

## Spectrum of Primary Tumor Sites of Liver Metastatic Deposits Established on Histopathological Findings

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### Abstract:

**Aim:** descriptive analysis of the histomorphological spectrum of metastatic deposits in liver from different primaries and categorize them according to age, sex, morphology and immunohistochemical interpretations.

**Materials and Methods:** Our study was carried out in the Pathology department of NIMS Medical College, Jaipur on 94 patients who were suspected for liver metastasis clinically and underwent biopsy for histopathological findings over a time duration of 3 years. Complete clinical history of the included patients was taken along with their radiological investigations, serum markers, cytological findings and treatment history.

**Results:** In this study maximum number of cases of liver metastasis were Gastrointestinal in origin (47 cases; 50%) including colorectal, gall bladder, pancreas, pancreatobiliary and gastric origin. Out of these most common sites for liver metastasis was observed from gall bladder; reported as adenocarcinomas (18 cases; 19.15%) confirmed on IHC findings of keratin 7 and 20 and keratin19. Amongst the 10 cases of pancreatic origin metastasis (CEA and CA19.9), predominant cases (9 out of 10) were pancreatic adenocarcinoma and one case of neuroendocrine tumor of pancreas was reported. 10 cases were reported as pancreatobiliary metastasis on the basis of IHC findings out of which 6 were confirmed to be adenocarcinomas of pancreatobiliary origin one case of extrahepatic cholangiocarcinoma and 2 cases of periampullary origin were found. Stomach primaries (4 cases) were mostly adenocarcinomas which deposited metastasis in liver while one case of gastrointestinal stromal tumor was observed with IHC confirmation. Second most common metastasis was from Lung primaries (23 cases; 24.5%).

**Conclusion:** Incorporating clinical history, radiological findings, and IHC is crucial to differentiate primary liver tumors from metastases, ensuring accurate diagnosis and appropriate treatment planning.

**Keywords:** IHC, liver, tumors.

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### Introduction

The liver is a predominant site for cancer metastasis, responsible for approximately 25% of all metastatic cases. [1] Liver tissue provides a favourable environment for cancer cells to grow, contributing to its vulnerability to metastatic disease. Metastasis to the liver is common due to the organ's unique anatomical and physiological characteristics.

The liver receives blood from two primary sources: the hepatic artery and the portal vein, the latter carrying nutrient-rich blood from the digestive tract. This dual blood supply exposes the liver to circulating cancer cells from various parts of the body, particularly from organs connected to the gastrointestinal system. As a filtration system, the liver's role in processing blood makes it a frequent site for secondary tumors. Cancers such as

colorectal, breast, lung, and pancreatic cancers frequently spread to the liver because of these circulatory connections. The most frequent sources of liver metastases are colorectal cancers, followed by pancreatic and breast cancers. In women under the age of 50, liver metastases more often originate from breast cancer, while in patients over 70, gastrointestinal cancers are the primary source. Notably, 92% of metastatic liver lesions are carcinomas, of which 75% are adenocarcinomas. [2,3]

Understanding these metastatic patterns is important for patients with both a known and unknown primary. Understanding the tumor cell morphology and identifying the primary site of origin are crucial for guiding targeted chemotherapy and assessing prognosis. While

diagnosis can sometimes be made based on morphology alone, additional biomarkers, such as cytokeratins, S100, and leukocyte-common antigen (LCA), Synaptophysin, Vimentin, EMA etcetera can further help categorize the tumor and pinpoint the specific organ of origin. These biomarkers aid in distinguishing between different types of tumors, facilitating more precise treatment plans. Study aimed at descriptive analysis of the histomorphological spectrum of metastatic deposits in liver from different primaries and categorize them according to age, sex, and morphology and immunohistochemical interpretations.

### Material and Methods

Our study was carried out in the Pathology department of NIMS Medical College, Jaipur on 94 patients who were suspected for liver metastasis clinically and underwent biopsy for histopathological findings over a time duration of 3 years. Complete clinical history of the included patients was taken along with their radiological investigations, serum markers, cytological findings and treatment history.

### Inclusion Criteria:

All histopathological specimens from liver, suspected for liver metastasis whose biopsy were sent to pathology department (mostly core needle biopsies) which were categorised as Metastatic deposits on light microscopic findings. Specimens labelled as benign/ inflammatory/ hepatocellular carcinomas and inadequate specimens were excluded.

### Establishing the tumor type:

Accurate clinical history is essential for the pathological interpretation of a liver biopsy when metastasis is suspected. Information such as a history of prior cancer, radiological findings, and

serum tumor marker levels enables the most accurate correlation with pathological findings. The initial step in evaluating a liver biopsy is to determine the general tumor type, distinguishing whether the neoplasm is a carcinoma, sarcoma, lymphoma, or melanoma. While morphology often provides a diagnosis, poorly differentiated tumors may require additional ancillary studies for confirmation. A panel of biomarkers, including cytokeratins, S100, and leukocyte-common antigen (LCA), helps further categorize the tumor. Carcinomas typically express cytokeratins, lymphomas (exception of anaplastic large-cell lymphoma) express LCA, and S100 is a sensitive marker for melanoma. Based on these results, additional antibodies can be used to narrow down the differential diagnosis and guide further management.

In our study histopathological findings of all cases were studied on the basis of metastatic growth patterns and cellular morphology and in view of clinical history and other investigation findings were categorised as known primaries from the specific site, which were confirmed on immunohistochemistry (IHC) later. Metastatic deposits from unknown primary sites were evaluated on IHC and categorised respectively.

### Results

Our study was done on a total of 94 patients who were investigated for Liver metastasis over a duration of 3 years. It was observed that 58 out of 94 cases were males (61.7%) while 36 were females (38.2%).

Majority of the cases were found in the age group of 41-60 years comprising of 48 out of 94 cases. Only 1 case was found in the age group of 1 to 20 years.

**Table 1: Final Histopathological diagnosis of Metastatic Liver primary**

Final Histopathological diagnosis of Metastatic Liver primary.	Total cases	Percentage
<b>Bladder</b>	<b>2</b>	<b>2.13%</b>
Urothelial carcinoma	2	
<b>Cervix</b>	<b>2</b>	<b>2.13%</b>
Squamous cell carcinoma	2	
<b>Gastrointestinal origin-</b>	<b>47</b>	<b>50%</b>
<b>Colorectal</b>	<b>5</b>	<b>5.32%</b>
Adenocarcinoma of Colorectum	5	
<b>Gall bladder</b>	<b>18</b>	<b>19.15%</b>
Adenocarcinoma of Gall bladder	18	
<b>Pancreas</b>	<b>10</b>	<b>10.64%</b>
Neuroendocrine tumor of Pancreas	1	
Pancreatic adenocarcinoma	9	
<b>Pancreatobiliary</b>	<b>10</b>	<b>10.64%</b>
Adenocarcinoma of Pancreatobiliary origin	6	
Adenocarcinoma of periampullary region	2	
Extrahepatic Cholangiocarcinoma	2	

<b>Stomach</b>	<b>4</b>	<b>4.26%</b>
Adenocarcinoma of stomach	3	
Gastro intestinal stromal tumor	1	
<b>Lung</b>	<b>23</b>	<b>24.47%</b>
Adenocarcinoma of Lung	15	
Neuroendocrine carcinoma of Lung	6	
Squamous cell carcinoma	2	
<b>Nasopharynx</b>	<b>1</b>	<b>1.06%</b>
Nasopharyngeal carcinoma	1	
<b>Oral cavity</b>	<b>1</b>	<b>1.06%</b>
Squamous cell carcinoma	1	
<b>Ovary</b>	<b>1</b>	<b>1.06%</b>
Serous carcinoma of Ovary	1	
<b>Kidney</b>	<b>4</b>	<b>4.26%</b>
Clear cell renal cell carcinoma	4	
<b>Leiomyosarcoma</b>	<b>1</b>	<b>1.06%</b>
Leiomyosarcoma	1	
<b>Liver primary</b>	<b>8</b>	<b>8.51%</b>
Hepatoblastoma	1	
Hepatocellular carcinoma	2	
Intrahepatic Cholangiocarcinoma	4	
Neuroendocrine carcinoma liver	1	
<b>Prostate</b>	<b>1</b>	<b>1.06%</b>
Prostatic adenocarcinoma	1	
<b>Unknown primary</b>	<b>3</b>	<b>3.19%</b>
Epithelial origin	2	
Unknown primary	1	
<b>Grand Total</b>	<b>94</b>	<b>100%</b>

All 94 cases came with a presentation of liver lesion and were clinically and radiologically suspected to be metastatic deposits. Out of these, 12 cases (12.7%) were unknown primaries initially and rest 82 (87.2%) were known cases of malignancies which were suspected with hepatic metastasis. On histopathological examination and further IHC categorization, 86 cases (91.4%) were classified into metastatic deposits in liver from the respective primary sites.

These were diagnosed on the basis of the clinical suspicion, radiological findings, known primary tumor history and most importantly on the basis of histomorphological and immunohistochemical findings.

8 cases which were clinically suspected as metastatic deposits were later found to be liver primaries, 4 of which were classified as Intrahepatic Cholangiocarcinoma, 2 cases were classified as Hepatocellular Carcinoma on histopathology and IHC results. 1 of these liver primaries was diagnosed as Hepatoblastoma.

Interestingly, a rare case of neuroendocrine carcinoma was also reported as a liver primary in a 51-year female patient who was earlier suspected for metastatic deposits in liver.

On radiological investigations, histopathological examination and IHC studies, it was confirmed to

be a case of neuroendocrine tumor of hepatic origin. 3 out of 94 cases was labelled as Unknown primaries initially. As the amount of biopsy sample received was limited in two cases, Metastasis was confirmed on histopathology and a HepPar 1 and keratin 7 and keratin 19 were added for evaluation after which these were labelled as metastatic deposits of epithelial origin. In one of our case, Tumor was confirmed but the small biopsy tissue got exhausted due to which we were unable to subtype the origin of the deposits and it remained an unknown primary.

As shown in Table 1 and illustrated in pie chart, in our study maximum number of cases of liver metastasis were Gastrointestinal in origin (47 cases: 50%) including colorectal, gall bladder, pancreas, pancreatobiliary and gastric origin. Out of these most common sites for liver metastasis was observed from gall bladder; reported as adenocarcinomas (18 cases; 19.15%) confirmed on IHC findings of keratin 7 and 20 and keratin 19.

Amongst the 10 cases of pancreatic origin metastasis (CEA and CA19.9), predominant cases (9 out of 10) were pancreatic adenocarcinoma and one case of neuroendocrine tumor of pancreas was reported.

10 cases were reported as pancreatobiliary metastasis on the basis of IHC findings out of

which 6 were confirmed to be adenocarcinomas of pancreatobiliary origin one case of extrahepatic cholangiocarcinoma and 2 cases of periampullary origin were found.

Stomach primaries (4 cases) were mostly adenocarcinomas which deposited metastasis in liver while one case of gastrointestinal stromal

tumor was observed with IHC confirmation. Second most common metastasis was from Lung primaries (23 cases; 24.5%). It was observed that most of these were Non-small cell carcinomas (17 cases). 6 out of the 20-lung metastasis were diagnosed as neuroendocrine in origin which was confirmed on IHC (CD56, Synaptophysin and chromogranin positivity).

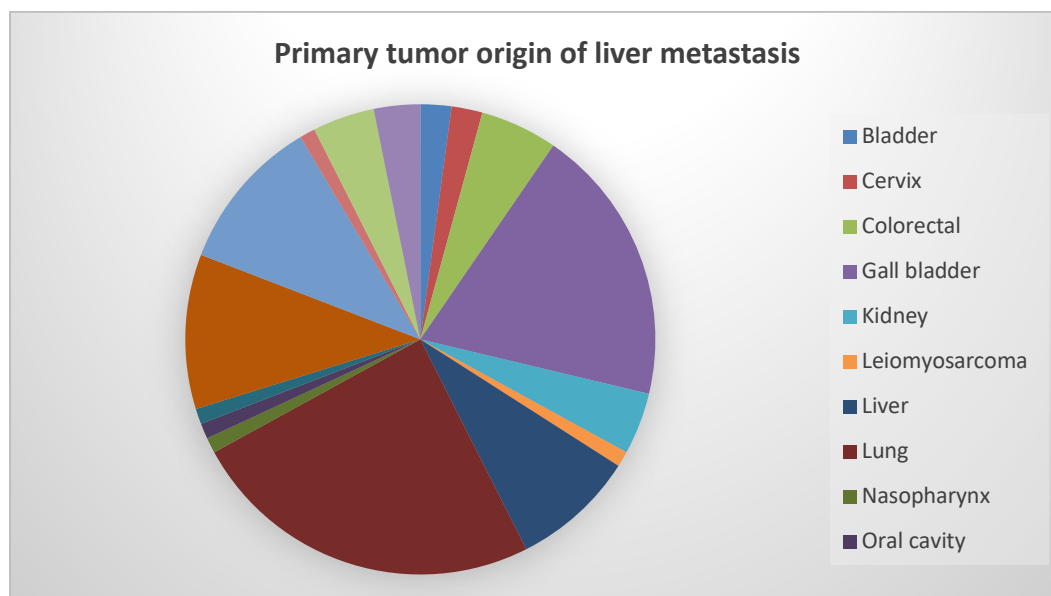


Figure 1:

Other usually uncommon sites from which primaries were reported in our study were from Bladder, cervix, kidney, ovary and nasopharynx. The bladder tumor origin was reported as urothelial carcinoma while the two cases of cervical primary and individual case of oral cavity was labelled squamous cell carcinoma confirmed on IHC findings along with clinical details. Two cases of metastatic deposits of Clear cell renal cell

carcinoma were done. Deposits in liver from individual cases of ovarian primary was classified as High-grade serous carcinoma of ovary, while one case each of nasopharyngeal carcinoma, Leiomyosarcoma (primary in retroperitoneum) and Prostatic adenocarcinoma were also reported.

The age wise distribution of histopathological type of metastatic tumors is shown in Table 2.

Table 2: Histopathological type of tumor

Table 2: Histopathological type of tumor	1-20	21-40	41-60	61-80	81-100	Grand Total
Adenocarcinoma of Colorectum		1	3	1		5
Adenocarcinoma of Gall bladder		1	10	7		18
Adenocarcinoma of Lung			5	9	1	15
Adenocarcinoma of Pancreatobiliary origin		1	2	3		6
Adenocarcinoma of periampullary region			1	1		2
Adenocarcinoma of stomach			1	2		3
Clear cell renal cell carcinoma			2	2		4
Epithelial origin			1	1		2
Extrahepatic Cholangiocarcinoma			2			2
Gastro intestinal stromal tumor			1			1
Hepatoblastoma	1					1
Hepatocellular carcinoma		1	1			2
Intrahepatic Cholangiocarcinoma			2	2		4
Leiomyosarcoma			1			1
Nasopharyngeal carcinoma			1			1
Neuroendocrine carcinoma of Lung			2	4		6
Neuroendocrine tumor of Pancreas			1			1

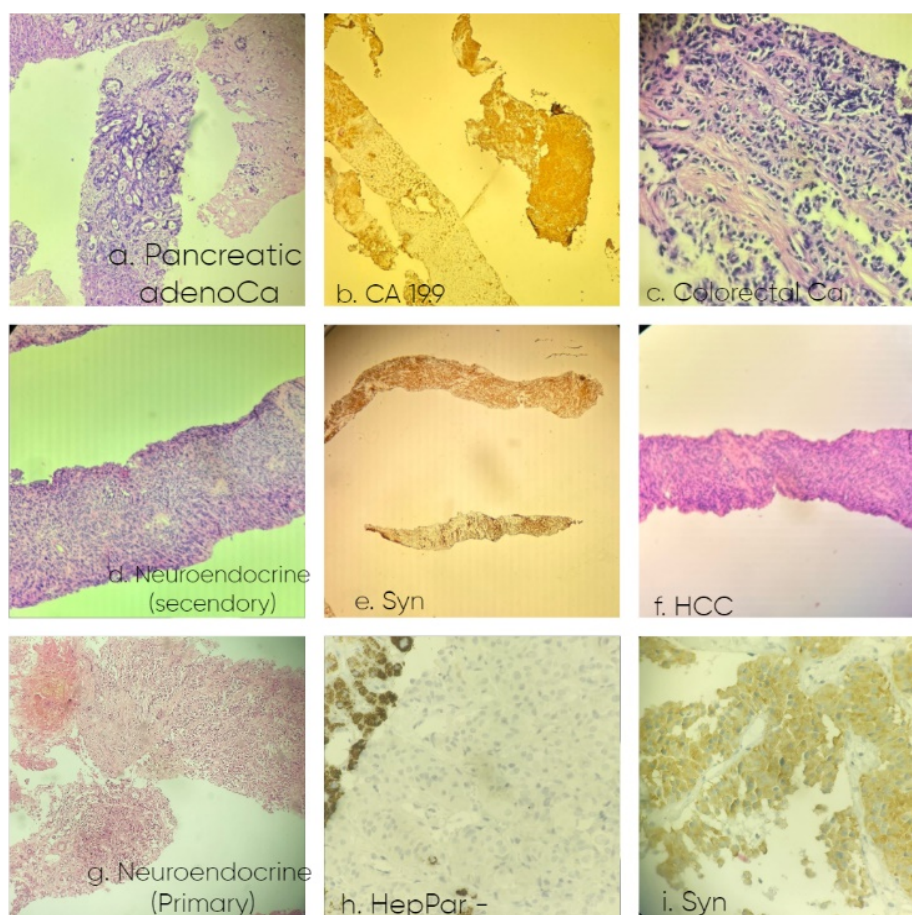
Pancreatic adenocarcinoma		1	6	2		9
Prostatic adenocarcinoma					1	1
Serous carcinoma of Ovary				1		1
Squamous cell carcinoma			3	2		5
Unknown primary			1			1
Urothelial carcinoma			1	1		2
Neuroendocrine carcinoma liver			1			1
<b>Grand Total</b>	<b>1</b>	<b>5</b>	<b>48</b>	<b>38</b>	<b>2</b>	<b>94</b>

## Discussion

The high frequency of liver involvement in metastatic disease can be explained by the different hypotheses of metastatic spread.

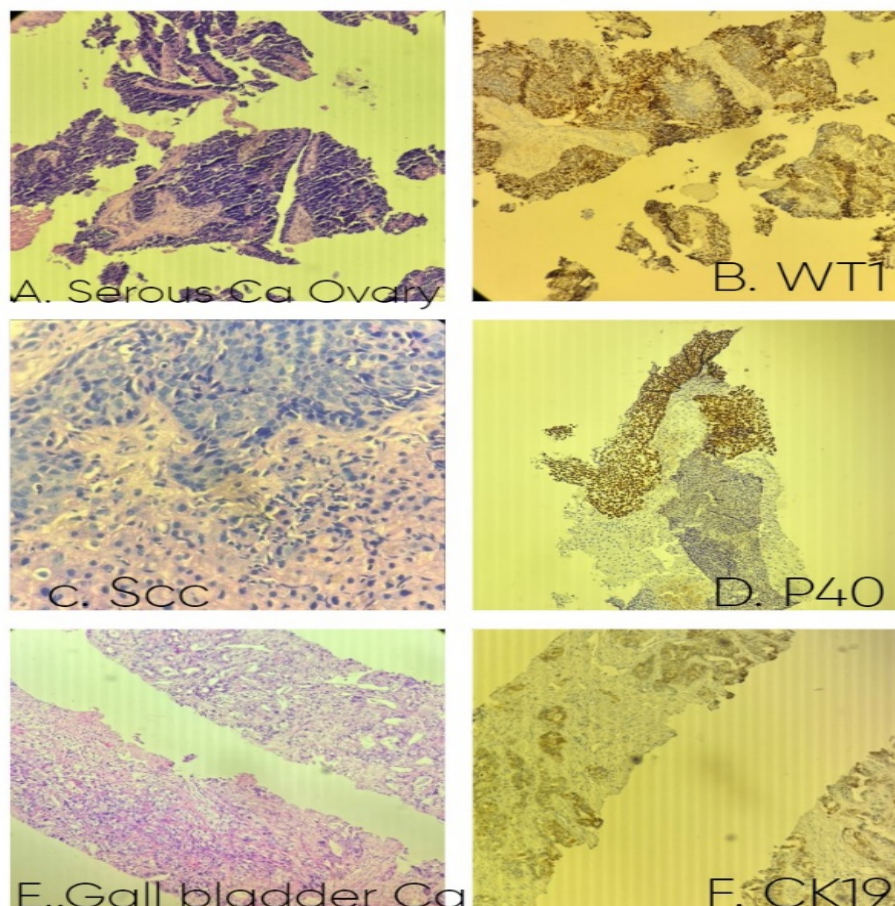
The double blood supply of the liver by the portal vein and the hepatic artery facilitates entrapment of circulating cancer cells, according to the

“mechanical or hemodynamic hypothesis”, which explains the high incidence of liver metastases in patients with gastrointestinal carcinomas. However, some primary tumors selectively target the liver as a metastatic location, according to the “seed-and-soil” hypothesis. [4] IHC can help determine whether a liver tumor is of primary hepatocellular or metastatic origin.



**Figure 2:** (A) Pancreatic Adenocarcinoma metastasis in liver (H and E stain, 100x). (B) CA19.9 positivity in pancreatic adenocarcinoma. (C) Metastatic deposits of colorectal carcinoma. (H and E stain, 400x). (D), (E) Neuroendocrine secondary deposits in liver (H and E stain, 100x) with synaptophysin positivity. (F) Hepatocellular carcinoma (H and E stain, 100x). (G),(H),(I) Primary neuroendocrine tumor of liver (H and E stain, 100 x), HepPar negative and Synaptophysin positive.





**Figure 3: (A), (B). Metastatic deposits of High-Grade serous carcinoma of ovary (Hand E stain,100X) showing WT1 positivity. (C), (D) Hepatic metastasis of squamous cell carcinoma (H and E stain) showing P40 positivity. (E) Gall bladder adenocarcinoma metastasis (H and E, 100x) with CK19 positivity.**

Colorectal cancers are mainly adenocarcinoma of various grades including well, moderate to poorly differentiate with histomorphologically different subtypes. [5] Liver metastasis is the most common site of distant spread, accounting for approximately 15–25% of colorectal cancer patients will have distant metastases at the time of primary diagnosis. [6] Liver metastasis can be presented as glandular formation, mucinous changes, signet ring cell morphology, and poorly differentiated form along desmoplastic stroma and dirty necrosis. Main differential diagnosis of a liver metastatic lesion of colorectal carcinoma is primary intrahepatic cholangiocarcinoma. There has been a huge paradigm shift in the treatment of Colorectal liver metastasis. [7] So, incorporating the complete clinical history, radiological findings, and IHC profile is critical to establish a definitive diagnosis, especially in challenging cases with unusual morphology or overlapping immunophenotypic features. Typically, colorectal carcinoma are CK7-negative, CK20-positive, CDX2-positive. CDX2 and SATB2 are key markers. Some poorly differentiated tumors may lack these markers. [8] Using this IHC profile, pathologists can differentiate metastatic colorectal adenocarcinomas from other liver lesions such as ICC, hepatocellular

carcinoma, and metastases from non-colorectal primaries.

#### **Gall bladder cancers**

The three major metastatic pathways of GBC include hematogenous metastasis, lymphatic metastasis, and direct infiltration. [9] More than half of the GBC could directly infiltrate into adjacent organs such. Due to the adjacency between the liver and the gallbladder, the liver is the leading metastatic site accounting for more than 50% of metastatic GBC. [10] In most of the cases, primary from gall bladder were rendered as per radiological findings and clinical history in previously operated cases. Neuroendocrine tumors are defined as neoplasms that are composed of atypical epithelial cells with neuroendocrine differentiation. Neuroendocrine tumors have site specific grading system which is based on mitotic count or Ki67 labelling index. [11] Neuroendocrine tumors are usually found in the small intestine, appendix, rectum, pancreas, and lung. [12]

Prosser JM et al reported a series of 23 needle biopsies of neuroendocrine tumors occurring in the liver. They examined aspirate smears, core biopsies, and touch preparations. Characteristic

cytologic attributes of neuroendocrine tumor, histomorphological findings i.e., thick fibrous stroma or small "nests" of tumor cells, along with use of immunohistochemical staining provides reliable evidence of the cell of origin in confusing cases. [13]

Characteristically, neuroendocrine tumors show immunoreactivity for neuroendocrine markers, including chromogranin A, synaptophysin, and cluster of differentiation molecule 56 (CD56) and Insulinoma-associated protein 1 (INSM1). [14]

Metastatic tumors show variable positivity of site-specific markers. According to study of Kaufmann and other study, substantial number of extrapulmonary small cell cancers expressed TTF-1.15 Therefore, immunohistochemistry for TTF-1 in such tumours should be interpreted with caution in case of unknown primary or multiple metastasis. However, CDX2 is quite site specific related to colorectal origin. Insulin gene enhancer protein Islet-1 (ISL1), is expressed in various NENs located in the pancreas but less specificity. [16]

Along with these, other challenges in determining if a NET/NEC is primary to the liver or metastatic disease because of lack of distinctive tumor morphology, less specific immunostains to indicate or exclude hepatic origin, small primary tumors and difficult to detect by endoscopy and imaging, and most importantly NET and NEC can involve multiple organs at presentation, including the liver.

We reported One case 51-year-old female presented as multiple Liver SOL with lytic bone lesions with unknown primary. Biopsy and immunohistochemistry showed neuroendocrine tumor grade 2. As per radiologically findings primary from liver origin kept.

#### **Lung non-small cell carcinoma**

Organ-specific colonization by malignant cells may occur because of specific and close interactions between the cancer cells and the target organ. [17] Lung cancer may cause biliary tract obstruction by metastasizing to lymph nodes in the porta hepatis or hepatic parenchyma.

According to Kagohashi et al, incidence of liver metastasis was 5.8% at the time of initial diagnosis of lung cancer. [18] A recent study found that liver metastasis in NSCLC is linked to a worse prognosis compared to metastases in the lung, brain, or bone. [19] In our study 17 out of 23 liver metastasis from lung shows features of Non-small cell carcinoma, in which maximum were diagnosed as metastatic deposits of Adenocarcinoma of lung. However, according to Kagohashi et al showed incidence of liver metastasis was high in patients with SCLC (17.5%; 28/160), whereas the incidence of liver metastasis in patients with adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma

was 4.1% (20/484), 3.6% (12/332), and 2.9% (2/68), respectively. [20]

We reported on case of Adenocarcinoma with gastric primary, as patient has multiple Liver SOL with gastric mass.

#### **GIST**

Gastrointestinal stromal tumours (GISTs) are the most frequent mesenchymal neoplasm occurring in the gastrointestinal tract. The most common sites for GISTs are the stomach (up to 60% of cases) and small bowel (up to 30% of cases). A significant proportion of patients who undergo complete resection of their primary GIST experience tumor recurrence, typically at a median interval of 18 to 24 months. Upon recurrence, approximately two-thirds of these patients will develop liver metastases, and about half will present with peritoneal involvement. [21]

Pathologically, the diagnosis of GISTs is based on morphological features as well as immunohistochemical findings, with CD117 (KIT) and/or DOG1 positivity. GIST should be differentiated from Schwannoma (S100 positivity) and leiomyoma/ leiomyosarcoma (H- Caldesmon positivity). [22]

In our study, one case presented as a metastatic leiomyosarcoma with the primary tumor originating from the peritoneum, should be differentiated from GIST.

Retrospective multicenter study in northern China on GIST patients with liver metastases showed that both imatinib monotherapy and combination therapy resulted in prolonged survival, with combination therapy offering greater clinical benefits. KIT mutation study along with evolving different types of therapeutic approaches help to improve survival outcome.23

Squamous cell carcinoma from head and neck region metastasizing into Liver is uncommon, but not least.

Liver metastasis in case of primary kidney mass in adult patient, we have 4 cases of clear cell type. Diagnosed with the help of IHC and clinical details.

#### **Conclusion**

Liver metastasis can arise from various primary tumors, each with distinct histomorphological features and immunohistochemical profiles that help guide diagnosis. Metastatic colorectal, gallbladder, neuroendocrine, lung, GIST, and even less common tumors like squamous cell carcinoma or renal clear cell carcinoma can present diagnostic challenges. Incorporating clinical history, radiological findings, and IHC is crucial to differentiate primary liver tumors from metastases,

ensuring accurate diagnosis and appropriate treatment planning.

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