

Original Research Article

Surgical resection for hepatic space occupying lesions: a histopathological analysis

Vani M.*, Jeena Sam Kachappilly, Geetha K.

Department of Pathology, Academy of Medical Sciences, Pariyaram, Kerala, India

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***Correspondence:**

Dr. Vani M,

E-mail: vanim250180@gmail.com

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ABSTRACT

Background: Hepatic resections are done for both neoplastic and non-neoplastic diseases of liver with malignancies constituting a major share of cases. The objective of this study was to assess the various neoplastic and non-neoplastic lesions in hepatic resection specimens and to categorize the various histopathological types of primary and secondary liver tumors.

Methods: The study was conducted in the Department of Pathology, Academy of Medical sciences, Pariyaram. This was a hospital based study which included 79 patients who underwent hepatic resection for space occupying lesions over a period of 5 years from January 2012 to December 2016. IHC was performed in cases with diagnostic dilemma.

Results: Of the 79 cases, there were 45 males and 34 females with the age range of 22-85 years. There were 70 neoplastic lesions out of which 11 were benign with 6 cavernous hemangiomas, 3 hepatic adenomas and one each of intraductal papillary neoplasm and mucinous cystic neoplasm. Among the 59 malignant lesions, hepatocellular carcinomas predominated followed by metastatic malignancies and cholangiocarcinomas. Of the metastatic malignancies, adenocarcinoma from gastrointestinal primary was the commonest followed by metastatic gastrointestinal stromal tumor.

Conclusions: Liver is a frequent site for many neoplastic and non-neoplastic diseases with malignant neoplasms forming the major bulk. Non-neoplastic lesions like simple liver cysts and focal nodular hyperplasia showed female predominance while benign neoplasms like cavernous hemangioma and hepatic adenomas were seen exclusively in females. Of the malignant liver tumors, hepatocellular carcinoma was the commonest followed by metastatic malignancy, gastrointestinal tract being the commonest source of primary tumor.

Keywords: Hepatic resection, Hepatocellular carcinoma, Metastasis, Non-neoplastic lesions

INTRODUCTION

Liver is a vital organ with diverse functions and can be affected by a variety of metabolic, infectious, inflammatory and neoplastic diseases. It is a potential site for blood borne metastatic malignancies as the portal area drainage flows to the liver and is also a common site for many different primary malignancies. Many non-neoplastic and neoplastic diseases can form diffuse or focal lesions in liver which are radiologically designated as space occupying lesions (SOLs). With the advances in

hepatic surgery and the increase in number of hepatic surgeries being performed there is a significant increase in the identification of histological types of hepatic space occupying lesions.¹

METHODS

During the period from January 2012 to December 2016, 148 patients had undergone hepatic resection in Academy of Medical Sciences, Pariyaram. 79 patients who underwent surgery for hepatic SOLs were included in the

study. The study was conducted in the Department of Pathology over a period of 5 years which included 3 years of retrospective study (January 2012 to December 2014) and 2 years of prospective study (January 2015 to December 2016). Needle core liver biopsies, total hepatectomy for liver transplants, 17 cases of hepatic resection for hilar cholangiocarcinoma and hepatectomy for lacerations were excluded from the study.

All resected cases were received in 10% buffered formalin. Partial sectioning after inking of resected margin was done to aid fixation. After fixation, specimens were sliced, grossly examined and relevant areas sectioned for tissue processing. All paraffin embedded blocks obtained after processing were sectioned and stained with hematoxylin and eosin (H and E) for histopathological examination. Immunohistochemistry (IHC) was done in cases with diagnostic difficulty.

For retrospective study, biopsy request forms with clinical details, histopathology reports and slides (H&E and IHC) were retrieved from the archives of Department of Pathology and analysed (statistical analysis used-descriptive statistics).

RESULTS

Of the 79 patients who underwent hepatic resection for SOLs there were 45 males and 34 females. The youngest patient was a 22-year-old male who developed hepatocellular carcinoma in chronic hepatitis B induced cirrhosis and the oldest was an 85-year-old male with carcinoma of stomach who developed hepatic metastasis (Table 1).

Table 1: Histopathological spectrum in hepatic SOLs.

Diagnosis	No. of cases	%
I Non-neoplastic lesions	9	11.4
1 Simple liver cyst	5	6.33
2 Inflammation, fibrosis	2	2.53
3 Focal nodular hyperplasia	1	1.27
4 Liver abscess	1	1.27
II Neoplastic lesions	70	88.6
A Benign	11	13.9
1 Cavernous hemangioma	6	7.6
2 Hepatic adenoma	3	3.8
3 Mucinous cystic neoplasm	1	1.27
4 Intraductal papillary neoplasm	1	1.27
B Malignant	59	74.7
1 Hepatocellular carcinoma	28	35.44
2 Metastatic malignancy	21	26.6
a Metastatic gastrointestinal adenocarcinoma	9	11.4
b Metastatic GIST	4	5.06
c Metastatic melanoma	2	2.53

d Metastatic NE carcinoma	2	2.53
e Metastatic sarcoma	1	1.27
f Metastatic RCC	1	1.27
g Metastatic myeloma	1	1.27
h Metastatic adrenocortical carcinoma	1	1.27
3 Cholangiocarcinoma	8	10.12
4 Combined HCC-CC	1	1.27
5 Carcinosarcoma	1	1.27

GIST-gastrointestinal stromal tumor; HCC-CC-hepatocellular carcinoma-cholangiocarcinoma.

Of the non-neoplastic lesions, simple liver cysts constituted 55.5% (n=5) of the cases with female to male ratio of 1.5:1 and an age range of 50-78 years. On gross examination, all were uniloculated cysts with smooth inner wall and the largest measured 20 cms in greatest dimension. Microscopy showed fibrocollagenous wall with cuboidal to attenuated lining in all the cases.

The single case of focal nodular hyperplasia was diagnosed in a 35-year-old female for whom hepatic resection was done with clinical suspicion of hepatic adenoma. It was a solitary lesion and measured 6 cms in diameter (Figure 1).

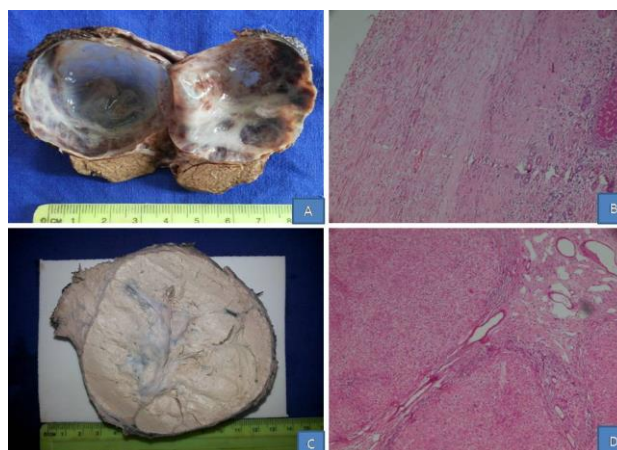


Figure 1: (A) Uniloculated hepatic cyst; (B) fibrocollagenous cyst wall lined by attenuated epithelium-H and E10x; (C) FNH-circumscribed gray white lesion with central fibrosis; (D) Pseudobulbes with thickened blood vessels in fibrous septae in FNH-H and E 10x.

Cavernous hemangioma constituted 55% cases of benign neoplastic lesions. All the 6 patients were females and the resected tumor had brownish spongy appearance except in one case which showed extensive sclerosis. All were solitary giant hemangiomas and the largest tumor measured 10 cms in diameter.

All the 3 cases of hepatic adenomas were in females with age range of 31to 41 years. One of the patients was 34 years old with history of clomiphene citrate therapy for infertility and had multiple hepatic adenomas (hepatic

adenomatosis) where as others had solitary lesions (Figure 2).

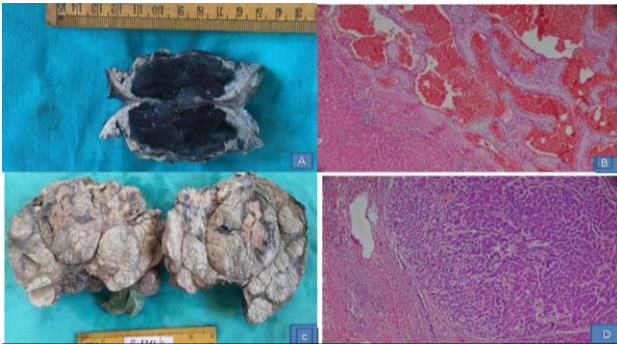


Figure 2: (A) Cavernous hemangioma-Circumscribed brownish black spongy lesion; (B) Cavernous type vascular spaces lined by flattened endothelial cells; H&E 10x (C)Hepatic adenomatosis- multiple circumscribed gray white lesions with necrosis in largest nodule; (D)Encapsulated tumor composed of well differentiated hepatocytes H and E10x.

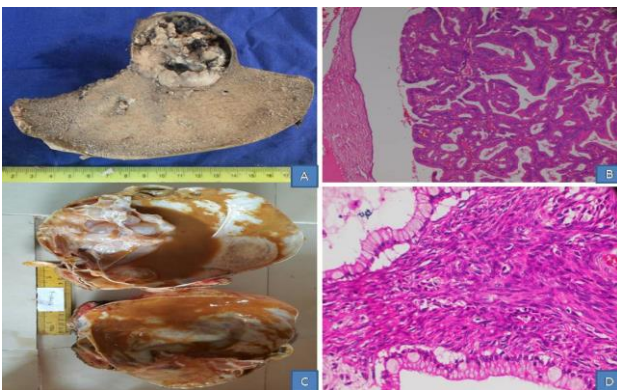


Figure 3: (A) Cystic intraductal papillary neoplasm-liver cyst with solid areas in the wall; (B) Cyst with intraluminal papillae and tubules lined by columnar epithelium with minimal atypia H and E10x; (C) Mucinous cystic neoplasm-multiloculated cyst with mucinous material; (D) Cyst wall with ovarian type stroma and lined by mucinous epithelium H and E 40x.



Figure 4: (A) Different gross appearances in HCC-single large tumor with hemorrhage and necrosis; (B) Small gray white tumor in cirrhotic liver; (C) Multiple tumors, largest with necrosis; (D) Multiple firm and fibrous tumor in scirrhous HCC.

Hepatocellular carcinomas constituted 47.5% of the malignant neoplasms (n=28) (Table 2) (Figure 4) (Figure 5).

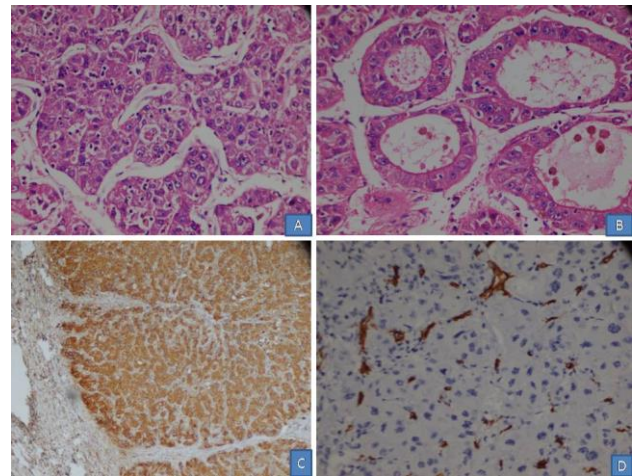


Figure 5: (A) HCC- with trabecular growth pattern; (B) Pseudoglandular pattern H and E10x; (C) HepPar1positive tumor cells, IHC; (D) Sinusoids with CD34 positivity, IHC.

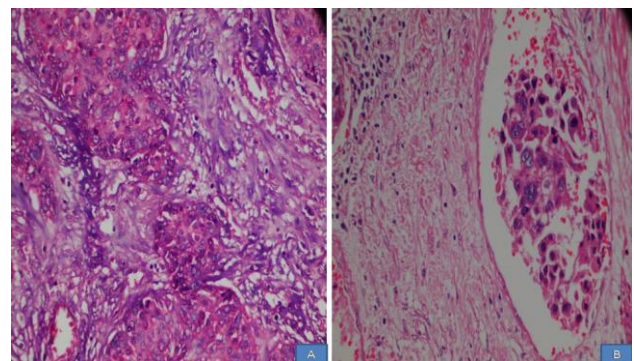


Figure 6: (A) Scirrhous carcinoma-cell nests with hepatocellular morphology in a sclerotic stroma, H and E40x; (B) Vascular invasion in HCC, H and E 40x.

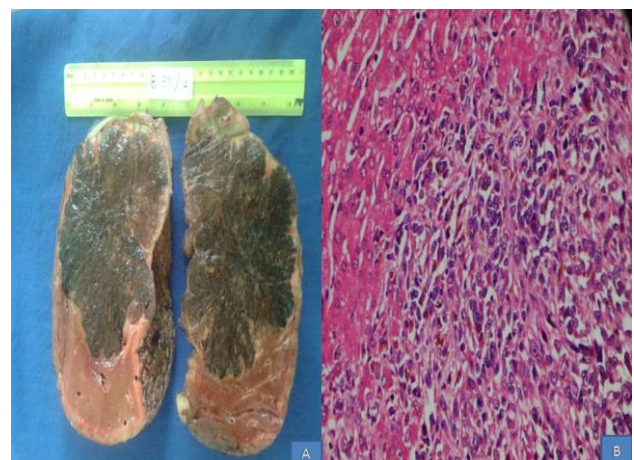


Figure 7: (A) Metastatic malignant melanoma: Large blackish tumor in liver; (B) Spindle shaped tumor cells with intracytoplasmic melanin in some cells.

Table 2: Pathology of hepatocellular carcinoma.

Age/sex	Tumor single or multiple/size in cms (of largest)	Differentiation/ Microscopic variant	Cirrhosis/ hepatitis B
67/M	S/ 14	PD	-/-
66/M	Mu/11	Sarcomatoid variant	-/-
69/F	Mu/6	MD	-/-
75/F	Mu/15	MD	-/-
65/M	S/15	Clear cell variant	-/-
43/M	S/1.5	WD	+/-
62/M	Mu/8.5	WD	-/-
55/M	S/20	WD	-/-
53/F	S/4	WD	+/-
54/M	S/7	WD	+/+
68/M	S/8	WD	-/-
60/M	S/9	WD	+/-
55/M	Mu/12	WD	+/-
22/M	S/14	MD	+/+
64/F	S/16	MD	-/-
63/M	S/6.5	WD	+/-
58/M	S/7.5	WD	+/-
63/M	Mu/10	Scirrhus variant	-/-
57/M	Mu/5	WD	+/-
53/M	Mu/11	MD	+/-
44/M	Mu/9	MD	-/-
65/M	S/3	WD	+/-
43/M	S/1.5	WD	+/-
55/M	S/2.3	WD	+/-
54/F	Mu/11	MD	+/-
65/F	S/5	WD	-/-
56/F	S/6.5	WD	+/+
60/M	Mu/2	WD	+/+

M-male; F-female; S-single; Mu-multiple; WD-well differentiated; MD-moderately differentiated; PD-poorly differentiated.

Table 3: Pathology of metastatic malignancy.

Age/sex	Tumor size single/multiple	Primary tumor	Diagnosis
75/F	2.5/S	Multiple myeloma	Met myeloma
56/F	3/Mu	Ca breast	Met ductal carcinoma
75/M	2/Mu	Signet ring cell Ca stomach	Met signet ring cell Ca
78/M	9/Mu	NEC small intestine	Met NEC
63/F	8/S	Ca stomach	Met

			adenocarcinoma
59/F	4/S	Renal cell Ca (RCC)	Met clear cell RCC
60/F	12/S	Nil	Met melanoma
52/F	9.5/S	Ca ovary	Met adenocarcinoma
62/M	6.5/Mu	Ca colon	Met adenocarcinoma
28/M	14/Mu	Ca colon	Met adenocarcinoma
59/M	9/Mu	GIST stomach	Met GIST
42/F	2/Mu	Ca rectum	Met adenocarcinoma
50/M	16/S	Neuroendocrine Ca (NEC) pancreas	Met NEC
78/M	2.5/Mu	Ca rectosigmoid	Met adenocarcinoma
42/M	2/S	Rectal melanoma	Met melanoma
85/M	3/Mu	Ca stomach	Met adenocarcinoma
31/F	15/S	GIST stomach	Met GIST
37/F	17/S	GIST stomach	Met GIST
74/M	5/M	Adrenocortical Ca	Met adrenocortical Ca
53/F	3.2/M	GIST stomach	Met GIST
49/M	5.5/S	GIST stomach	Met GIST

M-male; F-female; S-single; Mu-multiple; Ca-carcinoma; Met-metastatic

Vascular invasion was noted in 10 cases (Figure 6).

Metastatic malignancy formed 35.6% (n=21) of malignant neoplasms, the commonest being adenocarcinoma from gastrointestinal tract primary (Table 3), (Figure 7), (Figure 8).

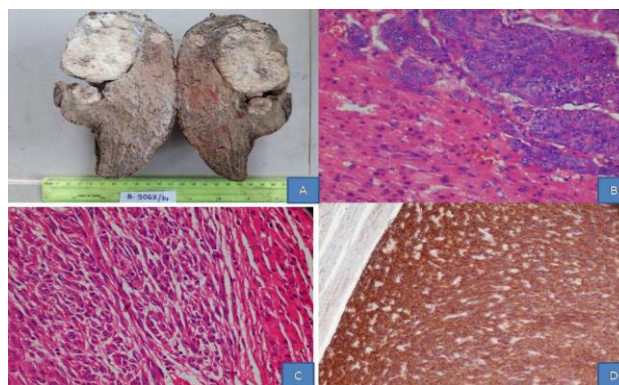


Figure 8: (A) Hepatic resection with multiple circumscribed lesions in metastatic adenocarcinoma; (B) Nests of tumor cells with stippled nuclear chromatin in metastatic neuroendocrine carcinoma-H and E10x; (C) Metastatic GIST-spindle cells in fascicles H and E10x; (D) CD117 positivity in GIST,IHC.

There were 8 cases of Intrahepatic cholangiocarcinoma with a male to female ratio of 1.6:1 and age range of 50-75 years. Macroscopically 6 cases were mass forming (with multiple lesions in 2 cases) and 2 cases were intraductal. The average tumor size for mass forming lesions were larger than that for intraductal lesions. Microscopically desmoplastic stroma was seen in all cases but perineural invasion was seen only in 5 mass forming lesions (Figure 9), (Figure 10).



Figure 9: (A) Intrahepatic cholangiocarcinoma-Mass forming type with multiple gray white lesions in liver tissue; (B) Intraductal type with gray white tumor within dilated ducts.

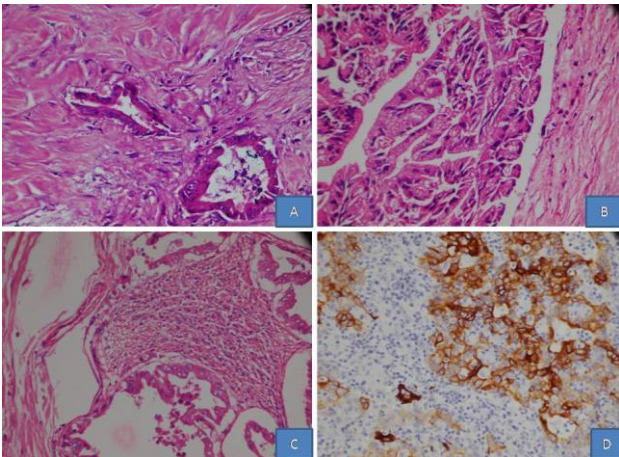


Figure 10: (A) Intrahepatic CC-cholangiolar type with glands lined by cuboidal epithelium in a desmoplastic stroma; (B) Bile duct type composed of tall columnar tumor cells; (C) perineural invasion by tumor cells, All H&E 40x; (D) Strong CK7 positivity in tumor cells, IHC.

The one case of carcinosarcoma was diagnosed in a 72-year-old male with Hepatitis C and cirrhosis. The tumor measured 35cms and showed firm fibrous areas and bile stained gray white friable areas. IHC was done to confirm the diagnosis (Figure 11), (Figure 12).

Combined HCC-CC was diagnosed in a 62-year-old female. A panel of IHC markers were done to confirm the diagnosis (HepPar1, polyclonal CEA, CK7, CK 19) (Figure 13).



Figure 11: Macroscopy of carcinosarcoma with graywhite bile stained friable areas and gray white firm areas.

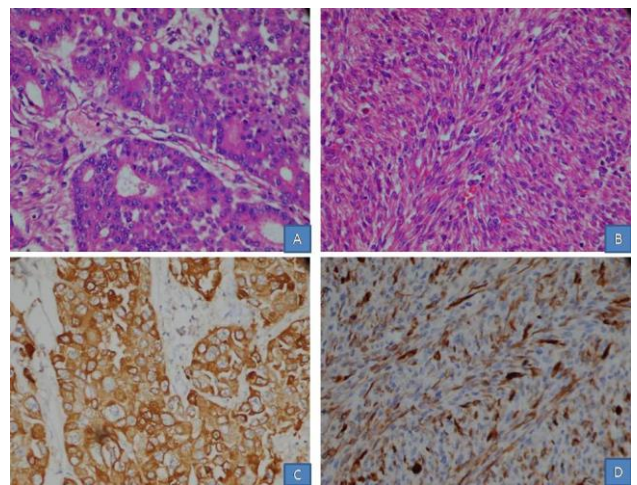


Figure 12: (A) Carcinosarcoma-HCC areas (carcinomatous element); (B) Fascicles of pleomorphic spindle cells with frequent mitoses (sarcomatous element) both H and E 10x; (C) Strong HepPar 1 positive tumor cells in HCC areas on IHC; (D) Vimentin positive tumor cells in sarcomatous area on IHC.

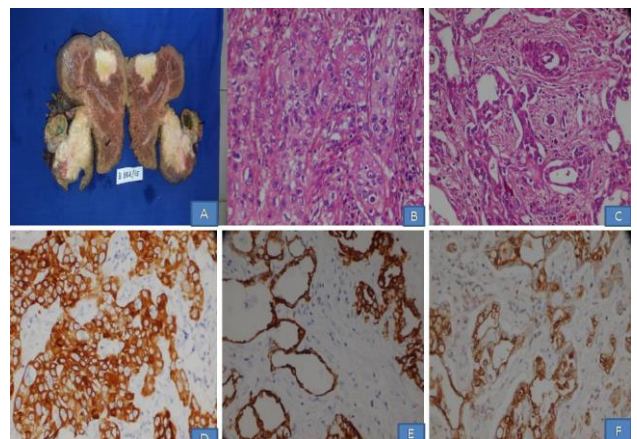


Figure 13: (A) Combined HCC-CC-two graywhite tumor masses in resected liver; (B) HCC area; (C) CC areas H and E40X; (D) HCC areas HepPar1 positive on IHC; (E) CC areas positive for CK7; (F) Polyclonal CEA on IHC.

DISCUSSION

Liver is a frequent site for many metastatic and primary neoplasms and can present as SOLs on radiological evaluation. In addition to malignancies a variety of inflammatory lesions, cysts and benign neoplasms of hepatocytic and non-hepatocytic origin can present as SOLs.²

Cong WM et al studied 31901 cases of primary hepatic SOLs of which non-neoplastic lesions accounted for 4.3% of cases.¹ In our study it accounted for 11.4% of cases of which simple liver cysts formed 55.5 % of cases.

Simple liver cysts are solitary non-parasitic cysts. They are believed to be congenital in origin, as an aberration of bile duct development. Increased prevalence in females was observed in our study like in other studies.^{3,4} The largest cyst which measured 20 cms was in a 78-year-old male, though there are studies stating that huge cysts are found almost exclusively in women over 50 years.⁴ Focal nodular hyperplasia (FNH) is a tumor like lesion with female preponderance and a controversial pathogenesis. A possible role of oral contraceptive pills or endogenous estrogen in the growth of FNH has been postulated. The patient in our study was a 35-year-old female.^{5,6} It can be mistaken for hepatic adenoma radiologically and macroscopically and needs histopathology for a conclusive diagnosis.

Cavernous hemangiomas and hepatic adenomas constituted the major bulk of benign tumors like in other studies.¹ Cavernous hemangiomas very rarely become symptomatic and warrant excision. Most of the symptomatic patients undergoing resection are females in their reproductive age group which supports the fact that estrogen has a role in their growth and development. Giant hemangiomas are larger than 4 cms and long standing ones can show extensive hyalinization like in one of our cases.^{7,8}

Patients with hepatic adenomas (HA) are mostly females with history of oral contraceptive pill intake.⁵ Though usually solitary, rare cases show multiple tumors and if more than 10 lesions are present it qualifies for hepatic adenomatosis. The one patient with hepatic adenomatosis in our study had history of clomiphene citrate intake for treatment of infertility and there are a few case reports with this association.⁹

Hepatic mucinous cystic neoplasms are rare tumors and are defined by WHO as a cyst forming epithelial neoplasm, usually showing no communication with the bile ducts, composed of cuboidal to columnar, variably mucin producing epithelium and having an ovarian type subepithelial stroma. The one patient in our study was a 63-year-old female with multiloculated cyst of diameter 23cms. Zen Y et al studied 29 cases of mucinous cystic neoplasm, all patients were females with median age of 45 years and 21 cases were multiloculated. A closely

related tumor is cystic type intraductal papillary neoplasm diagnosed on the basis of intraductal non-invasive papillary proliferation and absence of ovarian like stroma. In one study of 12 cases the male to female ratio was 1:1 and the median age was 62 years.¹⁰ Our patient was a 77-year-old male and the lesion was classified under benign group in our study as the tumor showed minimal atypia without evidence of invasion.

Hepatocellular carcinoma constituted 47.9% of malignant neoplasms. In many other studies, metastatic malignancy was the commonest.^{11,12} There is strong evidence of a role of hepatotropic viruses and cirrhosis in the pathogenesis of HCC and the youngest patient in our study, a 22-year-old male had hepatitis B and cirrhosis.¹³ In all studies males outnumbered females.^{12,14} In our study M: F ratio was 3:1 and macroscopically solitary lesions were commoner than multiple lesions. The average tumor size was smaller in HCCs arising in a background of cirrhosis when compared to those arising in a normal liver as observed in previous studies.¹⁴

Scirrhus HCC is a rare variant of HCC in which tumor cells with hepatocellular morphology are seen in a stroma with extensive fibrosis. It causes diagnostic challenge as tumor cells may be negative for HepPar1 and positive for CK7 and CK20 unlike traditional HCCs.¹⁵ The single case in our study was a 63-year-old male who had a firm, fibrous appearing tumor in liver with typical histopathological features. HepPar1 and CK7 were negative. Another variant we encountered was sarcomatoid HCC in which sarcomatoid areas on IHC showed positivity for pancytokeratin and vimentin.¹⁶

Hepatic carcinosarcoma is a rare tumor containing both sarcomatous and carcinomatous elements. The 72-year-old male with carcinosarcoma in our study had hepatitis C with cirrhosis. The carcinomatous component was conventional hepatocellular carcinoma with HepPar 1 positivity and the sarcomatous area had fibrosarcoma appearance with negative staining for epithelial markers. These tumors have a very poor prognosis.¹⁷

Liver is a common site for metastatic malignancy, the most frequent primary being gastrointestinal carcinoma as observed in our study.^{11,12} The second frequent lesion was metastatic GIST from stomach and diagnosis was confirmed in all the cases by expression of CD117. We encountered a rare case of nodular hepatic metastasis in a 75-year-old female with multiple myeloma (MM). When MM affects the liver diffuse and nodular patterns of infiltration have been described, and diffuse infiltration is said to be common.¹⁸

Intrahepatic cholangiocarcinoma (ICC) was the second most frequent primary hepatic malignancy in our study. ICCs are divided into two groups: CC arising in small intrahepatic bile ducts (peripheral type CC) and CC originating from the major intrahepatic bile ducts, including the hilum (hilar type CC). Bile duct carcinoma

arising near or at the confluence of the right and left hepatic ducts are known as hilar CC or Klatskin tumor. The term hilar CC is very commonly used to refer to this extrahepatic hilar bile duct carcinoma. The incidence of intra and extrahepatic CC in the literature has largely depended on how hilar CC, the commonest CC has been considered.¹⁹ 17 cases of hilar cholangiocarcinomas which we came across were not included in the present study. On the basis of gross morphology intrahepatic cholangiocarcinomas are classified into three subtypes: mass forming, periductal infiltrating and intraductal. Based on the morphology of tumor cells they are divided into bile duct type and cholangiolar type.^{20,21} In our study stromal desmoplasia and perineural invasion were more extensive in cases with mass forming type gross morphology. Both cases with intraductal type gross morphology were found to be of bile duct type on microscopy.

Combined hepatocellular-cholangiocarcinoma (c HCC-CC) is a rare form of primary liver carcinoma comprised of cells with histopathologic features of both cholangiocarcinoma (CC) and hepatocellular carcinoma (HCC). The most common is the classical type with areas of typical HCC intermixed with CC and a transition zone with tumor cells of intermediate morphology. IHC has an important role in identifying the two components.²² The one patient in our study had history of primary sclerosing cholangitis and showed intermixed classical HCC and CC areas confirmed by IHC.

CONCLUSION

Liver is a frequent site for many neoplastic and non-neoplastic diseases with malignant neoplasms forming the major bulk. Non-neoplastic lesions like simple liver cysts and FNH showed female predominance while benign neoplasms like cavernous hemangioma and hepatic adenomas were seen exclusively in females. Of the malignant liver tumors, hepatocellular carcinoma was the commonest, 2/3rd of patients were males and associated cirrhosis was seen in some cases. Metastatic malignancy formed the second largest group with primary in the gastrointestinal tract being the commonest. The rare lesions encountered were mucinous cystic neoplasm, hepatic adenomatosis, carcinosarcoma and cHCC-CC.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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