DOI: 10.7860/NJLM/2024/73268.2884

Original Article

Pathology Section

Role of Immunohistochemistry in Categorisation of Metastatic Tumours of Liver: A Cross-sectional Observational Study

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ABSTRACT

Introduction: The liver is the body's largest solid organ and receives a dual blood supply, making it an easy target for metastases from both extra-abdominal and abdominal lesions. In adults, the most common sites of primary lesions are the breast, colon, lung and pancreas. Liver biopsies are pivotal for managing patients with metastatic diseases, aiding in diagnosis and treatment planning. When primary cancer sites are undetectable, the diagnosis often falls under Carcinoma of Unknown Primary (CUP), which carries a poor prognosis. Immunohistochemistry (IHC) is critical in such cases, using antibodies to identify the cancer's origin when other methods fail. This technique is vital for confirming known malignancies and diagnosing elusive ones, thus informing treatment and improving patient outcomes.

Aim: To study the role of IHC in the categorisation of metastatic tumours of the liver.

Materials and Methods: A cross-sectional observational study was conducted in the Department of Pathology, Sri Aurobindo Medical College and Postgraduate (PG) Institute, Indore, Madhya Pradesh, India, between March 2021 and April 2024. Core needle biopsy samples of 65 cases were processed and analysed for Haematoxylin and Eosin (H&E) stain and IHC markers. Data on demographics and lesion characteristics were entered into Microsoft Excel and analysed with a trial version of Statistical Package for the Social Sciences (SPSS). Significance was assessed using Pearson's Chi-square test, with a p-value <0.05 considered statistically significant, and IHC findings were compared with radiological data.

Results: The mean±Standard Deviation (SD) age of the study participants was 54.26±11.858 years. During the study period, 65 cases were recorded, with a slight female preponderance (n=34) over males. Hepatomegaly (n=23) was the most common clinical finding noted. All cases were grouped according to the radiological findings with reference to whether the primary site of the lesion was known or unknown. Twenty-seven cases had a known primary lesion, while 38 cases were classified as unknown. Accordingly, an IHC marker panel of Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20) was initially applied, followed by the respective organ specific markers. With respect to all 65 cases, a concordance of 98.46% was recorded with the radiological findings, while a discordance of 1.54% was noted. A p-value <0.05 suggested that both IHC and the radiological findings regarding the nature of the primary lesion, whether known or unknown, were significant.

Conclusion: Immunohistochemistry is paramount in ascertaining the origin of the primary lesion in hepatic metastatic tumours, which is crucial for prompt therapeutic intervention and favourable patient outcomes. The integration of IHC with radiological data is essential for accurate diagnosis and treatment plans.

Keywords: Abdominal lesions, Malignancies, Radiology, Unknown primary

INTRODUCTION

The liver frequently serves as a receptacle for metastatic deposits, and the execution of a liver biopsy is integral to the clinical oversight of a multitude of patients. Its utility lies in substantiating the diagnosis of metastatic involvement, pinpointing the neoplasm's site of origin, discerning the histological subtypes of the tumour, and securing tissue samples for ancillary analyses imperative for clinical direction and prognostic determination [1,2].

In certain cases, the primary locus of the metastases may defy identification despite thorough clinical, radiological and pathological inquiry, leading to a diagnosis of CUP. The prognostic outlook for such instances is generally bleak [3,4].

Radiological manifestations of metastatic conditions can appear as multiple hepatic lesions; however, the presence of a singular hepatic lesion in an adult may also suggest metastasis. In this context, IHC assumes the role of an indispensable diagnostic tool, utilising a spectrum of antibodies. IHC is advantageous when the morphological features and the identification of the primary site of the oncogenic source remain elusive. Under these circumstances, an initial panel is constituted based on the histopathological findings and is then stratified by gender. This panel customarily includes cytokeratins 7 and 20, followed by markers specific to individual organs. For undifferentiated malignancies, markers such as pan-cytokeratin, Cluster Differentiation (CD45), vimentin or desmin, and S100 are employed to refine the search for the lesion's provenance [3-5].

The heterogeneity of metastatic neoplasms in hepatic biopsies is characterised by the incidence of various carcinomas, the intrinsic biological characteristics of distinct tumours that predispose them to hepatic dissemination, and the clinical rationale underpinning the biopsy indication. Strumfa I et al., found that 45% of hepatic tumours in a tertiary care setting were metastatic, with adenocarcinoma being the most frequent (65.5%), mainly from colorectal (48.2%) and other gastrointestinal cancers [5,6]. Neuroendocrine (NE) carcinomas were also common (16%), while lymphomas were scarce (0.4%) [7].

Malone M et al., (2022) highlighted the diagnostic importance of immunohistochemical markers such as Thyroid Transcription Factor 1 (TTF-1), CK7, Napsin A and p40 for identifying non small cell lung carcinoma, despite the lack of molecular assays. These markers are crucial for the early detection and treatment of primary cancer sites, significantly impacting healthcare costs. Liver-specific and metastatic adenocarcinoma markers are essential for pinpointing the origin of hepatic malignancies [8,9].

The present study delineates the attributes of IHC, which, in instances of established malignancy, serves as a confirmatory

assay, and in the context of unidentified primary malignancies, functions as a conclusive diagnostic procedure. Consequently, this renders IHC an essential tool, facilitating the expeditious and effective implementation of curative and therapeutic strategies, thereby enhancing the prospects of patient survival.

Hence the aim of the present research was to study the role of IHC in the categorisation of metastatic tumours of the liver. The objectives were to evaluate the radiological and clinical aspects of individuals presenting with metastatic tumours of liver, to establish the histomorphological characteristics of metastatic tumours of the liver, to explore the expression of several IHC markers for determining the site of origin of a metastatic tumour and to analyse the IHC findings in conjunction with the radiological findings regarding the primary site of the tumour.

MATERIALS AND METHODS

The present ambispective cross-sectional study was conducted in the Department of Pathology, Sri Aurobindo Medical College, Indore, Madhya Pradesh, India, from March 2021 to April 2024. The research retrospectively examined cases up to September 2023 and prospectively from October 2023. The three-year analysis encompasses 65 cases of liver metastasis. Institutional Ethical Committee approval was obtained (IEC No. SAIMS/IEC/39/23). A comprehensive review of immunohistochemically confirmed cases was conducted through the examination of both old and new pathology records and slides.

Inclusion criteria: All histopathology proven cases of metastatic tumours of the liver undergoing IHC were included in the study.

Exclusion criteria: Cases in which the biopsy was inadequate were excluded from the study.

Study Procedure

The present study included all histopathologically diagnosed and immunohistochemically confirmed metastatic liver tumours from the Surgical and Oncology Departments. Clinical and radiological data were collated and analysed. Core needle biopsies, fixed in 10% formalin, followed standard grossing protocols, were paraffin-embedded, and sectioned at 4-5 microns for H&E staining.

Immunohistochemistry profiling utilised markers with their respective antibodies mentioned alongside them, such as CK7 (KRT7), CK20 (KxT7), HepPar1 (HAS/E8), glypican 3 (GPC3-88) and AFP (C3), to classify the primary tumour and differentiate between hepatocellular carcinoma, metastatic liver tumours and cholangiocarcinoma. Additional markers included ER (EP1), PR (EP2), HER2/neu (EP3), Ki67 (MKI67/2462), GATA3 (QR018), p40 (QR020), p63 (4A4), Napsin A (QR052), Synaptophysin (SP11), Chromogranin (LK2H10), NSE (MIGN3), CD56 (123A8), EMA (E29), MUC2 (CCP58), CDX2 (CDX2.88), SATB2 (SATB26929), CEA (CEA31), CA19.9 (C241514), CK19 (RCK108), AMACR (RBTAMACR), CD10 (QR021), PSA, NKX3.1 (NKX3.1/2576), PanCK (AE1/AE3 PCK26), vimentin (V9), desmin (DER-11), CD45 (PD7/2416), HMB45, MelanA (A103), CK5/6 (D5/16D4), PAX8 (PAX8/2774R), CD117 (EP10), SOX10 (SOX10/991), and DOG1 (11), which were employed for specific cancer subtypes. IHC was performed on a Ventana Benchmark Gx fully automated workstation and these panels helped determine the tumour's origin and type.

Based on this subgrouping and the gender of the patient, a system-specific marker was used in cases with an unknown primary site of the lesion. However, with reference to the known primary lesion, a definitive marker was applied to confirm the origin [Table/Fig-1].

IHC diagnosis (origin)	Common organ specific IHC marker panels
Breast	ER, PR, HER2/neu, GATA3
Lung- ADCC	Napsin A, TTF1, p40
Lung- SCC	p40, p63, NapsinA
GIST metastases	CD117, DOG1
Gastrointestinal	CEA, CDX2, EMA, SATB2, MUC2
Gastric	CDX2, CEA, SATB2, CK5/6, GATA3
Colorectal	CDX2, SATB2, AMACR, CD10, B Catenin
Cholangiocarcinoma	CA19.9, EMA, CEA, CK19, TTF1, CA125
Pancreatobiliary	MUC1, SATB2, CEA, CA19.9, EMA, CK19, AFP, Synaptophysin
Biliary	CA19.9, HepPar1, CEA, CA125, CDX2, HER2/neu
Neuroendocrine metastases	Synaptophysin, Chromogranin A, NSE, CD56, Ki67, PanCK, TTF1
Nasopharyngeal carcinoma	PanCK, CD45, p63, p40
Undifferentiated/urothelial origin	Vimentin, Desmin, S100, MELANA, HMB45, p40, Synaptophysin, HepPar1, Glypican3, SMA, CD45, SOX10, CD34 CD117.
Renal	PanCK, CD10, PAX8, Vimentin, CEA, Synaptophysin
Gall bladder	CA19.9, CK19, MUC1, AFP, HepPar1, CDX2, CA125
Prostate	PSA, NKX3.1, PanCK, AMACR
Mets/primary HCC*	Glypican3, HepPar1, AFP, CEA, CDX2, CA19.9, CK19

[Table/Fig-1]: Common IHC marker panels that are applied apart from CK7, CK20 [10-14].
*The final diagnosis of the Mets/primary HCC lesion case was affirmed on IHC; Mets: Metastasis; ER: Oestrogen receptor; PR: Progesterone receptor; HER2/neu: Human epidermal growth factor receptor 2; GIST: Gastrointestinal stromal tumour; TTF-1: Thyroid transcription factor-1; CD: Cluster differentiation; DOG1: Discovered on gastrointestinal stromal tumours; CEA: Carcinoembryonic antigen; CDX2: Caudal-type homeobox 2; EMA: Epithelial membrane antigen; SATB2: Special AT-rich sequence-binding protein 2; AMACR: Alpha-methylacyl-CoA racemase; CA19.9: Carbohydrate antigen 19-9; AFP: Alpha fetoprotein; NSE: Neuron-specific enolase; HMB45: Human melanoma black 45; Paired box genes; PSA: Prostate-specific antigen

STATISTICAL ANALYSIS

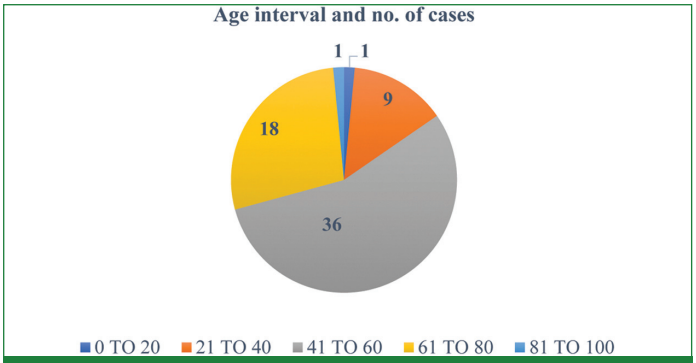
All the gathered data was categorised by age, gender, site, type, and number of lesions. The data was entered into Microsoft Excel (version 2019) and analysed using the trial version of the SPSS software. The Pearson's Chi-square test was applied, and a p-value of <0.05 was considered significant. Concordance and discordance analyses were performed between the IHC findings and the radiological findings.

RESULTS

In the current study, a total of 65 cases were recorded and categorised into various subgroups based on age, gender, clinical findings, radiological findings, histopathological diagnosis, and finally, the final IHC diagnosis established irrespective of whether the primary site of the lesion was known or unknown.

Patient demographics: Out of the 65 cases, 34 (52.3%) were of females, compared to 31 (47.7%) male cases. The male-to-female ratio was 0.91. The cases were divided by age group, and the number of cases in each interval was recorded accordingly. Metastatic tumours were most common in the 41-60 years age group 36 (55.38%), followed by the 61-80 years group 18 (27.69%), the 21-40 years group 9 (13.84%), and both the ≤20 and ≥81 years groups (1.53% each). The mean age was 54.26 years, with a SD of ±11.858 years [Table/Fig-2].

Clinical presentations: Hepatomegaly (23 cases) was the most prevalent clinical presentation, followed by nipple discharge and/or ulceration (11 cases). Abdominal pain, weight loss and fever with hepatomegaly accounted for six cases, while dyspnoea, weight loss and lung mass were recorded in five cases. Abdominal pain with anaemia was noted in some, along with sweating in a few cases, diarrhoea in others, and ascites with dyspnoea in addition to abdominal pain, which accounted for four cases each. Other symptoms included one case each of a retroperitoneal mass, haematuria, burning micturition and incontinence, as well as, one case of dyspnoea with weight loss [Table/Fig-3].



[Table/Fig-2]: Pie chart showing distribution of the number of cases with the age intervals (in years).

Clinical presentation	No. of cases, n	% of cases
Nipple discharge and/or ulceration, hepatomegaly	11	16.9
Dyspnoea, weight loss, lung mass	5	7.8
Anaemia under evaluation, abdominal pain	4	6.2
Hepatomegaly	23	35.4
Diarrhoea, abdominal pain	4	6.2
Abdominal pain, weight loss, hepatomegaly, fever	6	9.2
Haematuria, abdominal pain	1	1.5
Burning micturition, incontinence	1	1.5
Dyspnoea, abdominal pain, ascites	4	6.2
Retroperitoneal mass	1	1.5
Dyspnoea, weight loss	1	1.5
Abdominal pain, weight loss, sweating	4	6.2
Total cases (N)	65	100

[Table/Fig-3]: Clinical signs and symptoms along with the number of cases noted in each combination.

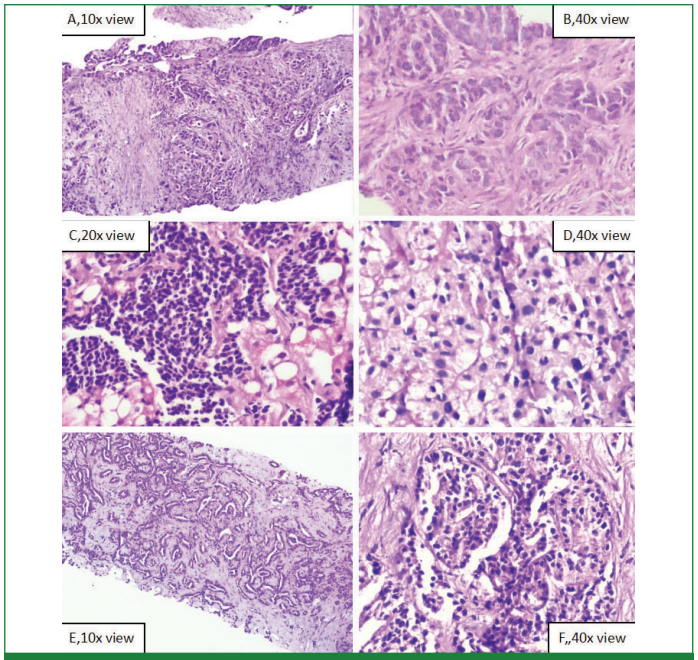
Histopathological diagnosis: The cases were subgrouped under metastatic adenocarcinoma, metastatic carcinoma, metastatic poorly differentiated carcinoma, metastatic mucinous adenocarcinoma, and doubtful cases of primary or metastatic hepatocellular carcinoma. A total of 47 (72.3%) of these cases had histomorphology consistent with metastatic adenocarcinoma, while the remaining 11 (16.9%) had histomorphology consistent with metastatic poorly differentiated carcinoma, 2 (3.1%) with metastatic carcinoma and 5 (7.7%) were classified as doubtful cases of hepatocellular carcinoma [Table/Fig-4a-f].

Radiological findings: The cases were divided based on whether the primary location of the liver lesion was known or unknown on radiology. Out of 27 cases with a known primary site of cancer, 18 had multiple lesions, and nine had a single lesion. In 38 cases with an unknown primary site of cancer, 24 had multiple lesions, while 14 had a single nodule [Table/Fig-5,6a,b].

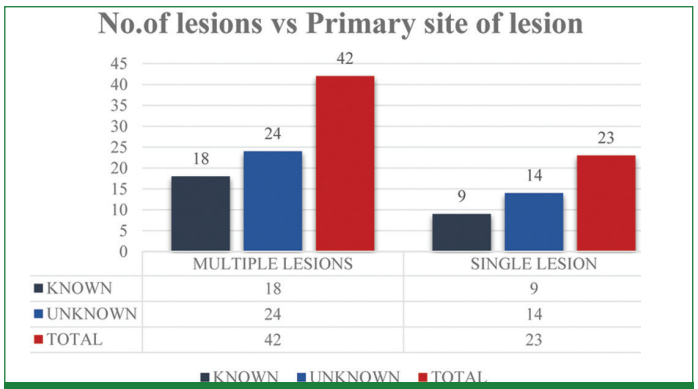
IHC in radiology proven known cases of cancer: Although IHC was applied to all 65 cases, in the 27 cases with a known primary lesion on radiology, IHC was used as a confirmatory test to affirm the final diagnosis. It was found that 26 (96.3%) of these 27 cases were consistent with the IHC final diagnosis, whereas 1 (3.7%) case revealed a discrepancy in the final diagnosis. This case was a recognised example of a pancreatic tumour with liver lesions, and the IHC results indicated metastatic adenocarcinoma of gastrointestinal origin. This demonstrates that in most cases, IHC can be considered a definitive method for determining the origin of the primary lesion.

The concordance and discordance analysis were conducted between the IHC findings and the radiological findings for all 65 cases, as IHC was applied to all of them [Table/Fig-7].

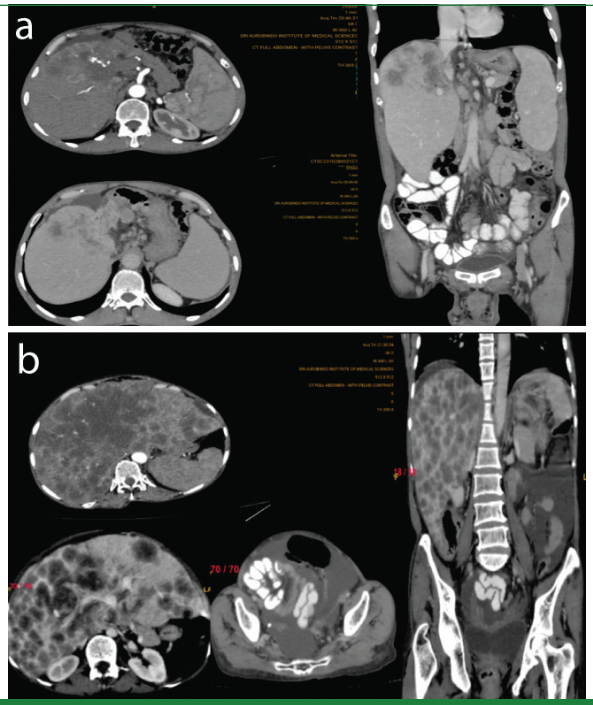
Based on the above table, it is evident that IHC has a 98.46% concordance with the radiological findings and a discordance



[Table/Fig-4]: Represents the scanner and high-power view of the histomorphological spectrum seen in metastatic tumours of liver; a) Metastatic adenocarcinoma liver (H&E, 10x); b) Metastatic squamous cell carcinoma liver (H&E, 40x); c) Metastatic neuroendocrine tumours of liver ((H&E, 20x); d) Trabecular pattern of hepatocellular carcinoma (H&E, 40x); e) Metastatic carcinoma of colon-liver (H&E, 10x); f) Metastatic prostate carcinoma liver (H&E, 40x).



[Table/Fig-5]: Illustrates the relationship between the number of lesions and the primary site of the lesion based on the radiological findings.



[Table/Fig-6]: a) Radiological images of a single Space-occupying Lesion (SOL) in liver (arterial-venous phase, axial and coronal); b) Radiological images of a multiple secondaries in the liver with ascites (arterial-venous phase, axial and coronal).

Analysis	IHC and radiology	Value	%
Concordance	64	0.9846	98.46
Discordance	1	0.0154	1.54
Total cases	65	-	100

[Table/Fig-7]: Concordance and discordance between the IHC findings and the radiological findings for the entire case load of 65 cases.

of merely 1.54%, according to the present study. Therefore, it is confirmed that IHC is the definitive method for the final diagnosis of any known or unknown lesion.

Based on IHC, breast cancer was the most common origin of metastatic liver lesions, accounting for 23.1% of cases, with the majority presenting multiple lesions. Gastrointestinal cancers comprised 13.8% of cases, divided between multiple and solitary lesions, with most being of unknown primary origin. Pancreatobiliary and neuroendocrine tumours each represented 12.3% of cases, predominantly with unknown primary sites. Gallbladder cancers accounted for 7.69% of cases, squamous cell and adenocarcinoma of the lung for 6.2%, and colorectal origins for 4.62%. The remaining cases included undifferentiated origins, as well as, renal, nasopharyngeal, prostate and cholangiocarcinoma, with varying distributions of known and unknown primary sites and lesion numbers. One doubtful primary/metastatic case of hepatocellular carcinoma was noted. The diagnosis of this case was inconclusive on histopathology due to an unknown primary site of the lesion. The data reflect a diversity of primary origins for metastatic liver lesions, with a notable number of cases lacking identified primary sites.

The IHC diagnosis was found to be strongly dependent on the knowledge of the primary site of the lesion as determined by imaging, and statistically indicated by a Chi-square test. The p-value of 0.0365, which is <0.05, indicates that the IHC findings were dependent on the knowledge of the primary site, thereby making both entities necessary for establishing a definitive diagnosis and further ascertaining a treatment plan for the patient in the future. On the other hand, the p-value >0.05 highlighted that the IHC results were not dependent on the number of lesions [Table/Fig-8].

IHC diagnosis (Origin)	n (%)	Radiological findings (n) Single	Multiple	Known	Unknown
Breast	15 (23.1)	4	11	12	3
Lung (ADCC)	4 (6.2)	0	4	2	2
Lung (SCC)	4 (6.2)	1	3	2	2
Gastrointestinal	9 (13.8)	4	5	2	7
Colorectal	3 (4.62)	2	1	1	2
Cholangiocarcinoma	3 (4.62)	1	2	1	2
Pancreatobiliary	8 (12.3)	4	4	0	8
Neuroendocrine origin mets+	8 (12.3)	3	5	4	4
Nasopharyngeal carcinoma	1 (1.53)	0	1	1	0
Undifferentiated/Urothelial origin	2 (3.07)	0	2	0	2
Renal	1 (1.53)	1	0	0	1
Gall bladder	5 (7.69)	2	3	1	4
Prostate	1 (1.53)	0	1	1	0
Mets/primary HCC	1 (1.53)	1	0	0	1
Total cases	65 (100)	23	42	27	38
Statistical analysis					
Chi-square test	-	χ^2=11.14267		χ^2=23.455	
p-value	-	0.599		0.0365	

[Table/Fig-8]: Summarised version of all the Immunohistochemistry (IHC) diagnosis recorded with the radiological findings.
mets: Metastases; ADCC: Adenocarcinoma; SCC: Squamous cell carcinoma; Hepatocellular carcinoma

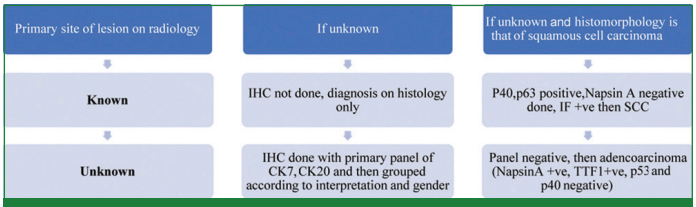
Among the 65 cases studied, CK7 and CK20 IHC markers were applied to 45 cases as the primary panel [Table/Fig-9]. Based on their interpretation (positive or negative), as well as, the gender of the patient, four groups were created. Among these 45 cases, five cases were both CK7 and CK20 positive, 28 were CK7 positive and CK20 negative, 2 were CK7 negative and CK20 positive, and 9 were both CK7 and CK20 negative. In one case, CK7 was applied while CK20 was not. In 20 cases, the above panel was not applied, and other markers such as ER and PR were used instead.

IHC marker group	No. of cases, n
CK7+ and CK20 +ve	5
CK7+ and CK20 -ve	28
CK7-ve and CK20 +ve	2
CK7-ve and CK20 -ve	9

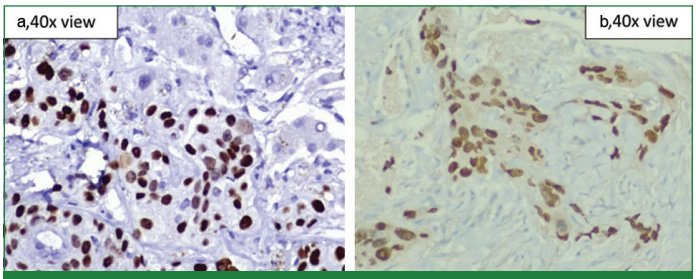
[Table/Fig-9]: CK7 and CK20 Immunohistochemistry (IHC) marker interpretation.

There were 38 cases in the current study where the original lesion was undetermined. These lesions were first evaluated to determine the histomorphology, which was either metastatic carcinoma, metastatic adenocarcinoma, or poorly differentiated carcinoma. Once the morphology was established, a primary panel of IHC markers, including CK7 and CK20, was applied. Based on the interpretation of these markers, four groups were created: CK7 positive and CK20 positive; CK7 positive and CK20 negative; CK7 negative and CK20 positive; CK7 negative and CK20 negative.

To differentiate between squamous cell carcinoma and adenocarcinoma, p40, p63 and Napsin A were applied in cases of primary lung tumours [Table/Fig-10,11a,b].



[Table/Fig-10]: Depicts the main simplified algorithmic approach concerning the primary site of the lesion.



[Table/Fig-11]: Shows a) p63 positive staining (40x); b) p40 positive staining case of squamous cell carcinoma with metastases to the liver (40x).

DISCUSSION

The liver is the second most common site for metastasis after the lymph nodes. These cases occur across various age groups and genders. It is important to differentiate these lesions from primary liver cancers by determining the primary site, the number of lesions, and the clinical presentations. Radiological findings help identify whether the lesions have a known primary source and if there are multiple secondary lesions or just a solitary lesion. On the other hand, IHC helps solidify those findings. The present study explores the relevance of IHC as both a confirmatory and diagnostic tool in cases of known primary cancer as well as in cancers of unknown primary origin.

Of the 65 cases in the current study, 34 (52.3%) were females, while 31 (47.7%) were males. The age group of 41-60 years had the highest percentage of metastatic tumours (56.7%), followed by the 61-80 years age group (26.2%), with a median age of 55 years, a

Variables	Present study (n=65)	Strumfa I et al., (2012) [7]	Khadim MT et al., (2011) (n=130) [8]	Armutlu A et al., (2021) (n=509) [14]	Kasper HU et al., (2005) (n=611) [15]	Bläker H et al., (2001) (n=804) [16]
Common age group	40-60 years 60-80 years	NA	60 years and 70 years	40-60 years	60 years and 70 years	NA
Age (Mean±SD)	54.26±11.858 years	NA	51±13.7 Years	59 years	63.3 years	NA
Median age	55 years	NA	NA	61 years	NA	NA
Male:female ratio	0.91	NA	2.02	0.96	1.174	NA
Multiple lesions, n (%)/%	42 (64.6%)	NA	55%	NA	NA	NA
Single lesions	23 (35.4%)	NA	45%	NA	NA	NA
Common organ of origin	Breast (23.1%), gastrointestinal (13.8%), lung, pancreatobiliary, neuroendocrine (12.3%)	Colorectal ADCC (48.2%) Pancreatic (13.5%) Breast (13%)	Gastrointestinal (45.3%) NE (10.7%) Gall bladder (10%)	Colon ADCC (38%) NE (10.6%) Breast (9.8%) PB (9.4%)	Colorectal ADCC (48.2%) Neuroendocrine (16%) Pancreatic (13.5%) Breast (13%)	Lung (27%) Colorectal (15%) Pancreatic (10%) Breast (9%)
Common IHC markers used	CK7, CK20, CDX2, SATB2, ERPR, HER2/neu, CA19.9, CK19, AFP, TTF1, HepPar1, Glypican3, p40, NapsinA PSA, CEA, chromagranin, synaptophysin, neuron-specific enolase	CK7, CK20, ER, PR, HER2/neu, CA19.9, TTF1, HepPar1, glypican3, chromogranin, synaptophysin	PanCK, CEA, CA125, CK7, CK20, TTF1, HepPar1, AFP, PSA, PSAP, chromagranin, NSE, vimentin, desmin, CD45, GCDFP15, CD56	PanCK, CK7, CK20, p63, CDX2, TTF1, GATA3, PAX8, synaptophysin chromogranin, PSA, PSAP, AMACR, ER, PR	CK5/6, CK7, CK20, CDX-2, TTF-1, ER, S-100, Melan A, PSA, CD56, synaptophysin, CA19.9	PanCK, CK7, CK20, ER, PR, HER2/neu, PSA, synaptophysin, chromogranin, NSE, CK19, CA19.9, CEA, EMA
Added IHC markers	S100, SOX10, p63, CD117 MelanA, HMB45, Desmin, Vimentin	GCDFP15, mammoglobin	CD30, GCDFP15 MelanA, Inhibin, Calretenin, PSAP, RCC PLAP	p501	CK8, CD34	CK8, CK18, CK13, VEA, RCC, thyroglobulin

[Table/Fig-12]: Shows a comparison between our study and various other studies done [7,8,14-16].

mean age of 54.26 years, and a SD of 11.858 years. Our study was consistent with the findings of Khadim MT et al., (2011) and Armutlu A et al., (2021), wherein the most common age group was from 40 to 60 years, with the mean ages being 51 and 59 years, respectively [8,14]. In the present study, male-to-female ratio closely resembled that of the study by Armutlu A et al., [14].

A total of 42 (64.6%) cases with multiple lesions and 23 (35.4%) solitary liver lesions were accounted for in the current study, which was similar to the 55% multiple lesions and 45% solitary lesions documented by Khadim MT et al., (2011) [8]. The prevalence of cases with multiple secondaries in the liver in India is concordant with studies from North America, showing a ratio of 40:1 in comparison to primary Hepatocellular Carcinomas (HCCs) [Table/Fig-12] [7,8,14-16].

IHC demonstrated that 15 (23.1%) of the 65 cases in the present study were of breast origin, while 9 (13.8%) were of gastrointestinal origin. Eight cases (12.3%) were of lung, pancreatobiliary and neuroendocrine origin, respectively. In comparison to the current study, Khadim MT et al., (2011) found that the most common primary location was the gastrointestinal tract, with 59 cases (45.3%), followed by neuroendocrine tumours (14 cases, or 10.7%), gallbladder (13 cases, or 10%) and lung (8 cases, or 6.15%). The present study shared similarities with that of Bläker H et al., as the lung was considered a common site in both studies. Additionally, studies by Strumfa I et al., Khadim MT et al., and Kasper HU et al., found that pancreatobiliary, neuroendocrine, and gastrointestinal sites were the most common locations [7,8,14-16].

All the studies listed above shared the primary panel of CK7 and CK20 with ours, while the additional markers in the studies by Strumfa I et al., Khadim MT et al., Armutlu A et al., and Bläker H et al., included GCDFP15, RCC, VEA, thyroglobulin, PLAP, p501 and mammaglobin, respectively [7,8,14,16]. Among the morphologic patterns, the present study accounted for 47 (72.3%) cases of metastatic adenocarcinoma and 11 cases of poorly differentiated carcinoma, which was consistent with the 205 (62%) cases of adenocarcinoma and 11 cases of poorly differentiated carcinoma recorded by Wang JD et al., [17]. The present study was also consistent with studies conducted by Singh N et al., [18].

An initial study on liver metastases identified the primary site in only 27% of cases through pathological examination [19]. A subsequent investigation into metastatic adenocarcinoma (Ad-Ca) of unknown origin showed improved identification rates of 66% using a standardised panel of four IHC markers [20]. More recent research using a panel of ten IHC markers identified primary sites in 88% of cases [21]. Another study demonstrated that IHC accurately predicted the primary site in 83.3% of cases across various differential diagnosis, using an average of 8.3 stains [22].

Limitation(s)

The main limitation of the present study was the small sample size.

CONCLUSION(S)

In summary, the present research provides a concise evaluation of metastatic liver lesions, pinpointing their origins through IHC. The study reveals a diverse range of primary cancers, with a higher frequency of multiple lesions, reflecting the diagnostic challenges posed by unknown primary sources. The vital role of IHC in diagnosis and management is highlighted, alongside the potential of molecular profiling to improve diagnostic accuracy. These findings are crucial for personalised treatment and for understanding the epidemiology of metastatic liver lesions, with a noted higher prevalence in females and the identification of various cancer origins. The integration of IHC with radiological data is essential for accurate diagnosis and treatment plans.

Author's contribution: The work was carried out in collaboration with all the authors. Analysis and interpretation were done by AV and PN. Data collection and compilation was done by PN, SSA and PG. The final manuscript was approved and overviewed by all the authors.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 05, 2024
- Manual Googling: Jul 20, 2024
- iThenticate Software: Aug 03, 2024 (4%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jun 04, 2024**
Date of Peer Review: **Jul 01, 2024**
Date of Acceptance: **Aug 05, 2024**
Date of Publishing: **Oct 01, 2024**