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"DIFFERENT ULTRASOUND PATTERNS OF HEPATIC METASTATIC DISEASE."

Radiology

Meena Dharm Raj* MD. Professor. Department Radio diagnosis. Government Medical College, Kota. Rajasthan. INDIA.324005. *Corresponding Author:

Saxena Sangeeta MD. Professor and Head, Department Radio diagnosis. Government Medical College, Kota. Rajasthan. INDIA. 324005. Co-author

Harshvardhan Assistant Professor. Department Radio diagnosis. Government Medical College, Kota. Rajasthan. INDIA. 324005. Co-author

Juria Richa Final Year Resident Doctor. Department Radio diagnosis. Government Medical College, Kota. Rajasthan. INDIA. 324005. Co-author

ABSTRACT

Background - The purposes of this study were to report the sonographic features of hepatic metastases and to highlight the spectrum of different ultrasound patterns of metastases in different primary malignancies.

Methods - The sonographic study of hepatic metastatic disease was done in all cases referred to the department of radio-diagnosis from various departments of Govt. Medical College, Kota, Rajasthan in a period of one year from 1st May 2015 to 30th April 2016. Ultrasound criteria included in the study to describe metastatic hepatic disease were lesion number, margin, shape, appearance (solid/ cystic), echogenicity, presence of halo, target appearance, vascularity, displacement of vessels, calcification and type of primary malignancy.

Results – Most of the lesions were multiple, rounded or oval shaped with well defined margin. Solid halo containing lesions were most common, in which halo containing lesions without target appearance were more frequent than typical target appearing lesions, while cystic lesions were least frequently found. Most of metastatic lesions were hypo-vascular or avascular on Doppler imaging and displacement of hepatic vasculature was also evident. Most of metastatic lesions were non calcified, exceptionally calcified metastases found in mucinous carcinoma of bowel or bone malignancy. Fatty liver texture due to obesity or chemotherapy alters metastatic lesion appearance; and with this most lesions appeared as hypoechoic without halo.

Conclusions – we found that two-third of the metastatic lesions had characteristic peripheral hypoechoic halo with or without target appearance on sonography and most of the lesions were multiple, well defined, hypo vascular in nature, non calcified and leading displacement of adjacent hepatic vessels.

KEYWORDS

cystic lesion; displacement of vessels; fatty liver; halo; hyperechoic; hypoechoic; hypovascular; metastases; ultrasound; target appearance pattern.

Introduction:

Liver metastases are common in many types of cancer, and liver is the second common site for metastatic disease after lymph node, because of its rich and dual blood supply. Metastatic tumors in the liver are twenty times more common than primary tumors; and they may be present even with the original (primary) cancer or may occur months or years after the primary tumor removal The most common primary tumors resulting in liver metastases, in decreasing order of frequency; are gallbladder, colon, stomach, pancreas, breast, and lung; and most of the metastases are blood-borne through the hepatic artery or portal vein, but lymphatic spread of tumors from stomach, pancreas, ovary, or uterus may also occur.

The evaluation of suspected hepatic metastases is one of the most important indications for oncology imaging and role of hepatic imaging also applies to the patients with known liver disease for differentiation of metastasis versus benign masses or for pre-surgical segmental localization for evaluation of resectability; including visualization of vascular structures for tumor invasion and vascular anomalies.

Advances in imaging techniques have increased our ability to detect and characterize focal liver lesions, resulting in improvements in diagnostic capability and monitoring of liver metastases. Out of which, ultrasound examination is very sensitive technique for detecting such metastases in patients with oncologic history; and additionally this method can incidentally detect metastases in asymptomatic patients. Early identification (small size, small number) is important to establish an optimal course of treatment, which can be chemotherapy, radiofrequency ablation, and surgical resection.

In this series, we aimed to perform a study to derive the spectrum of different ultrasound pattern of hepatic metastases and variation in appearance in a particular primary malignancy at our institution.

Method:

A descriptive observational study was conducted in the department of radio-diagnosis, Govt. Medical College and Associated group of Hospitals, Kota, Rajasthan from 1st May 2015 to 30th April 2016, after ethical clearance from institution's ethical committee and data were collected using predesigned performa. During this period total 78 patients referred from teaching hospitals attached to Govt. Medical College and Associated Group of Hospitals; including M.B.S. Hospital, J.K. Loan Hospital and New Medical College Hospital, Kota were found to have hepatic metastasis, were included in the study. During the study, ultrasound imaging was done with following ultrasound machines: 1. Siemens Sonoline G50, 2. Siemens Sonoline G60, 3. GE CISPR11/EN (LOGIQ P5), 4. Toshiba Nemio 30, 5. Micromax Sonosite and 6. ECUBE 15 using low frequency curvilinear probe and high-resolution linear transducer.

The parameters included in the study were lesion number (< 5 lesion and >5 lesion/multiple lesions), shape of lesion (rounded/ oval and irregular shape), margin (well define or ill define), ultrasound appearance of lesion (solid/ cystic/ both), echogenicity (hypoechoic/ hyperechoic/ isoechoic), presence of necrosis and hemorrhage in solid lesion, characterization of cystic lesion(thick wall, septation, debris), presence of halo (hypoechoic peripheral rim of variable thickness around lesion), target appearance (alternate concentric hypoechoic or hyperechoic layer, mostly due to central hypoechoic necrotic zone), pattern of vascularity on doppler imaging, effect on adjacent hepatic vasculature, calcification and characterization of lesion according to primary malignancy. Study data were analyzed using Microsoft Excel 2010, software.

Observation & Discussion:

A total of 78 patients (41 male and 37 female) with hepatic metastatic disease were included in the study. Age of patients those suffering from hepatic metastatic disease were ranged from 20 to 82 years. Most of the patients (33%) with hepatic metastases belonged to age group 61-70 yrs followed by 51-60 yrs age group (27 % patients) and the least number of patients were seen in below 20 year age group and above 80 year age group, as it is a well known fact that malignancies are more commonly affect middle age adult and elder patients.

In this study, 74 out of 78 patients were having known primary malignancy and only 4 had unknown primary malignancy with hepatic lesion showing characteristic metastatic appearance on ultrasound.

Further focusing on primary malignancy, in this study, maximum numbers of patients were from pancreaticobilliary system [n-15], in which 13 patients of gallbladder malignancy and two patients of pancreatic malignancy including neuroendocrinal tumour were there. After these, second maximum numbers of patients were from primary GIT/bowel malignancy [n-11], this was followed by liver [n-10], breast [n-10] and lung malignancy [n-10] patients [Table 1].

PRIMARY	LUNG	BREAST	GIT	HEPATIC	PANCREATO -BILIARY	RENAL	REPRODUCTIVE TRACT	HEAD & NECK	UNKNOWN
NO. OF PATIENT	10	10	11	11	14	6	6	4	6

Table-1. Number of patient with hepatic metastatic disease with a particular primary malignancy observed in study.

Other primary malignancies observed in this study were renal cell carcinoma [n-6], ovarian malignancy [n-3], carcinoma cervix [n-2], and prostate neoplasm [n-1].Apart from common primary malignancy, few uncommon malignancies with metastasis were also included in the study; these were medullary carcinoma thyroid [n-1], laryngeal carcinoma [n-2], malignant myxoid sarcoma [n-1], buccal mucosa squamous cell carcinoma [n-1], and large cell carcinoma of axillary lymph node [n-1].

During ultrasound observations in the study, we found that 71% patients with hepatic metastatic disease were having multiple lesions [Figure 1], and also showing most common involvement of

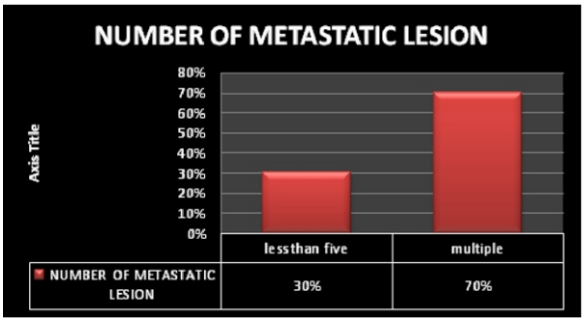


Figure-1. Graphical presentation of number of metastatic hepatic lesions.

both liver lobes, followed by 19% patients were showing predomina ntly right lobe lesions, and least common was involvement of left lobe noted in only 10% patients [Table 2].

LIVER LOBE	NO. OF PATIENT	PRESENTAGE
BILATERAL LOBE	55	71%
RIGHT LOBE	15	19%
LEFT LOBE	8	10%

Table-2. Predominant liver lobe involvement in hepatic metastatic disease.

According to ultrasound appearance, about 86% patients were showing solid appearing lesion on ultrasound, only 4% patients were showing predominantly cystic lesions and rest 10% patient were showing both solid and cystic hepatic lesions [Table 3].

PREDOMINNT USG APPERANCE	NO. OF PARIENT	PRESENTAGE
SOLID	67	86%
CYSTIC	3	4%
BOTH	8	10%

Table-3. Distribution of various appearance of hepatic metastatic lesion on ultrasound.

Solid appearing lesions [Figure 2] further classified in four categories according to their echogenicity and presence of peripheral hypoechoic halo [Figure 3, 4].

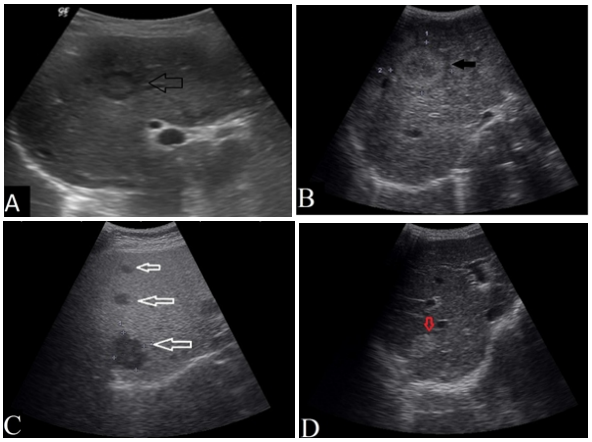


Figure-2 **(A)**. Known Case of gall bladder malignancy was showing typical solid halo containing lesion without target appearance (black arrow) in right lobe of liver. **(B)**. Target appearing (solid black arrow) solid hepatic lesion in Breast carcinoma patient. **(C).** Diffuses fatty infiltration in liver with multiple hypoechoic metastatic lesions without halo (white arrow) in carcinoma cervix patient. **(D).** Postoperative case of renal cell carcinoma shows a hyperechoic metastatic lesion without hyperechoic halo (red arrow) involving VII segment of liver.

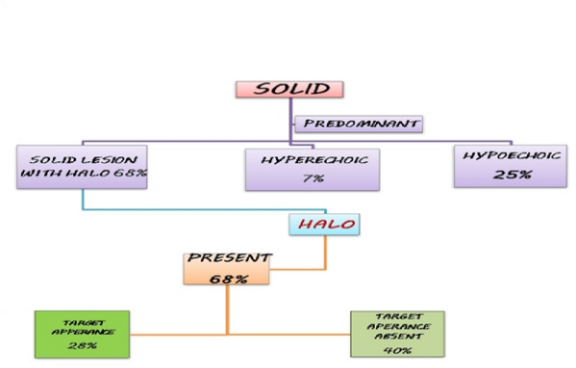


Figure-3. Flow chart of presentation of Different solid hepatic metastatic lesion in study.

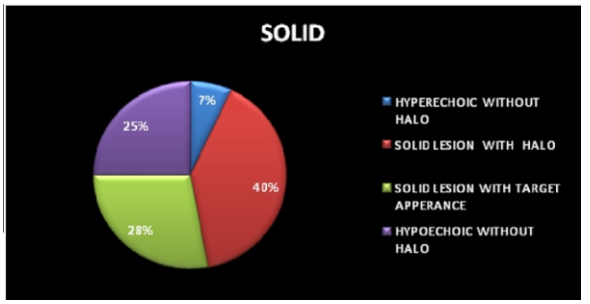


Figure-4. Graphic presentation of different type of solid pattern on USG in hepatic metastatic disease.

Halo containing lesion without target appearance,

1) Target (hypo-hyper-hypo pattern) appearing lesion,
2) Hyperechoic lesion without halo and
3) Hypoechoic lesion without halo,

In present study 68% cases were having solid appearance with peripheral hypoechoic halo [Figure 2A]; in which 28% of total patients were showing typical target appearance [Figure 2B]. Central area of solid lesion might show hyperechoic, hypoechoic, isoechoic appearance; however in this study, predominantly hyperechoic or isoechoic central areas (40%) were noted.

In our study, 25% cases were having hypoechoic lesion without hyper/hypoechoic halo [Figure 2C], Hypoechoic lesions without halo in present observation were found in lung, breast, GIT, GB, reproductive tract malignancies (arranged according frequency).

Least common appearance was hyperechoic lesion without peri-lesional hypoechoic halo [Figure 2D], found in 7% cases in the study. In present study, hyperechoic lesions without halo were seen most commonly in HCC (17% cases). After HCC, echogenic metastases were also noted in renal cell carcinoma (17% cases), lung malignancy (10% cases), GIT malignancy (9% cases).

About 14% cases were showing cystic lesions in which only 4% cases were having predominantly cystic lesions, while rest 10% were having both solid and cystic patterns.

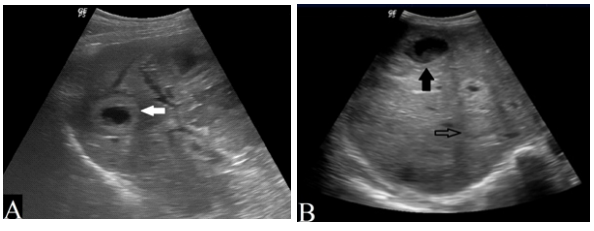


Figure-5 (a). Patient with ovarian malignancy, a thick wall cystic hepatic lesion (solid white arrow) in right lobe. **(b).** Patient with carcinoma colon, cystic hepatic lesion with dependent debris (solid black arrow) and one other peripheral halo containing solid metastatic lesion (black arrow).

	LUNG [10 patient]	BREAST [10 patient]	GIT [11 patient]	HCC [11 patient]	GB [12 patient]	RENAL [6 patient]	REPODUCTIVE [5 patient] Cervix[2] ovary [3]
Solid lesion with halo	7 [70%]	7 [70%]	7[64%]	8[73%]	8[62%]	2[33%]	4[80%]
Target lesion[+]	3[43%]	4[57%]	4[57%]	2[25%]	2[25%]	–	2[50%]
Target lesion[-]	4[57%]	3[43%]	3[43%]	6[75%]	6[75%]	2[100%]	2[50%]
Hyperechoic without halo	1[10%]	–	1[9%]	2[18%]	–	1[17%]	–
Hypo echoic without halo	2[20%]	3[30%]	2[18%]	1[9%]	5[38%]	1[17%]	1[20%]
Predominant cystic	–	–	1[9%]	–	–	2[33%]	–

Table-4. Different Ultrasound pattern in particular type of primary malignancy.

Pattern study was done in individual primary malignancy [Table 4], most common pattern was solid halo containing lesion [Figure 6A&B], in which lesions without target appearance were noted in lung malignancy, hepatocellular carcinoma (HCC), gallbladder maligna ncy, renal cell carcinoma (RCC) and lesions with target appearance [Figure 6C] were noted in breast and GIT malignancy. Second common pattern was hypoechoic lesion without halo found in most of malignancy like lung, breast, GIT, gallbladder, reproductive tract malignancy, except hepatocellular carcinoma and RCC; while second most common pattern in HCC was solid hyperechoic lesion without halo, and in RCC, cystic appearing lesion was second common pattern.

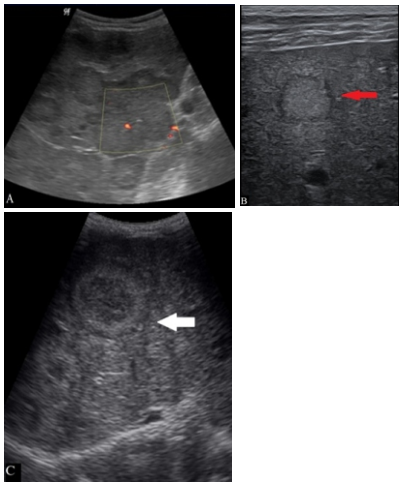


Figure-6 (a). Multiple hepatic lesions. (b). Peripheral hypoechoic halo containing solid hepatic lesion (red arrow). (c).Target appearing lesion (white arrow), alternate hypoechoic-hyperechoic-hypoechoic layer.

In context of shape and margin of lesions, most lesions were having well defined margin and rounded or oval shape [Figure 7 A & B]. In current study, 73% patients were showing rounded/oval lesions and 18% patients were showing irregular shape while in 9% patients both patterns were noted. 91% patients with hepatic metastases were having well defined margin and only in 9% cases ill-defined margin of lesion were noted.

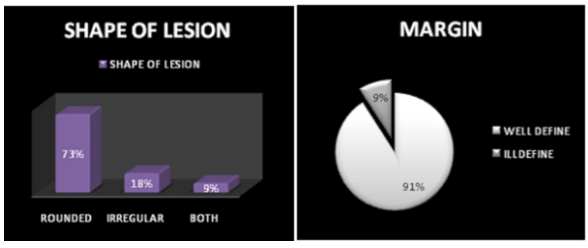


Figure-7(a). Distribution of lesion according shape. (b) Distribution of lesion according margin.

In respect of vascularity on color Doppler imaging, most of the lesions were having no internal vascularity in our observation; and 82% cases of hepatic metastatic disease were avascular or hypo-vascular and only 18% cases were having vascularity [Figure 8] [Table 5].

Vascularity	PATIENT	PERCENTAGE
Absent	64	82%
Present	14	18%

Table-5. Distribution of metastatic lesion according to vascularity on Doppler ultrasound.

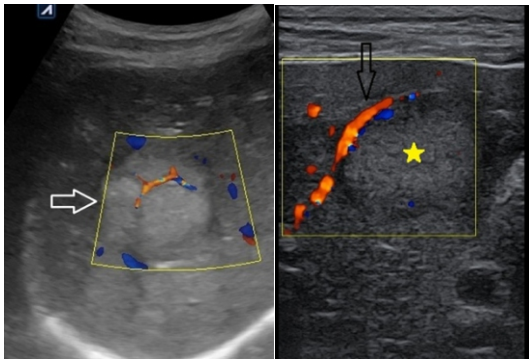


Figure-8 (a). Vascular hyperechoic metastatic lesion (white arrow) in right lobe of liver in lung carcinoma patient, on doppler study show central vascularity. (b) Avascular hyperechoic metastatic lesion (Yellow star) on ultrasound with high frequency probe, show no intralesional vascularity with displacement of hepatic vasculature (black arrow).

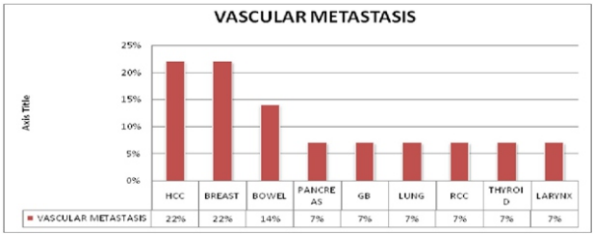


Figure-8 ©. Graphical representation of vascular metastatic lesion in a particular primary malignancy.

In our study, highest numbers of vascular metastases were found in hepato cellular carcinoma, followed by breast, RCC, bowel, lung; and apart from this, one case of neuroendocrinal tumor of pancreatic origin was also seen with vascular hepatic metastases plus hemorrhagic conversion and surprisingly two cases of laryngeal carcinoma were also present in study with hyper-vascular metastases.

Furthermore in ultrasound criterion, effect on adjacent hepatic vasculature was evident in most of the lesions and showed as displacement of adjacent hepatic vessels mainly [Figure 8B] and even presented with invasion or distortion of vessels. However in small size lesions, displacement of vessels and internal vascularity on colour Doppler were not well appreciated.

Regarding calcification of lesion, no intra-lesional calcification was noted in patients with hepatic metastatic disease with exception of one case only which was mucinous adenocarcinoma of appendix presented with multiple hyperechoic metastases without halo and most of these lesions were having dense central calcification and giving distal acoustic shadowing [Figure 9].

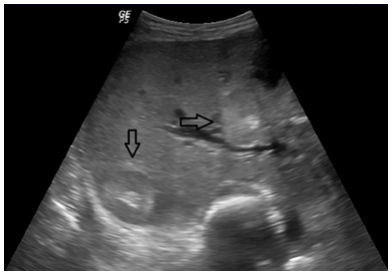


Figure-9. Calcified metastatic lesion in patient with mucinous adenocarcinoma of appendix. On ultrasound multiple well define isoechoic to hyperechoic metastatic lesion with central non shadowing calcification.

Discussion:

Hepatic metastasis is common in various types of advance malignancy and it important to differentiate metastatic lesion from other benign and malignant lesions in liver. so in this study we were trying to describe common patterns of metastasis and appearance in different type of primary malignancy.

In present Hepatic metastatic ultrasound pattern study was done on various types of proven primary malignancies either on imaging or biopsy; however some unknown primary malignancies were also included in the study because they were having characteristic metastatic ultrasound appearance of hepatic lesions.

In this study, maximum numbers of patients were from pancreaticob illiary system especially from gallbladder malignancy this was followed by primary GIT/bowel malignancy, liver, breast and lung malignancy patients. These findings were in accordance with literature report by Stephanie R et al [1] which stated that the most common primary tumors resulting in liver metastases, in decreasing order of frequency, were malignancies of gallbladder, colon, stomach, pancreas, breast, and lung.

During ultrasound observations in the study, we found that most of the patients with hepatic metastatic disease were having multiple lesions and most commonly involve both liver lobes, with right lobe lesions predominance. According to Nawaz Khan A et al [2], most of the liver metastases are multiple, while single liver metastasis is not common and according Wernecke K et al, only in 10% of cases there are solitary metastasis [3]; and liver involvement can be segmental, lobar (involving both lobes in 77% of patients but more common in right lobe) or generalized (in this situation a pronounced hepatomegaly occurs). So, present study findings were quite similar to literature in this aspect.

In context of shape and margin of lesions, most lesions were having well defined margin and rounded or oval shape [Figure 7 A&B]. Presence of hypoechoic halo around lesion is usually helpful to delineate the lesion's shape and margin. Most of the small lesions were not containing a defined halo and usually had ill defined margin.

Most of lesions were showing solid appearance on ultrasound, only 4% patients were showing predominantly cystic metastatic lesions.

Solid appearing lesions further classified in four categories according to their echogenicity and presence of peripheral hypoechoic halo.

1) Halo containing lesion without target appearance,
2) Target (hypo-hyper-hypo pattern) appearing lesion,
3) Hyperechoic lesion without halo and
4) Hypoechoic lesion without halo,

In present study 68% cases were having solid appearance with peripheral hypoechoic halo and according to Wernecke K et al, solid lesion of varying sizes with hypoechoic halo is the most common pattern (65%) which is also a concerning feature to differentiate between benign and malignant hepatic lesions [3].Central area of solid lesion might show hyperechoic, hypoechoic, isoechoic appearance; however in this study, predominantly hyperechoic or isoechoic central areas (40%) were noted. Due to hypo-vascular nature of most metastatic lesions, the central part starts to develop necrotic changes, gives rise to target appearance (alternate hypoechoic and hyperechoic layer); and only 28% of total patients were showing this typical target appearance . Peripheral halo is related to a combination of compressed normal hepatic parenchyma around the mass and a zone of cancer cell proliferation. However this pattern is not specific for metastases, as it can also be seen in primary malignant liver neoplasm (e.g. HCC) and benign liver lesions like liver abscesses. [3-6]

According to Stephanie R et al [1] hypoechoic metastases are generally hypo-vascular in nature, and in absence of halo, hypoechoic metastases are less frequently found. In presence of fatty liver, most metastases appear hypoechoic; which are commonly found in breast cancer, lung cancer, while less frequently in neoplasm of oesophagus, stomach, pancreas, and lymphoma. In our study, 25% cases were having hypoechoic lesion without hyper/hypoechoic halo [Figure 2C], and these kind of lesions were commonly seen in patients with fatty liver which can be due to radio/chemotherapy, however this pattern was also noted in very small size metastatic lesions.

Least common appearance was hyperechoic lesion without peri-lesional hypoechoic halo [Figure 2D], found in 7% cases in the study. Echogenicity denotes vascular nature of lesion and according to Tanaka S et al, [7] and Rubaltelli L, [8] the more vascular the tumor is, the more likely the lesion will be echogenic; which is mostly arise from a gastrointestinal origin carcinoma or from HCC, while metastases from renal cell carcinoma, neuroendocrine tumors, carcinoid, choriocarcinoma, and islet cell carcinoma also tend to be hyperechoic. This particular group of tumors may mimic with hemangioma on sonography. In present study, hyperechoic lesions without halo were seen most commonly in HCC. After HCC, echogenic metastases were also noted in renal cell carcinoma, lung malignancy and GIT malignancy.

About 14% cases were showing cystic lesions in which only 4% cases

were having predominantly cystic lesions, while rest 10% were having both solid and cystic patterns. Cystic metastatic lesions on ultrasound showed complex cystic nature with thick hyperechoic wall and internal debris [Figure 5]. Extensive necrosis within solid lesion also gives appearance similar to cystic lesion. There are two different pathologic mechanisms which explain the cyst like appearance of hepatic metastases; and first one described by Lewis K H [9] and Sugawara Y [10] which stated that hypervascular metastatic tumors with rapid growth may lead to necrosis and cystic degeneration. This mechanism is frequently demonstrated in metastases from neuroendocrine tumor, sarcoma, melanoma, and certain subtypes of lung and breast carcinoma. While, second explanation of cystic appearance of metastases is due to cystic primary and this is seen with mucinous adenocarcinoma of colorectal or ovarian origin. [11-13]

Pattern study was done in individual primary malignancy [Table 4], most common pattern was solid halo containing lesion [Figure 6A&B], and Second common pattern was hypoechoic lesion without halo in most of different type of primary malignancy except hepatocellular carcinoma and RCC. Second most common pattern in HCC was solid hyperechoic lesion without halo, and in RCC, cystic lesions was second common pattern.

In respect of vascularity on colour Doppler imaging, most of the lesions were avascular/ hypovascular in our observation; only 18% cases were having vascularity [Figure 8] [Table 5]. Vascularity in lesion was suggestive of either hyper-vascular primary malignancy or intra-lesional vascularity due to neovascularisation as found in larger lesions.

According to literature, hyper-vascular metastasis most commonly found in neuroendocrinal tumor, followed by RCC, breast, thyroid carcinoma, HCC and melanoma [14]. While in our study, highest numbers of vascular metastases were found in hepato cellular carcinoma, followed by breast, RCC, bowel, lung; and apart from this, one case of neuroendocrinal tumor of pancreatic origin was also seen with vascular hepatic metastases plus hemorrhagic conversion. These findings were match with literature as mentioned above; however surprisingly two cases of laryngeal carcinoma were also present in study with hyper-vascular metastases.

Furthermore in ultrasound criterion, displacement of adjacent hepatic vasculature was evident in most of the lesions [Figure 8B] and even presented with invasion or distortion of vessels. However in small size lesions, displacement of vessels and internal vascularity on colour Doppler were not well appreciated. According to Halvorsen RA et al, Displacement of hepatic vessels by metastatic lesion is an important feature to distinguish malignant and metastatic lesion from focal fatty infiltration, however not used as strict criteria. [15]

Regarding calcification of lesion, no intra-lesional calcification was noted in patients with hepatic metastatic disease with exception of one case only which was mucinous adenocarcinoma of appendix presented with multiple hyperechoic metastases without halo and most of these lesions were having dense central calcification and giving distal acoustic shadowing [Figure 9]. According to Miele AJ et al, [16] calcified metastases are rare and mucinous carcinoma of bowel is the most common primary malignancy causing calcified metastases in liver, while less frequently seen with osteogenic sarcoma, chondrosarcoma, teratocarcinoma, and neuroblastoma. Calcification within hepatic metastatic lesions may also be seen in patients receiving chemotherapy [10]. Calcium may appear as large, echogenic, and shadowing foci or more often shows as innumerable tiny punctate echogenicities without clear shadowing. [17]

Conclusion:

We concluded by our observation that advanced imaging with ultrasonography provided significant spectrum of hepatic metastatic disease affecting all age groups, more commonly involving middle and elder age group and highlighted that solid lesion with peri-lesional hypoechoic halo with target appearance is the most characteristic and common pattern, found in majority of patients with different type of malignancies; and derived statistical data indicated that most of these lesions were multiple, well define, hypo-vascular in nature, non calcified and causing displacement of adjacent hepatic vessels.

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