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Clinicopathological Features of Liver Metastasis of Solid Tumors at National Institute of Cancer Research and Hospital

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ABSTRACT: ***Background:*** Liver metastasis is a common site of secondary malignancy in many solid tumors, but its diagnosis is often made at a late stage, making treatment challenging. Despite its significance, limited research has been conducted on the clinicopathological features of liver metastasis in solid tumors, especially in Bangladesh. ***Objective:*** This study aims to evaluate the clinicopathological features, including the clinical signs, primary tumor sites, and histological patterns of liver metastasis in Bangladeshi patients. ***Methods:*** A cross-sectional observational study was conducted at the National Institute of Cancer Research and Hospital (NICRH) in Dhaka, Bangladesh, from January 2019 to December 2019. A total of 105 patients with diagnosed liver metastasis were included. Ethical clearance and written informed consent were obtained from all participants. Data were analyzed using Statistical Package for Social Science (SPSS) version 20. Descriptive statistics were used, and results are presented with mean, standard deviation, and p-values. ***Results:*** The mean age of the patients was 54.91 ± 12.45 years. A higher proportion of men (57.1%) were affected. Common clinical features included yellow discoloration of the skin (80%), change in bowel habits (61.9%), weight loss (58.1%), nausea/vomiting (55.2%), and abdominal pain (51.4%). The most common primary tumor sites were colorectal (38.1%) and pancreas (22.9%). Histologically, adenocarcinoma was the most prevalent type (82.8%), with 92.4% presenting multifocally. A significant correlation was observed between the age of the patients and the occurrence of liver metastasis ($p = 0.03$). ***Conclusion:*** The study highlights key clinical features and common primary sites associated with liver metastasis in Bangladeshi patients. Early detection and targeted treatment are crucial for better prognosis.

Keywords: Liver metastasis, colorectal cancer, adenocarcinoma, clinical features, Bangladesh.

INTRODUCTION

The liver is a vital organ involved in numerous metabolic and physiological functions, including detoxification, protein synthesis, and digestion. Among the various diseases that affect the liver, hepatic tumors are particularly significant due to their high prevalence, mortality, and morbidity rates. Hepatic tumors can either be primary or secondary, with the latter, liver metastases, being far more common. Secondary liver malignancies, or liver metastases, arise when cancer cells from a primary tumor spread to the liver, often through the blood vessels or lymphatic system. Liver metastasis is a major cause of death for many patients with primary adenocarcinomas, particularly those originating in the colon, pancreas, and breast [1]. The burden of liver metastases is profound and continues to challenge clinicians in terms of timely diagnosis and effective treatment. The liver is one of the most common sites of metastatic disease, especially in patients with solid tumors. Colorectal adenocarcinoma, hepatobiliary cancer, and breast carcinoma are known to frequently metastasize to the liver [2]. The liver's unique anatomical and physiological features, including its large blood supply and its role in metabolism, make it a preferential site for the dissemination of cancer cells. Other malignancies, such as pancreatic adenocarcinoma, neuroendocrine tumors, and gastrointestinal stromal tumors, can also lead to liver metastases, albeit less frequently. Despite the

significant impact of liver metastasis on patient prognosis, it remains a relatively under-researched topic in oncology, especially when considering the independent roles of various etiologic factors. In patients diagnosed with primary colorectal cancer, liver metastasis occurs in approximately 20-25% of cases at the time of initial diagnosis, with 14.5-17.7% of patients presenting with liver involvement [3]. The incidence of liver metastasis is closely related to the stage of the primary disease and can vary according to the type and location of the primary tumor. Studies have shown that the detection of liver metastases at the time of diagnosis is increasing due to advancements in imaging technology and improved screening methods. This highlights the importance of early diagnosis and the potential for more effective treatment strategies in these patients. However, the majority of patients diagnosed with liver metastases are often left with limited therapeutic options, as metastases are typically diagnosed too late for surgical resection, and the prognosis remains poor despite advances in chemotherapy. The prognosis of patients with liver metastasis is poor, with less than 20% of cases being amenable to surgical resection. Studies indicate that only 20% of patients with colorectal liver metastases (CLM) have respectable disease, with the remaining 80% having an overall poor prognosis despite receiving several lines of chemotherapy [4]. The limited respectability of liver metastases is a significant issue in oncology, as surgery remains the most effective treatment option for metastases that are confined to the liver. This highlights the urgent need for improved early detection and novel therapeutic approaches, including systemic treatments such as targeted therapies, immunotherapy, and innovative surgical techniques. The epidemiology of liver metastasis is influenced by several factors, including the type of primary cancer, gender, and age. Several studies have reported that liver metastases are more common in males, a finding that persists after adjustment for age [5]. Men are known to have a higher incidence of colorectal cancer (CRC), which is the most frequent malignancy to metastasize to the liver. Additionally, younger patients tend to present with more advanced stages of liver metastasis, characterized by a longer interval between the onset of symptoms and the diagnosis of the primary tumor. This delay in diagnosis may be attributed to the often-asymptomatic nature of early-stage liver metastasis and the nonspecific nature of the symptoms that patients present with. Liver cancer, particularly hepatocellular carcinoma (HCC), remains a leading cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 85–90% of all cases [6]. HCC typically develops as a complication of cirrhosis, a condition most commonly caused by chronic hepatitis infection, alcohol use, or metabolic diseases. In comparison, metastatic liver cancer is much more prevalent, with an incidence rate 20 times higher than that of primary liver cancer. Among metastatic tumors, colorectal cancer is the most frequent primary malignancy to spread to the liver, followed by breast and pancreatic cancer [7]. Studies have reported that colorectal cancer metastases to the liver (CRC-LM) occur in approximately 15-25% of patients at the time of diagnosis, and a similar proportion develops metachronous metastases following colorectal resection have also reported that liver metastases of solid tumors are the largest group of neoplasms, with adenocarcinomas being the most common histological type. Specifically, 48.2% of these metastases were due to colorectal cancer, with smaller percentages attributable to pancreatic cancer, breast cancer, gastric cancer, lung cancer, and esophageal cancer [8]. Neuroendocrine tumors also contribute significantly to the burden of liver metastasis, accounting for approximately 16% of cases. These statistics highlight the prevalence of liver metastases, particularly from adenocarcinomas, and underscore the importance of early detection and appropriate management strategies. Despite the widespread nature of liver metastases, the diagnosis remains a challenge. Advanced imaging techniques, including CT scans, MRIs, and PET scans, have improved the ability to detect liver metastases at earlier stages. However, there remains a need for improved diagnostic tools to predict the onset of liver metastasis more accurately and to differentiate between malignant and benign lesions in cirrhotic livers [9]. Additionally, clinical management strategies must continue to evolve to address the growing burden of metastatic liver disease, including the development of novel targeted therapies and surgical techniques such as liver resection and transplantation. This research seeks to address the gap in knowledge surrounding liver metastases, specifically focusing on the clinicopathological features of liver metastasis of solid tumors. The study aims to evaluate the relationship between demographic factors such as age and sex, clinical symptoms, radiological findings, and the

frequency of malignant versus benign tumors. By understanding these relationships, clinicians may be better equipped to make accurate and timely decisions regarding the diagnosis and treatment of liver metastases, ultimately improving patient outcomes.

Aims and Objective

The primary aim of this study is to evaluate the clinicopathological features of liver metastasis in solid tumors. Specific objectives include identifying clinical presentations, determining the proportion of liver metastasis in primary solid tumors, analyzing the pattern of metastasis (unifocal or multifocal), and assessing biochemical changes in the liver.

MATERIALS AND METHODS

Study Design

This study adopted a cross-sectional observational design to evaluate the clinicopathological features of liver metastasis in solid tumors. The study was conducted at the Department of Medical Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, from January 2019 to December 2019. A total of 105 patients with liver metastasis from solid tumors were selected based on specific inclusion criteria. The study aimed to explore the clinical and biochemical characteristics, metastasis patterns, and the frequency of various types of solid tumors responsible for liver metastasis. The study design facilitated a detailed evaluation of patient demographics, clinical symptoms, and the pathological features of liver metastasis in a cohort of Bangladeshi patients, providing valuable insights into the disease's presentation and prognosis.

Inclusion Criteria

The inclusion criteria for this study were cytopathologically confirmed cases of liver metastasis from solid tumors. All patients who were diagnosed with liver metastasis at the NICRH during the study period and were willing to participate were eligible. Additionally, patients with a history of solid tumors, including colorectal, pancreatic, and breast cancers, who had confirmed liver metastasis through imaging or biopsy, were included. Only adult patients, aged 18 years and above, were considered eligible for participation to ensure a homogenous study population.

Exclusion Criteria

Patients diagnosed with primary liver cancer, such as hepatocellular carcinoma or cholangiocarcinoma, were excluded from the study due to the different pathophysiological mechanisms and treatment protocols. Additionally, patients who were unwilling to participate in the study, or who could not provide informed consent due to cognitive or medical impairments, were also excluded. This exclusion criteria ensured the study focused on liver metastasis originating from solid tumors and reduced the potential confounding effects of primary liver malignancies.

Data Collection

Data for this study were collected through face-to-face interviews with the patients, using a pre-tested structured questionnaire. The patients were informed about the purpose of the study, and their informed consent was obtained prior to participation. A case record pro-forma was used to document the clinical features, physical examination findings, and relevant investigations. Additionally, laboratory reports, imaging findings, and histopathological diagnoses were reviewed to confirm the presence of liver metastasis. A total of 105 eligible patients participated in the study, and their data were collected with the utmost confidentiality.

Data Analysis

The collected data were entered and analyzed using SPSS version 20.0. Descriptive statistics were employed to summarize the patient demographics, clinical characteristics, and pathological features. Frequency distributions, percentages, mean values, and standard deviations were calculated for relevant variables. To compare baseline characteristics and determine statistical significance, appropriate tests, including chi-square and t-tests, were applied. A p-value of less than 0.05 was considered statistically significant. Data were also visually represented through charts and tables for better interpretation and understanding.

Procedure

Upon patient admission to the NICRH Department of Medical Oncology, the study team approached eligible participants and provided them with information about the study's objectives and procedures. After obtaining written informed consent, each patient underwent a thorough physical examination and a review of their clinical history. A

structured questionnaire was used to document clinical symptoms such as jaundice, weight loss, abdominal pain, nausea, and vomiting. Relevant laboratory tests, including liver function tests, complete blood counts, and biochemical markers, were carried out to assess the extent of liver involvement. Imaging studies, including ultrasound, CT scans, and MRI, were reviewed to confirm the presence of liver metastasis and identify the primary tumor site. Histopathological samples were obtained to confirm the diagnosis of liver metastasis, and the type of tumor was recorded. The collected data were then verified for accuracy and completeness. Following the data collection phase, the information was entered into a secured database for further statistical analysis. All findings were compared with existing literature to validate the observations. Statistical methods were used to determine the significance of clinical features, demographic variables, and the relationship between primary tumor sites and liver metastasis.

Ethical Considerations

Ethical approval for the study was obtained from the Ethical Review Committee (ERC) of NICRH. The study adhered to ethical principles, ensuring participant confidentiality and voluntary participation. Informed written consent was taken from all participants, and they were assured of their right to withdraw from the study at any point without penalty. No financial incentives were provided, and all procedures were explained to ensure transparency and participant autonomy.

RESULTS

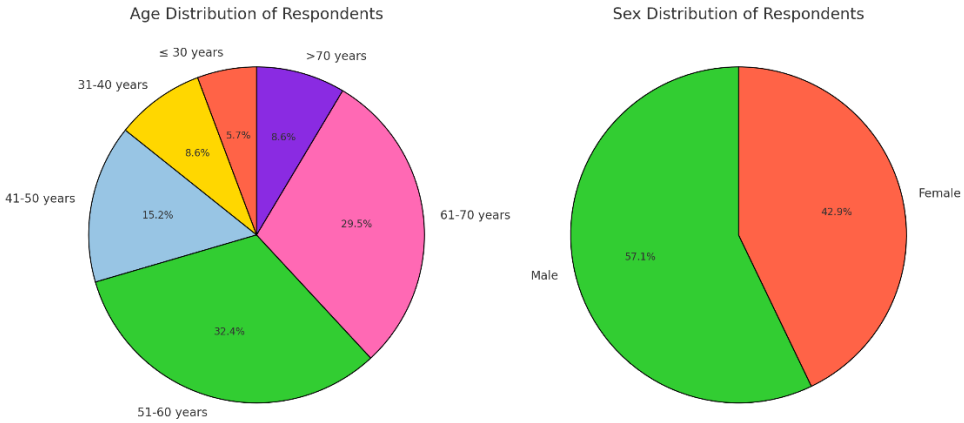

Figure 1: Distribution of respondents by age (n=105)

Majority respondents were in the age group 51-60 years (32.4%, n=34) and followed by in decreasing order by 61-70 years (29.5%, n=31) and 41-50 years (15.2%, n=16). Mean age of respondents was 54.92±12.45 years with maximum and minimum age of 78 years and 25 years. A larger proportion of male patients (57.1%, n=60) were observed, reflecting a higher prevalence of liver metastasis in males compared to females (42.9%, n=45). This trend is consistent with earlier studies that report a higher incidence of liver metastasis in men. The male-to-female ratio in this study was 1.33:1, indicating a gender disparity in liver metastasis.

Table 1: ECOG performance status among respondents (n=105)

ECOG performance score	Frequency (n)	Percentage (%)
ECOG status 1	0	0
ECOG status 2	7	6.7
ECOG status 3	32	30.5
ECOG status 4	66	62.8
ECOG status 5	0	0
Total	**105**	**100.0**

*ECOG: Eastern Cooperative Oncology Group

ECOG performance status of study population showed that 62.8% had ECOG-4 followed by 30.5% ECOG-3 and 6.7% ECOG-2.

Table 2: Most Common Clinical Presentations of Liver Metastasis of Solid Tumors Among Respondents (n=105)

Clinical Presentations	Frequency (n)	Percentage (%)
Yellow color of skin, sclera or urine	84	80.0
Altered bowel habit	65	61.9
Weight loss	61	58.1
Nausea / Vomiting	58	55.2
Abdominal pain	54	51.4
Bleeding manifestation	53	50.5

*Multiple response considered

Common clinical presentation of liver metastasis of solid tumors is stated above in descending order. Among total study population, major symptoms were yellow skin color, sclera or urine (80.0%) followed by change of bowel habit (61.9%), weight loss (58.1%), nausea / vomiting (55.2%), abdominal pain (51.4%) etc.

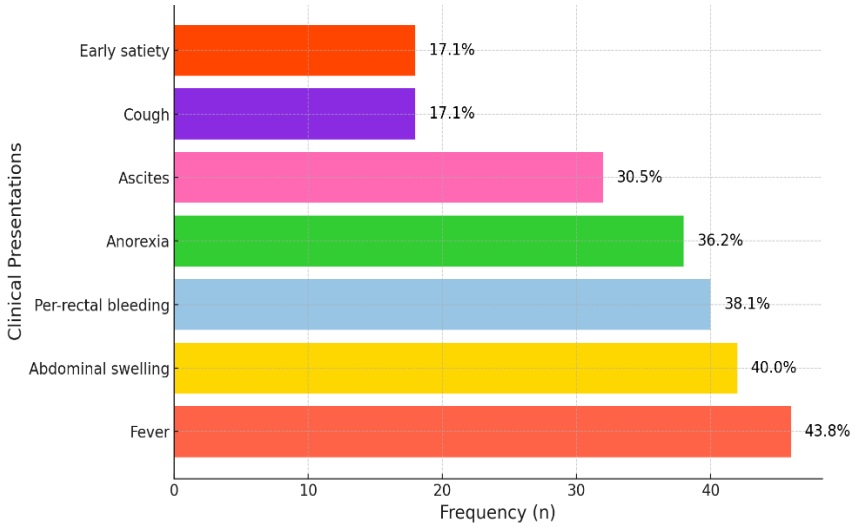

Figure 2: Other Clinical Presentations of Liver Metastasis of Solid Tumors Among Respondents (n=105)

Table 3: Distribution of Respondents by Location of Primary Lesion (n=105)

Location of primary lesion	Frequency (n)	Percentage (%)
Colo-rectal	40	38.1
Pancreas	24	22.9
Lung	20	19.0
Breast	12	11.4
Gastric	8	7.6
Esophagus	1	1.0
Total	**105**	**100.0**

Majority primary lesion was in colorectal region (38.1%) followed by 22.9% from pancreas, 19.0% from lungs, 11.4% breast, 7.6% gastric region and rest 1% esophagus.

Table 4: Distribution of respondents by histological type of primary lesion (n=105)

Histological type of primary lesion	Frequency (n)	Percentage (%)
Adenocarcinoma	87	82.8
Neuro-endocrine	8	7.6
Small cell carcinoma	6	5.7
Squamous cell carcinoma	3	2.9
Large cell carcinoma	1	1.0
Total	105	100.0

Most liver metastases were histologically adenocarcinoma subtype (82.8%) followed by 7.6% neuro-endocrine and 5.7% small-cell carcinoma.

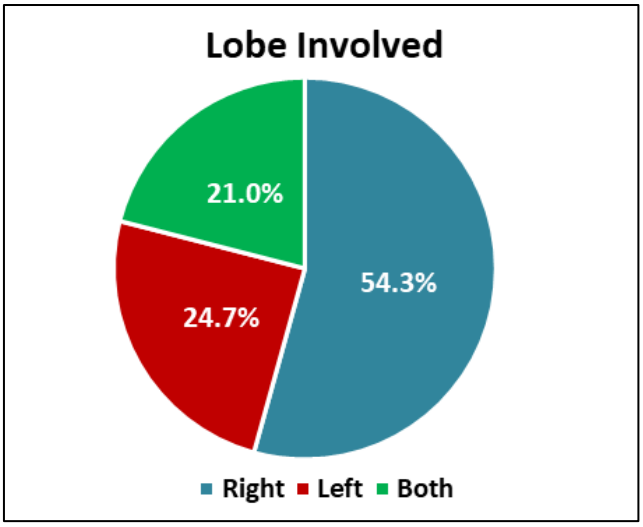

Figure 3: Distribution of respondents by involvement of lobes of liver (n=105).

About 54.3% had the right lobe involvement while 24.7% had left lobe involvement.

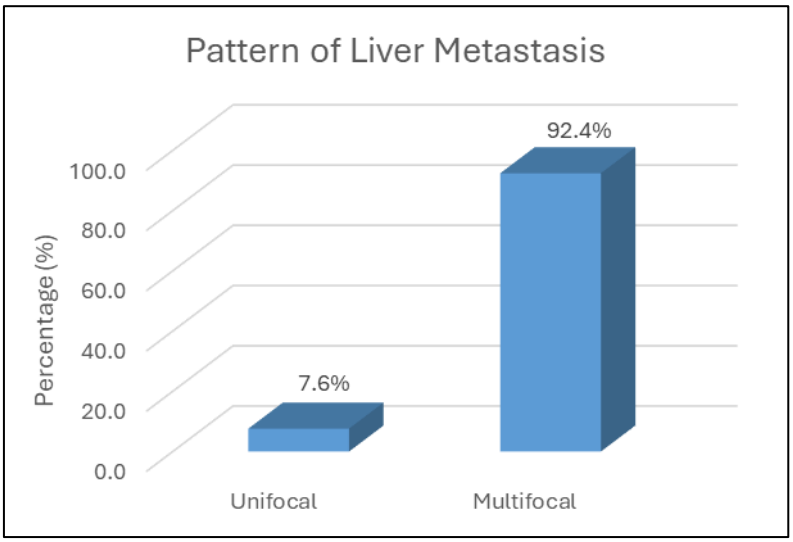

Figure 4: Distribution of Study Population by Unifocal or Multifocal Pattern of Liver Metastasis (n=105)

About 92.4% of the study population had multifocal pattern of liver metastasis and only 7.6% had unifocal pattern of liver metastasis.

Table 5: Levels of Different Biochemical Changes in Patients with Liver Metastasis of Solid Tumors (n=105)

Biochemical levels	Mean ± Std. Deviation	Minimum	Maximum
Serum Bilirubin (mg/dL)	2.66 ± 1.36	0.21	4.82
SGPT or ALT (IU/L)	29.01 ± 13.97	10.36	79.56
SGOT or AST (IU/L)	27.82 ± 11.94	10.34	66.87
ALP (IU/L)	101.66 ± 52.44	22.1	220.81
AFP (ng/mL)	7.56±4.68	1	24.40
CEA (µg/L)	52.16 ± 45.73	16.78	225.33

SGPT or ALT: Serum glutamic pyruvic transaminase or alanine aminotransferase; SGOT or AST: Serum glutamic oxaloacetic transaminase; ALP: Alkaline Phosphatase; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen. Mean and standard deviation values of serum bilirubin, SGPT, SGOT, ALP, AFP and CEA were given in above table.

Table 6: Serum Bilirubin with Alpha-Fetoprotein in Patients with Liver Metastasis of Solid Tumors (n=105)

Serum bilirubin increased	Frequency (n)	Percentage (%)
Yes	84	80.0
No	21	20.0
Alpha-fetoprotein increased		
Yes	7	6.7
No	98	93.3
Total	**105**	**100.0**

Serum bilirubin increased in 84 (80.0%) study population. Alpha-fetoprotein was increased in only 7 (6.7%) study population.

Table 7: ALP in Patients, Serum CEA with Liver Metastasis of Solid Tumors (n=105)

ALP increased	Frequency (n)	Percentage (%)
Yes	30	28.6
No	75	71.4
CEA increased		
Yes	55	52.4
No	50	47.6
Total	**105**	**100.0**

ALP increased in 30 patients (28.6%) in the study population. Carcinoembryonic antigen (CEA) was increased in 55 patients (52.4%).

DISCUSSION

Liver metastasis is a significant cause of morbidity and mortality in patients with solid tumors. Understanding the clinical features, histological characteristics, and biochemical markers associated with liver metastasis can significantly aid in the early diagnosis and management of the disease [10]. This study aimed to explore the pathologic features and clinical characteristics of liver metastasis, with a particular focus on the most common primary tumor sites and the biochemical markers associated with liver dysfunction. The findings from this study provide valuable insights into liver metastasis and offer a comprehensive look at the factors that contribute to its progression.

Epidemiology and Demographic Profile

The mean age of the study population was 54.92 ± 12.45 years, with the majority of patients falling within the 51-60 years age group (32.4%, n=34) and the 61-70 years group (29.5%, n=31). These findings suggest that liver metastasis predominantly

affects middle-aged to older adults. This age distribution is consistent with previous studies, including de Ridder *et al.*, who found that the majority of patients with liver metastasis were older than 50 years, though their findings showed an even higher proportion of patients above 50 (90.2%) [11]. This trend may be explained by the cumulative effects of aging, exposure to environmental carcinogens, and the progressive nature of certain cancers over time. Matsubayashi *et al.* also reported a mean age of 59.7 ± 11.99 years, which is slightly higher than the mean age in this study [12]. The slightly younger average age in our study could be indicative of a difference in study populations or geographical factors. Regardless, the consistent finding across studies that liver metastasis is more common in older adults underlines the need for vigilant screening and early detection in these age groups.

Gender Distribution and Male Predominance

The study found a male-to-female ratio of 1.33:1, with 57.1% (n=60) of the respondents being male and 42.9% (n=45) female. This male predominance is consistent with previous studies, such as those by Zdravkovic *et al*., which have shown a higher prevalence of liver metastasis in males [13]. The gender disparity observed in our study could be attributed to several factors, including differences in lifestyle, hormonal influences, or genetic predisposition. Chun *et al*. reported an even higher male-to-female ratio of 3:1 to 4:1, which further supports the concept that men are more likely to develop liver metastasis [14]. These findings emphasize the need for gender-specific preventive measures and early intervention strategies.

Clinical Presentations and Symptomatology

The most common clinical presentation in our study was jaundice, reported by 80.0% (n=84) of the participants, followed by altered bowel habits (61.9%, n=65) and weight loss (58.1%, n=61). These symptoms are typical of liver involvement and are consistent with findings from previous studies. Patel *et al*. found that abdominal pain and upper abdominal masses were the most common presenting symptoms, while jaundice was reported in 28.8% of their study population [15]. Burazor *et al*., also observed abdominal pain as the predominant symptom, a finding that aligns with our study's presentation of abdominal pain in 51.4% (n=54) of patients [16]. The association of gastrointestinal symptoms, such as altered bowel habits and weight loss, with liver metastasis is particularly noteworthy as it indicates that the liver's involvement often correlates with the progression of the primary tumor, particularly those originating in the gastrointestinal tract. The high percentage of patients presenting with jaundice also emphasizes the liver's critical role in detoxifying blood and managing bilirubin, which is disrupted in metastatic liver disease.

Histological Types and Primary Tumor Sites

The majority of liver metastasis cases in this study were adenocarcinomas (82.8%, n=87), followed by neuroendocrine tumors (7.6%, n=8) and small cell carcinoma (5.7%, n=6). This is consistent with previous studies, including those by Gurzu *et al*., who identified adenocarcinoma as the most frequent histological type for liver metastasis [17]. Colorectal carcinoma, in particular, is known to metastasize frequently to the liver due to the liver's role in filtering blood from the gastrointestinal tract. The prominence of adenocarcinoma in our study suggests that cancers originating from the colon, pancreas, and other gastrointestinal organs are major contributors to liver metastasis. Interestingly, small cell carcinoma, neuroendocrine tumors, and squamous cell carcinoma also accounted for a portion of liver metastasis, although at much lower frequencies. The low proportion of these types highlights the fact that adenocarcinomas remain the dominant histological subtype responsible for liver metastasis.

Primary Tumor Locations and Colorectal Cancer as a Major Contributor

In this study, colorectal carcinoma was the most common primary tumor site for liver metastasis, accounting for 38.1% (n=40) of cases. This finding is consistent with the literature, which suggests that the liver is the most common metastatic site for colorectal cancer, as reflected in the findings of. Pancreatic cancer was the second most common source of liver metastasis in our study (22.9%, n=24), followed by lung cancer (19.0%, n=20) and breast cancer (11.4%, n=12). Other cancers such as gastric (7.6%, n=8) and esophageal cancer (1.0%, n=1) also contributed to liver metastasis. The high frequency of liver metastasis from colorectal cancer is well-documented, with approximately 20% of patients with colorectal cancer presenting with liver metastasis at the time of diagnosis vander Geest *et al*., [18]. Liver resection is a standard treatment option for patients with

respectable colorectal liver metastases. The liver's unique anatomical and physiological characteristics, such as its dual blood supply, facilitate the metastasis of colorectal cancer cells, making the liver the most common site of distant metastasis for this malignancy.

Right Lobe Predominance and Multifocal Metastasis

In our study, 54.3% (n=57) of patients had involvement of the right lobe of the liver, 24.7% (n=26) had left lobe involvement, and 21.0% (n=22) had both lobes affected. These findings are similar to those of Roy *et al*., who reported that 51.9% of patients had right lobe involvement [19]. The right lobe is typically more involved in liver metastasis due to its larger size and more extensive blood supply compared to the left lobe. The majority of patients in this study (92.4%, n=97) had multifocal liver metastases, while only 7.6% (n=8) had a unifocal lesion. This is consistent with previous reports, where multifocal lesions are more commonly observed in liver metastasis. Multifocal liver metastasis is associated with more advanced disease and poorer prognosis. The presence of multiple lesions in the liver often indicates extensive metastatic spread and may limit treatment options such as liver resection. The fact that the majority of patients in this study had multifocal liver metastasis underscores the aggressive nature of metastatic solid tumors and the need for early intervention and comprehensive management strategies.

Biochemical Markers and Liver Function

Serum bilirubin levels were elevated in 80.0% (n=84) of patients, with a mean value of 2.66 ± 1.36 mg/dL. This finding indicates significant liver dysfunction, as elevated bilirubin levels often reflect impaired bile secretion and liver function. Similarly, other liver function tests such as SGPT (29.01 ± 13.97 IU/L), SGOT (27.82 ± 11.94 IU/L), and ALP (101.66 ± 52.44 IU/L) were elevated in a substantial proportion of patients. These results are consistent with previous studies by Hall *et al*., who found that elevated liver enzymes and bilirubin are common in patients with liver metastasis [20]. CEA (carcinoembryonic antigen), a well-known tumor marker, was elevated in 52.4% (n=55) of patients in this study, further supporting its role as a diagnostic and prognostic marker in metastatic disease. The significant elevation of CEA in patients with liver metastasis aligns with previous findings, where CEA levels were found to correlate with tumor burden and disease progression. Elevated levels of ALP, AFP, and CEA in this study indicate their potential utility in monitoring disease progression and assessing liver function in patients with metastatic solid tumors.

CONCLUSION

This study highlights that the majority of patients with liver metastasis were aged over 50 years, with a male predominance. Key clinical features included yellow discoloration of the skin, sclera, and altered bowel habits, along with significant weight loss. The most common primary sites were colorectal cancer and pancreatic cancer, with adenocarcinoma being the predominant histological type. Liver metastasis predominantly affected the right lobe, and most cases were multifocal. However, due to the limitations of a small sample size from a single center, further studies with larger, multi-center samples are necessary to provide more accurate and generalized conclusions.

Recommendations

Conduct a multi-center, large-scale study to better understand the clinicopathological patterns of liver metastasis.

Focus on identifying additional biomarkers to aid in early detection and prognosis.

Investigate the role of personalized treatment strategies based on primary tumor types and metastasis patterns.

Acknowledgement

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