RESEARCH ARTICLE

CORRELATION AMONG CLINICAL INDICATIONS, IMAGING PATTERNS AND HISTOPATHOLOGY OF LIVER LESIONS IN PATIENTS REFERRED FOR ULTRASOUND GUIDED LIVER BIOPSIES AT MOI TEACHING AND REFERRAL HOSPITAL (MTRH), KENYA.

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Manuscript Info

Abstract

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Background: Liver biopsy is a core investigation tool in the evaluation and subsequent management of patients with liver neoplasms or inflammatory conditions. Liver biopsy is useful in making diagnosis, assessing the prognosis of liver diseases and in making decisions for therapeutic management. Interventional radiology is a rapidly growing subspecialty, with very few personnel generally, more so in developing countries. Ultrasound guided percutaneous liver biopsy is currently being done in only two public facilities in Kenya. This study evaluated the clinical indications, imaging and histopathological diagnosis of liver diseases observed in our setting from ultrasound guided liver biopsies.

Objectives: To describe the clinical indications, imaging patterns and histopathological diagnoses of liver diseases diagnosed by ultrasound guided liver biopsies at Moi Teaching and Referral Hospital.

Methods: This was a cross sectional study done at the Moi Teaching and Referral Hospital (MTRH) in Kenya, in the departments of Radiology &Imaging and Histopathology. All consenting patients referred for ultrasound guided liver biopsy were studied with a sample size of 36 patients, over one year period. Data was collected prospectively from the patients. A structured data entry form was used to gather all the information. Data was analyzed using descriptive statistics with the aid of STATA version 12 special edition. The test for agreement between two raters was done using Kappa test.

Results: The working clinical diagnosis from the referring clinician showed that 22(63%) participants had hepatocellular carcinoma (HCC), 1(3%) had hydatid, 1(3%) had an incidental finding, 3(9%) had lymphoma, 1(3%) and 7(20%) had metastasis. On the histopathology results, HCC was the commonest pathology that was diagnosed (n=21). Most HCC lesions were larger than 5cm (n=18, 90%) and 85% of these lesions were heterogeneous on sonography. There was a moderately strong kappa value (kappa=0.511) for the level of agreement between sonographic and histological diagnosis of liver cancer. The only complication was pain (n=21, 60%).

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Conclusions: The commonest indication for patients referred for ultrasound guided liver biopsies was to establish a diagnosis for suspected malignancy. Hepatocellular carcinoma was the commonest liver malignancy diagnosed in Moi Teaching & Referral Hospital. There was a good agreement between sonographic and histopathological diagnosis. The major indication for ultrasound guided biopsy is diagnosis for suspicions of hepatocellular carcinoma and metastases to the liver.

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Introduction:-

Traditionally, liver biopsy has been performed by physicians as a bedside procedure using the so-called blind biopsy. The site was identified based on the clinical acumen of the clinician, which depended highly on the physical examination of the patient, more so, palpation of the site, available history as well as clinical investigations that have been done. This method was associated with many difficulties. Identification of the organ might be difficult especially in the face of other complications such as ascites or anatomical variation in individuals' liver. This could result in failure to obtain hepatic tissue during biopsy without imaging. The other disadvantage of blind biopsy is that the quality of biopsy might be compromised and fragmentation would occur.

In everyday clinical practice, an increasing number of liver biopsies are performed by radiologists under ultrasound control[1,2]. Ultrasonography, as well as being a good screening test for liver disease allows selection of the optimal puncture site before performing biopsy[2]. The use of ultrasonography by marking the site for percutaneous biopsy has been reported to increase diagnostic yield and decrease complication rates[3]. Currently, ultrasound guidance is used in more than half of percutaneous liver biopsies. This has led to a decrease in the rate of severe complications by one third[4].

Whether or not a histological diagnosis may be useful for optimal management of a patient can best be judged if the clinical question has been well defined before the biopsy is performed. Morisod J. *et al* (1988) found that liver biopsy confirmed the clinical diagnosis in 62.4% of the cases reviewed and fundamentally modified the diagnosis in 20.2%, concluding that liver biopsy remains an indispensable diagnostic procedure in the field of hepatology, since it can result in modification of the clinician's diagnosis in one out of five cases.[5]

Ultrasound guided biopsies are generally a costly procedure for patients in resource scarce settings as compared to the blind percutaneous biopsies. It costs on average $50 in a setting where about 50% of the population earns less than a dollar per day. It also requires skilled personnel that are only found in well-equipped facilities which more often are in the bigger cities. These facilities are normally out of reach for the general population. Interventional radiology is a relatively new field in Kenya and its use in our set up has not been evaluated.

There is paucity of information on the liver diseases observed in Kenya. The available data is from clinical records in Nairobi and Eldoret based Cancer registry centers. This documents malignancies only. Liver cancer causes high morbidity and mortality in Sub-Saharan Africa.[6] Nairobi cancer registry revealed an age standardized liver cancer incidence rate of 5.3% and Eldoret Cancer Registry documents it at 2.5%.[7]

Hepatitis B virus is prevalent in Kenya. It has a strong preference for infecting liver cells inducing diseases such as chronic hepatitis, cirrhosis and hepatocellular carcinoma. A study in rural Turkana in Kenya documents a Hepatitis B Virus (HBV) surface antigen prevalence at 8% among males and 9.41% among females. The study also found that of the 88 biopsies done, 89% had hepatocellular carcinoma.[8]

The study aimed at documenting the patterns of liver diseases observed. It also described the sonographic patterns of liver diseases diagnosed and assess the level of agreement with the definitive histological diagnosis.

There has been a progressive increase in the number of liver biopsies being done in the Department of Radiology and Imaging at Moi Teaching and Referral Hospital (MTRH). This is attributable to the benefits accrued from direct visualization of biopsy site in ultrasonography as opposed to blind biopsies. Ultrasound is an available modality that

can identify most liver pathologies with no radiation. There is paucity of information on liver diseases in Kenya yet the liver is an easily accessed organ for interventional procedures.

With the increase in image guided liver biopsies, an analysis of the liver disease patterns observed in our setting can be studied and documented, taking stock of the clinical indications and complications during the procedure.

The study acts as a baseline for development of subsequent related studies in Kenya especially in interventional procedures.

Percutaneous liver biopsy (PLB) is a commonly performed procedure carried out for the diagnosis and management of patients with parenchymal liver diseases[9].

Indications of Liver Biopsy:-
Percutaneous liver biopsy remains an important diagnostic procedure for the management of hepatobiliary disorders. Modern biochemical, immunologic and radiographic techniques have facilitated the diagnosis of liver disease but have not made biopsy obsolete. In each individual case the indication for liver biopsy depends on assessment of the risks relative to the potential benefits of the procedure.

In a study by Gilmore *et al* (1995) (n=1500), the indications varied by age; in those under 65, 50% were performed for suspected chronic liver disease and 25% for suspected malignancy, whereas in those over 65 these percentages were reversed to 25% and 50% respectively[10].   Of those biopsies performed for suspected malignancy, 10% were seeking definitive evidence of a primary hepatocellular carcinoma. Follow up of liver transplantation, accounted for only 1% overall

Diagnosis of Hepatic Neoplasms and Other Focal Lesions:-
Diagnosis of space-occupying lesion (SOL) is one of the traditional application of liver biopsy and even remains useful today as more and more SOL are being identified as incidental findings or during routine screening for cancer or other conditions. FNA might be able to provide tissue diagnosis in most of these cases. In a Kenyan study by Shiramba *et. al* (2010)(n=120) on utility of FNA on liver diseases diagnosis, 42% of the patients had malignant cells; 30% had necrotic material aspirates 4% showed fatty changes which later showed to be liver cirrhosis; 22% showed normal hepatocytes.[11]

Core liver biopsy may be necessary to provide sufficient tissue for immunohistochemistry for identifying unknown primary. Biopsy of focal lesions should be done only after clinical and imaging data have confirmed a solid mass. Biopsies must not be performed on cysts, abscesses, or haemangiomas. If biopsy of a focal lesion is necessary for diagnosis, it is best obtained by ultrasound- or CT-guided fine-needle aspiration. A solid tumour in a cirrhotic liver or an alpha fetoprotein level >400 ng/mL in the presence of a solid tumour is diagnostic of hepatocellular carcinoma, and biopsy rarely adds to management. However, increased alpha fetoprotein levels in the setting of active liver disease without a focal lesion may reflect a diffuse tumour and in such cases biopsy may be helpful. The role of percutaneous liver biopsy in the diagnosis of focal liver lesions depends largely upon the clinical picture. In most patients with malignant hepatocellular carcinoma ultrasound scanning, CT, and measurement of serum alfa fetoprotein will allow a diagnosis to be made (in the context of a space-occupying lesion in a cirrhotic patient). Similarly, a patient with a history of colonic resection for neoplasia who presents with a solitary lesion in the liver associated with raised serum carcinoembryonic antigen, may not require a biopsy of the lesion to make the diagnosis of a potentially resectable metastasis. Liver biopsy also carries a documented risk of seeding tumours down the biopsy track.[12] The magnitude of this risk is currently unknown. Modern imaging techniques can also help to define other types of focal hepatic lesions such as haemangioma and focal nodular hyperplasia. In these situations, some experts believe that the risk of bleeding after biopsy of a malignant tumour is greatest when the tumour is superficial and so recommend traversing normal liver before sampling tumour tissue[13]. Fine needle aspiration biopsy may be a safer option if material for histological examination is required in the case of a suspected angioma.[14]

Unexplained Hepatomegaly:-
The liver may enlarge as a result of various insults, including amyloid disease, Cushing's syndrome, genetic metabolic disorders, alcoholic liver disease, cryptogenic cirrhosis, and neoplasms. Biopsy can often identify the cause of hepatomegaly and perhaps exclude an incorrect clinical diagnosis.[13]

Methods:-

Study site: The study was conducted at Moi Teaching and Referral Hospital (MTRH), in North-West Kenya. It is a fully-fledged referral facility with 800-bed capacity. It offers a wide range of health services both Out-Patient and In-Patient. It also provides specialized services such as Oncology, Neurosurgery, Cardiothoracic, HIV care, Pediatric surgery amongst others. Most patients referred for the specialized services require specialized investigations including radiological investigations like Computerized Tomography (CT) scans, Ultrasounds and Ultrasound guided biopsies, Contrast studies; Histopathology; Immunochemistry and biochemical investigations.

Study design: This was a cross sectional study.

Study population: All patients referred to radiology department at MTRH for ultrasound guided liver biopsies.

Study variables: The dependent variables were clinical indications, ultrasound and histological diagnosis made from the biopsy sample collected under ultrasound guidance.

The independent variables were socio-demographic data such as age, sex, alcohol consumption, history of hepatitis, outcome of the biopsy, liver function tests, complete blood count, coagulation profile, other investigations like ultrasound, abdominal CT scan.

Data collection technique: Data was collected from the hospital records and the other information obtained from the patients or guardians.

Technique: The technique used was ultrasound guided percutaneous core biopsy using a non-suction tru-cut biopsy needle as per our hospital protocol. Some patients had ascites. The ascites was drained prior the biopsy procedure and the drain remained in situ after the procedure. The children were mildly sedated by a paediatrician on site during the procedure.

The definitive diagnosis from the histopathology results was then recorded.

Data processing and analysis:-

Data was analysed using descriptive statistics to give frequency of the indications for the biopsy, ultrasound diagnosis and histopathological diagnosis. Measures of central tendency like the mean and median age were analysed. Analytic statistics was used to assess for the association between the independent and the dependent variables

Results:-

Clinical Impression:-

There were 2(6%) participants who had confirmed liver disease. The two were positive for hepatitis B. The working clinical diagnosis showed that 22(63%) participants had HCC, 1(3%) had hydatid, 1(3%) had an incidental finding, 3(9%) had lymphoma, 1(3%) had hematoma, and 7(20%) had metastasis (Figure 1). The results (Table 1) on indications for biopsy showed that 8(24%) participants required establishment of the diagnosis while 25(74%) required the confirmation of establishment of the diagnosis. The diagnosis in the later was suspicion for HCC or metastasis. One had an incidental finding.
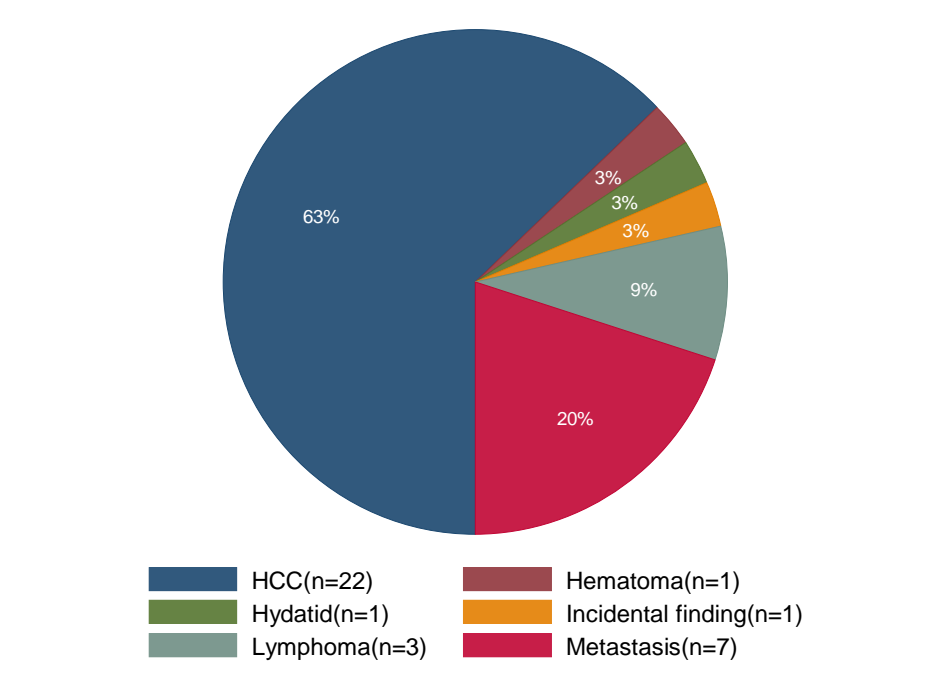
Figure 1:- Working clinical diagnosis

Table 1:- Clinical details

Variable	Sample size	Levels	n(%)
Confirmed liver disease	36	Yes	2(6%)
		Find	8(24%)
Indication for biopsy	36	Suspicion of HCC & Metastasis	25(74%)
		Incidental	1(3%)

Ultrasound patterns of the liver diseases:-
The ultrasound findings showed that 35(97%) participants had discrete lesions. Of those with discrete lesions were 28(80%) with lesions >5cm in size. The number of lesions were grouped into multiple and solitary. There were 19(54%) participants with multiple numbers of discrete lesions. The rest had solitary discrete lesions.

More than three quarters of the participants had heterogeneous discrete lesions. The margins of these lesions for 17(48%) participants were circumscribed, lobulated for 10(29%) participants, obscured for one participant and indistinct for 7(20%) participants. The shape of the lesion was round for majority of the participants, 19(54%). One quarter of the participants had the lesion located in the left lobe 14(40%), while 12(34%) were located on the right lobe.

Indications for ultrasound guided liver biopsies at MTRH:-
Out of 39 participants, 36(92%) qualified for ultrasound guided liver biopsy. One of those who did not qualify had a gall bladder neck mass and the risk of biliary peritonitis was high. The other two participants had INR values greater than 1.5. The indication for ultrasound guided biopsy in 74% of the participants was to confirm a diagnosis, whereby the clinician suspected HCC or metastasis. In 24% of the participants it was to establish a diagnosis. There was one case of incidental finding.

Liver biopsy samples were obtained by percutaneous core needle biopsy. The biopsy route of access was sub costal for 33(94%) participants and transthoracic in 2(6%) participants. The number of passes made was two for 3(9%) participants, three for 26(74%) participants and more than three times for 6(17%) participants. Of those who had more than 3 passes, 85% developed pain as a complication.

The immediate complication observed was pain among 21(60%) participants of which 20(95%) had pain at the sub costal percutaneous core needle biopsy route. Fourteen did not report/develop any complication. No one was admitted because of these complications. Two thirds, 14(67%), of those who had pain were female. This represented 67% among the female participants compared to 50% among the male participants. The test for association between the complications and gender was not statistically significant (P=0.324).

The histological findings were non-specific in 2(6%) participants. Thirty three, 94%, yielded positive findings. The histological findings were as shown in Figure 2.
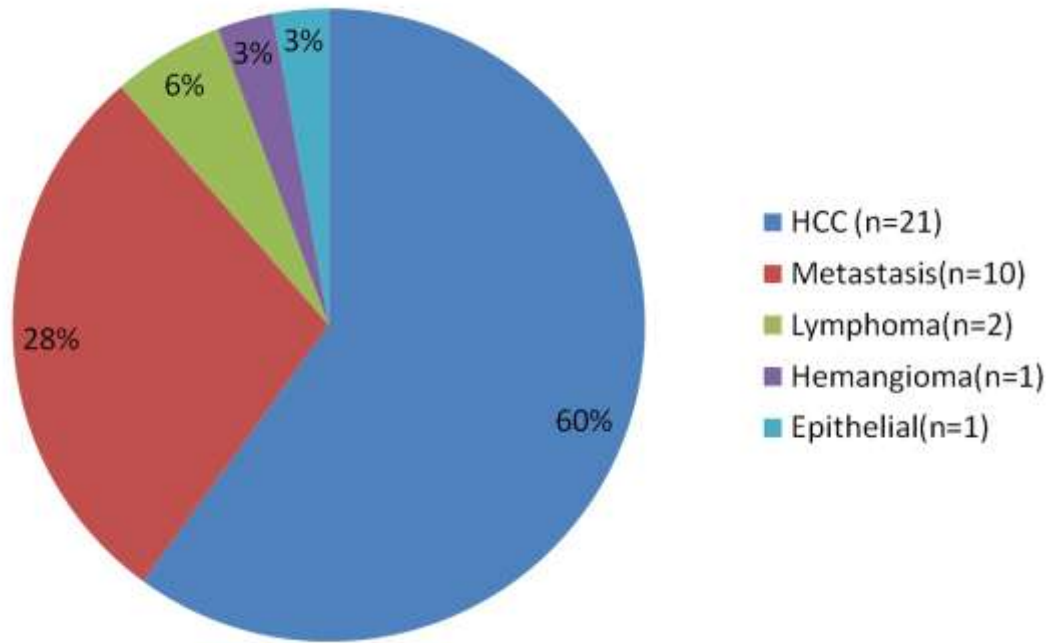

Figure 9:- Specific histological findings

Stratified by gender the specific histological findings were as given in Figure 9.
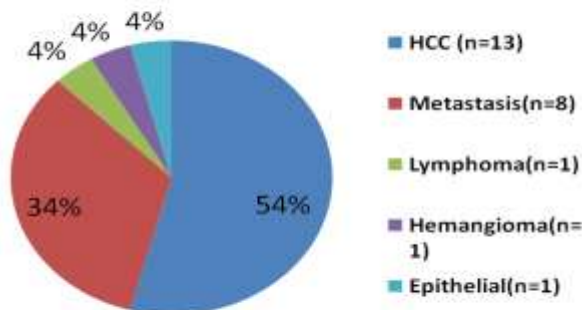

Figure 10:- Specific histological findings by gender

The test for association between the specific histological findings and gender was not exP=0.630).
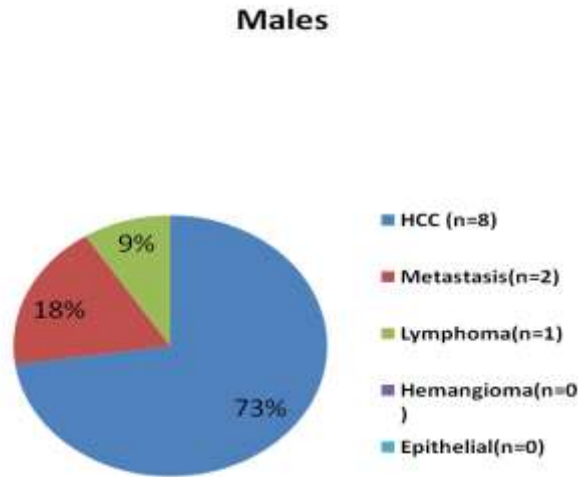
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Fig 2: Specific histological findings

Figure 10:- Specific histological find
Figure 3:- Specific histological findings by gender

Sonographic findings with histological diagnoses of liver diseases:-
The agreement between the sonographic finding and the histological findings was assessed and the test for agreement conducted. A weighted kappa value was used. This was meant to give more credit to the observers who were able to agree with the finding and a small weight when they were so different.

The calculated kappa was 0.511 = (51.1%), 95% CI: 23.3% - 78.9%. This value is significantly different from zero (P=0.0002) implying that the level of agreement between the two raters was not due to chance (Table 2). This value of Kappa demonstrates that the level of observed agreement of 83.9% is of moderate strength (Landis and Koch, 1997)[15].

Table 2:- Agreement between the sonographic and histological diagnosis

		B							
		HCC	Hama	Hema	Lymph	Mets	Epith	Adeno	Total
	HCC	16	0	0	1	3	1	0	21(60%)
	Hama	1	0	0	0	0	0	0	1(3%)
	Hema	0	0	1	0	0	0	0	1(3%)
A	Lymph	1	0	0	1	1	0	0	3(9%)
	Mets	1	0	1	0	5	1	1	9(26%)
	Adeno	0	0	0	0	0	0	0	0
	Epi	0	0	0	0	0	0	0	0
	Total	19(54%)	0	2(6%)	2(6%)	9(26%)	2(6%)	1(3%)	35(100%)
Observed Agreement: 83.9%, Expected Agreement: 66.9%, Kappa: 0.511, Std. error: 0.142, Z: 3.60, P=0.0002									

Key
A: Sonographic impression
B: Histological findings
Hama: Hamartoma, Lymph: Lymphoma, Mets : Metatasis, Epi: Epithelial tumours,   Adeno: Adenocarcinoma, Incid: Incidental finding, Hyd: Hydatid

Similarly, the agreement between the histological diagnosis and the working clinical diagnosis was assessed (Table 8) and the Kappa test of agreement performed. The level of observed agreement was 81.3% against the expected agreement of 72.5%. The value of Kappa calculated was 0.318 = (31.8%), 95% CI: 5.3% - 58.3% and it was

significantly different from zero (P=0.0009) implying that the level of agreement was not due to chance. This value of Kappa shows that the level of observed agreement of 81.3% was fair according to Landis and Koch (1997)[56].

Table 3:- Agreement between the working clinical diagnosis and histological diagnosis

		HCC	Hama	Hema	Lymp	A Mets	Epi	Adeno	Incid	Hyd	Total
	HCC	14	0	1	1	3	2	0	0	0	21(62%)
	Hama	1	0	0	0	0	0	0	0	0	1(3%)
	Hema	0	0	0	0	0	0	0	0	0	0
B	Lymp	1	0	0	1	1	0	0	0	0	3(9%)
	Mets	1	0	1	0	4	0	1	0	0	7(21%)
	Incid	0	0	0	0	1	0	0	0	0	1(3%)
	Hyd	1	0	0	0	0	0	0	0	0	1(3%)
	Total	18(53%%)	0	2(6%)	2(6%)	9(26%)	2(6%)	1(3%)	0	0	34(100%)
Observed Agreement: 81.3%, Expected Agreement: 72.5%, Kappa: 0.318, Std. error: 0.135, Z: 3.36, P=0.0009										

Key
A: Histological diagnosis
B: Working clinical diagnosis
Hama: Hamartoma, Lymp: Lymphoma, Mets : Metatasis, Epi: Epithelial tumours,   Adeno: Adenocarcinoma, Incid: Incidental finding, Hyd: Hydatid
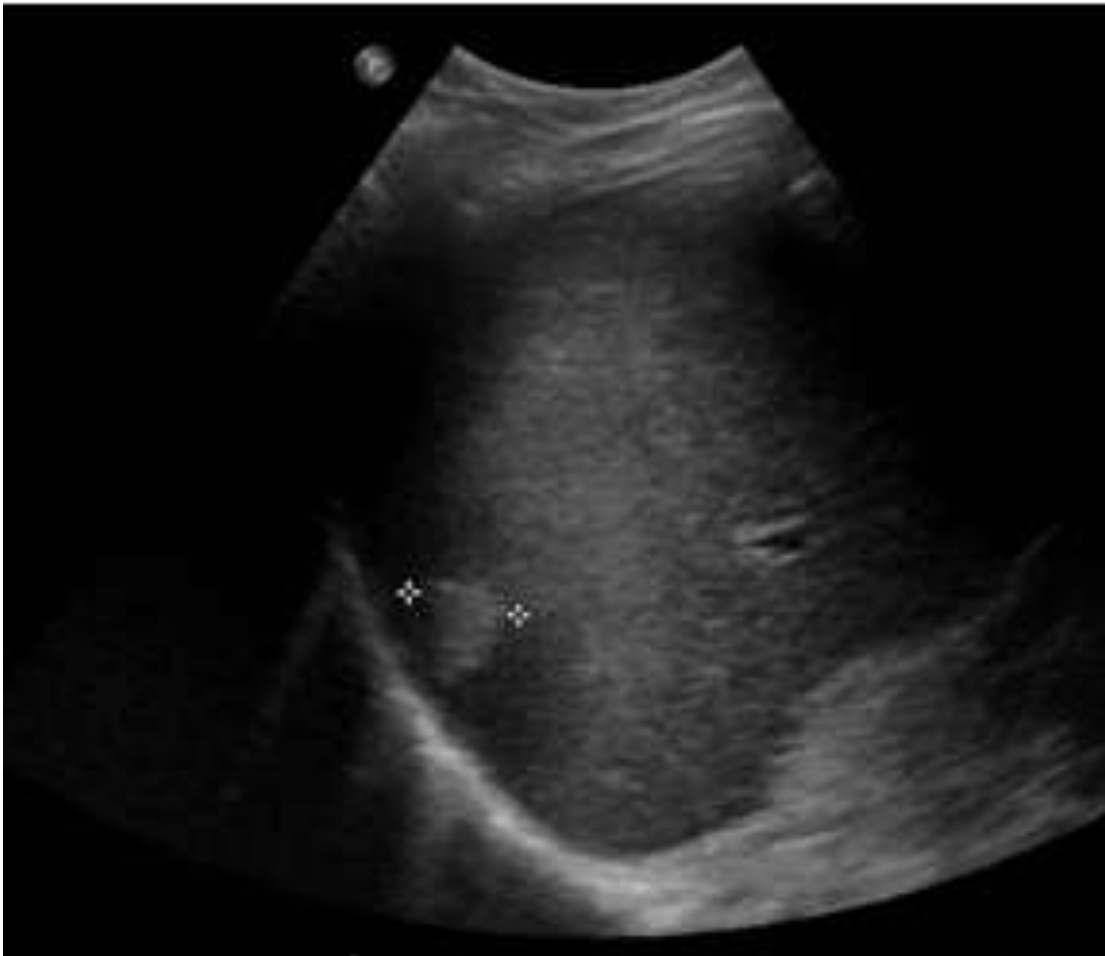
Some of the Images

Figure 4:- Ultrasound Image of a 60yr female with a solitary right lobe lesion: Histopathology confirmed it was a hemangioma

Figure 5:- Ultrasound image of a 40 year male on anti-retrovirals for HIV/AIDs with a solitary slightly hyperechoic right lobe mass of the liver. Histopathological diagnosis was a lymphoma

Discussion:-

Demographic characteristics of liver diseases:-

According to Spilios *et al* (2007), Liver cancer prevalence varies by gender and most common among men[3]. In this study, 22(61%) participants were female. More than half of the participants, 19(53%), were aged above 40 years with those aged at least 60 years contributing the greatest proportion in this group. Among those aged below 40 years were those aged between 30 and 40 years who contribute the largest, 33%, among this group of participants

The analysis was further restricted to HCC. The age distribution of patients with HCC showed two peaks and 60% of the participants were females. The participants aged between 30 to 40 years contributed the highest percentage, 44%. The second peak was among participants above 60 years who accounted for 31%. This result is similar to a study done by Mwangi *et al*. (1993) in Kenya which showed that HCC had a peak incidence at 40 years of age[16]. Among the Caucasians, the incidence is two & a half times more common in men with a peak in the 6th & 7th decades of life. Tanioka found a peak incidence of HCC in the seventh decade of life in both men and women in Nagasaki Japan[17]. A study in rural South Africa by Kew, found HCC incidence in the black population peak in the third, fourth & fifth decade whereas in the South African whites the peak was in the sixth, seventh & eight decades.[18]

This study found that hepatocellular carcinoma is the most commonly (63%) diagnosed type of liver cancer, followed by metastasis. This could be attributed to high levels of aflatoxin due to poor grain storage in Kenya as described by Mwangi *et al*(1993) [16]. There is also increased prevalence of hepatitis B and C virus, which is prevalent in Sub-Sahara Africa and Asia. In their review of HCV prevalence in Africa, Karoney *et al* (2013) concluded that there is a high prevalence at 5.3%[19]. In this study, 7% of the participants had hepatitis B virus. According to WHO data there is an elevated prevalence of chronic hepatitis B virus (HBV) infection in Sub-Saharan Africa, with over 8% of the populations in these regions chronically infected with the virus.

Normal Liver Function Tests (LFTs) do not always mean that the liver is normal. This is in keeping with a study by Lopez *et. al* (1996) which concluded that it seems unlikely that LFTs serve a useful function in diagnosis of HCC[20]. Patients with lymphoma can also present with normal or deranged parameters. Both patients who were diagnosed with lymphoma had deranged tests. In a study by John Ryan *et al* (2006) on Primary liver lymphomas, some patients had normal tests while others had deranged parameters[21].

Agreement of sonographic findings with histological diagnoses:-
The accuracy of the test conducted using the sonography and histology are the main concern of physicians and radiologist. There are issues such as availability of these test as well as their cost effectiveness especially in developing countries (Spilios et al., 2007)[3]. This study found a moderately strong kappa value (kappa=0.511) for the level of agreement between sonographic and histopathological diagnosis of liver cancer. This means that there was no statistically significant difference between the two diagnostic techniques. For instance, the study found that Hepatocellular carcinoma was diagnosed almost equally by the two methods (54%-histopathological and 60% sonographic). Mestatasis was diagnosed equally (nine times each) by the two independent techniques.

Although histopathological diagnosis is the decisive mode in Moi Teaching and Referral Hospital (MTRH), these findings show that ultrasound diagnosis is equally good. Similar studies (Don, et al., Sherlock et al. and Newman et al 2009, 1997 &2009)[9, 22 & 23], showed that histopathological diagnosis will remain a valuable diagnostic tool. Although the availability of the histopathological diagnosis is a challenge in many developing countries including Kenya, Ultrasound could still be used for clinical management of liver cancer diagnosis with fairly accurate test results in settings where histopathological test may not be available.

When these histopathological diagnosis results were compared with the clinical diagnosis in MTRH, it was found to be conforming. The kappa test was different from zero (kappa=0.318) and this shows that it was beyond chance alone according to Landis et al (1997)[15]. This indicates that patient management in the hospital is informed significantly by the histological diagnosis, among other tests including sonography.

Main indications for ultrasound guided liver biopsies at MTRH:-
Suspicion of hepatocellular carcinoma was the most common indication for ultrasound and was diagnosed among 60% of the patients compared to 54% by histopathology. This is similar to a study by Medizinische *et al*.(1993) which clinically diagnosed 50 hepatocellular carcinoma patients and confirmed by histology among the 34 (68%) patients.[24]

In a study by Gilmore *et. Al* (1995). The indications varied by age; in those under 65, 50% were performed for suspected chronic liver disease and 25% for suspected malignancy, whereas in those over 65 these percentages were reversed to 25% and 50% respectively.[10]
Of those biopsies performed for suspected malignancy, 10% were seeking definitive evidence of a primary hepatocellular carcinoma. This contrast with this study that 24% of the indications were for suspicion of malignancy. Follow up of liver transplantation, accounted for only 1% overall. There were no transplant patients in this study.

Conclusions:-
The commonest indication for patients referred for ultrasound guided liver biopsies was to establish a diagnosis for suspected malignancy. Hepatocellular carcinoma is the commonest liver malignancy diagnosed in Moi Teaching & Referral Hospital. There is a good agreement between sonographic and histological diagnosis. The major indication for ultrasound guided biopsy is diagnosis for suspicions of hepatocellular carcinoma and metastases to the liver.

Acknowledgements:-

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