 32 Slice scanner. Scan parameters were identical for each phase: 1:1pitch, 110-130kV, 80-100mAs and 5-mm slice thickness.

The scan time and number of slices were varied with the volume required to cover and the patient's ability to hold his or her breath. Multiple slices covering 14.5 cm were obtained with a breath-hold of 16sec. Scanning was performed after IV injection of 1.5mls/kg of Iohexol.

Administered starting at 4mls/sec and titrated depending on the weight of the patient using 18-gauge IV catheter placed in an antecubital vein.

Our triphasic helical CT examinations consisted of obtaining images during the unenhanced hepatic arterial and portal venous phases. Initial images were obtained without IV contrast material. Arterial phase images were obtained after a delay of 8-10seconds for early arterial and 12-15 seconds for late arterial after injection of contrast material, and portal venous phase images were obtained 20-25 seconds after injection, and delayed images after 3 min.

Image Evaluation

Hard copy images were read by the principal investigator and reviewed two consultant radiologists who were unaware of patient history. The unenhanced phase, hepatic arterial phase, and portal venous phase images were viewed for the presence of focal liver lesions. The CT appearance of each lesion in each phase was characterized by its attenuation compared with that of the surrounding hepatic parenchyma in that phase. Masses were categorized as hypervascular-hyperdense relative to the surrounding parenchyma or hypovascular -hypodense compared with the surrounding parenchyma. Lesion size and conspicuity on each phase were then noted. Images of the different phases initially were analyzed separately at different times without knowledge of results of the other phases and subsequently were interpreted together. Total lesion number was established by combining those visualized on each scan phase that were subsequently proven by biopsy. Lesion conspicuity was graded.

Appendix V: Procedure for Doing an Ultrasound Guided Liver Biopsy

The biopsy procedure was explained to the patient and informed consent sought to carry out the procedure.

The skin of the area to be biopsied was washed with antiseptic and draped.

A fine needle was used to give local anaesthetic to numb the area for biopsy.

Then a small nick or cut was made in the skin.

Under antiseptic precautions and using a coaxial needle size 17 or 19 and during suspended respiration several core biopsies were taken from the liver.

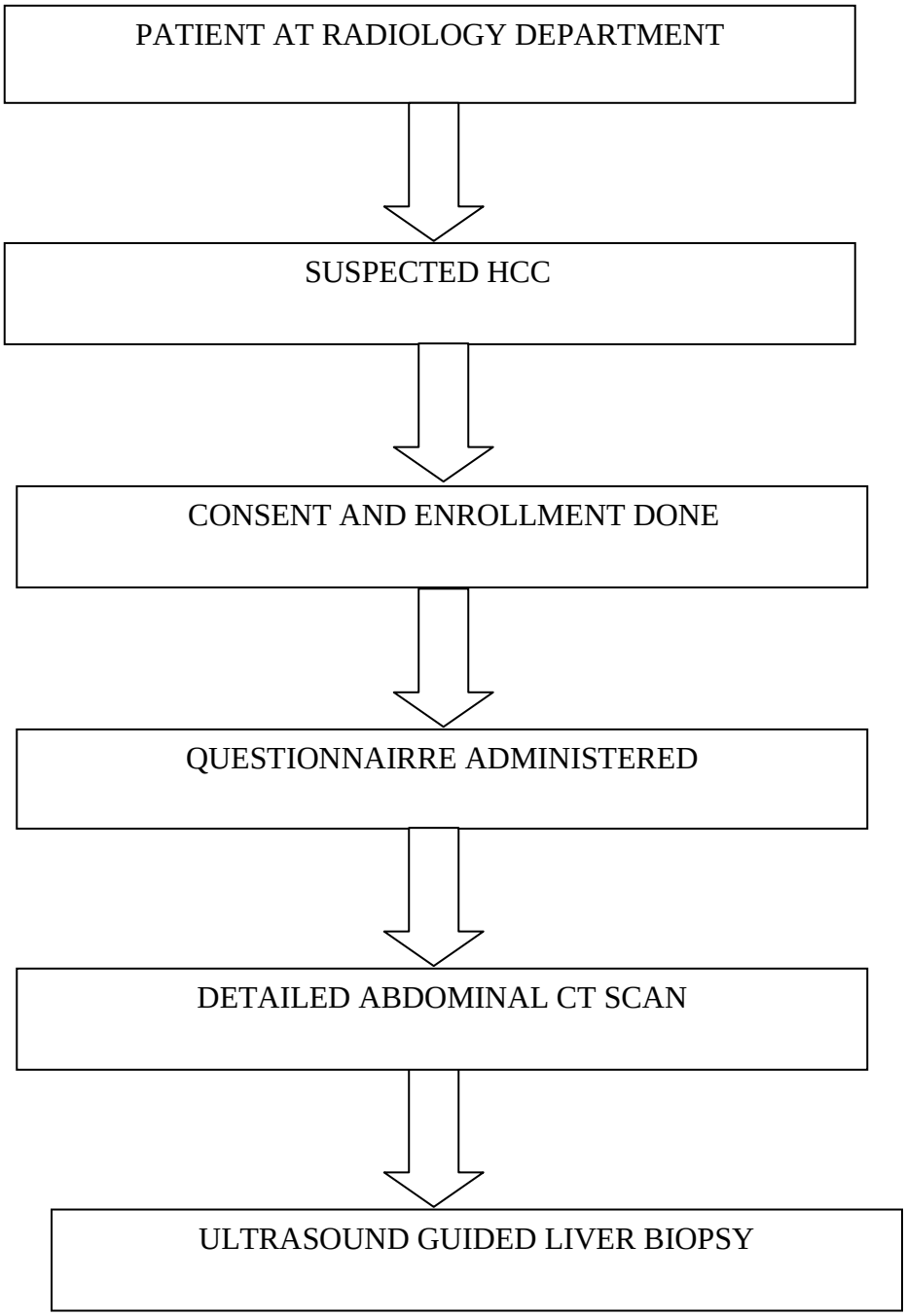
Monitoring of pulse, respiration and blood pressure was done for 4-6 hours. Several samples between 3 and 6 were taken.

After the samples were taken, the biopsy area was pressed for a few minutes to reduce bleeding, and then dressed.

The samples were processed and sent for histopathology analysis and smears were prepared and fixed in 95% methanol for Papanicolaou (PAP) and hematoxylin and eosin (H and E) and examined under a microscope.

Findings were recorded for analysis. The results of biopsy were evaluated and categorized into benign, malignant and inflammatory groups

Appendix VI: STUDY PROCEDURE



Appendix VII: Consent for doing a Biopsy

I……..having been explained to the procedure of doing a liver biopsy, its advantages and possible complications do hereby agree to undergo the procedure at my own free will.

Name:

Signature:

Witness

Name……

Signature:

Appendix VIII: IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference IREC/2017/66
Approval Number: 0001950

16th August, 2018

Dr. Kenneth Nyaga Gitonga,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
16 AUG 2018
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Gitonga,

RE: APPROVAL OF AMENDMENT

The Institutional Research and Ethics Committee has reviewed the amendment made to your proposal titled:-

"Triphasic Liver CT Evaluation of Hepatocellular Carcinoma in Comparison to Histopathology in MTRH, Eldoret".

We note that you are seeking to make an amendment as follows:-

1. To change the title to above from ***"Validating the Use of Triphasic Liver CT in Correlation to Histopathology in Evaluating Suspected Hepatocellular Carcinoma in MTRH, Eldoret".***

The amendment has been approved on 16th August, 2018 according to SOP's of IREC. You are therefore permitted to continue with your research.

You are required to submit progress(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change(s) or amendment(s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: CEO - MTRH; Dean - SPH; Dean - SOM
Principal - CHS; Dean - SOD; Dean - SON

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2017/66
Approval Number: 0001950

27th September, 2017

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
27 SEP 2017
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dr. Kenneth Nyaga Gitonga,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Gitonga,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"Validating the Use of Triphasic Liver CT in Correlation to Histopathology in Evaluating Suspected Hepatocellular Carcinoma in MTRH, Eldoret".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1950*** on 27th September, 2017. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 26th September, 2018. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix IX: Hospital Approval

An ISO 9001:2008 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone:(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

3rd October, 2017

Dr. Kenneth Nyaga Gitonga,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Validating the Use of Triphasic Liver CT in Correlation to Histopathology in Evaluating Suspected Hepatocellular Carcinoma in MTRH, Eldoret".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

03/10/2017

DR. WILSON K. ARUASA
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - DCEO, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM