

## Evaluation of Tumors Presented with Hepatic Metastasis of Unknown Primary

You Wang\*, Alya A. Zobair\*\*, Ahmed Ali Albakr\*\*\*, Bassam Jasim\*\*\*\*

\*Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, Wuhan, China, \*\*Head of Department of Oncology, Medical Research and Care Centers, University of Mosul, Mosul, Iraq, \*\*\* Oncology and Nuclear Medicine Hospital, Nineveh Health Directorate, Mosul, Iraq, \*\*\*\*College of Medicine, University of Nineveh, Mosul, Iraq

Correspondence: aliaabdulaziz@uomosul.edu.iq

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### ABSTRACT

**Background:** liver metastases are a common site for metastatic disease, little is known about how frequently different malignancies manifest as liver metastases.

**Aim:** To identify the most prevalent primary tumors and assess the effects of therapy and primary tumor detection on patient survival.

**Patients and Methods:** This prospective study comprised 42 patients initially presenting with hepatic metastases of unknown primary origin at Mosul Oncology Hospital between 2018 and 2021. A thorough clinical and diagnostic evaluation was done to know the primary tumors, and the patient's ultimate diagnosis and survival were prospectively analyzed

**Results:** Gastrointestinal tumors were found to be the most frequent primary tumors that metastasize to the liver followed by lung and breast cancer, patients with primary breast cancer had better survival compared with other primary that metastasize to the liver.

**Conclusion:** The most common primary tumors that metastasize to the liver are gastrointestinal tumors, followed by lung and breast cancer. Because the prognosis of hepatic metastasis varies depending on the primary tumor, it is highly advised to undergo a thorough clinical, radiological, and pathological examination to identify the primary tumors. This will allow more tumor-specific treatment to be administered.

**Keywords:** cancer of unknown origin, liver, metastatic cancer.

### تقييم الأورام المقدمة مع ورم خبيث كبدي غير معروف المنشأ

يو وان\* ، علياء عبد العزيز نجم ال زبير\*\* ، احمد مؤيد علي البكر\*\*\* ، بسام اسماعيل جاسم\*\*\*\*  
\*قسم الأورام والعلاج الإشعاعي، مستشفى جونا، جامعة ووهان، ووهان، الصين ، \*\*رئيس قسم الأورام،  
المراكز البحثية الطبية، جامعة الموصل، الموصل، العراق ، \*\*\*مستشفى الأورام والطب النووي، دائرة صحة  
نينوى، الموصل، العراق ، \*\*\*\*كلية الطب، جامعة نينوى، الموصل، العراق

### الخلاصة

**الخلفية:** تعد النقائل الكبدية موقعًا شائعًا للمرض النقيلي، ولا يُعرف سوى القليل عن مدى تكرار ظهور الأورام الخبيثة المختلفة على شكل نقائل الكبد.

**الهدف:** هدفت هذه الدراسة إلى التعرف على الأورام الأولية الأكثر انتشارًا وتقييم آثار العلاج والكشف عن الورم الأولي على بقاء المريض على قيد الحياة.

**المرضى والطرق:** شملت هذه الدراسة الاستطلاعية 42 مريضًا ظهرت عليهم في البداية نقائل كبدية مجهولة المنشأ في مستشفى الأورام بالموصل بين عامي 2018 و 2021. تم إجراء تقييم سريري وتشخيصي شامل لمعرفة الأورام الأولية، وتم التشخيص النهائي للمريض وبقائه على قيد الحياة. تحليلها مستقبليًا

**النتيجة:** وجد أن أورام الجهاز الهضمي هي الأورام الأولية الأكثر شيوعًا التي تنتقل إلى الكبد يليها سرطان الرئة وسرطان الثدي، وكان المرضى الذين يعانون من سرطان الثدي الأولي لديهم فرص أفضل للبقاء على قيد الحياة مقارنة بالأورام الأولية الأخرى التي تنتقل إلى الكبد.

**الاستنتاج:** الأورام الأولية الأكثر شيوعاً التي تنتقل إلى الكبد هي أورام الجهاز الهضمي، يليها سرطان الرئة وسرطان الثدي. نظرًا لأن تشخيص النقائل الكبدية يختلف اعتمادًا على الورم الرئيسي، ينصح بشدة بالخضوع لفحص سريري وإشعاعي ومرضي شامل لتحديد الأورام الأولية. وهذا سيسمح بتقديم المزيد من العلاج الخاص بالورم.

**الكلمات المفتاحية:** ورم منتشر، كبد، ورم غير معروف المنشأ.

## INTRODUCTION

The term "tumor of unknown primary" describes a reported case of metastatic illness without a clearly defined source primary.<sup>1,2</sup> Tumors of unclear origin are detected in about 5% of cancer patients. 10 to 30 percent of them have liver metastases.<sup>3</sup> with short median survival. The minority of cases, despite intensive workup, do not reveal the primary tumor, and adenocarcinoma was found to be the most frequent histological subtype detected following biopsy.<sup>4</sup> In Iraq over the past few years, metastatic spread from an undetected original tumor was reported in 2-3% of all cancer cases that were officially registered.<sup>5</sup>

The various concepts of metastatic spread can account for the high prevalence of liver involvement in metastatic disease.<sup>2</sup> The "mechanical or hemodynamic hypothesis" states that the liver's dual blood supply from the portal vein and hepatic artery makes it easier for cancer cells to become trapped in the bloodstream, and it explains why patients with gastrointestinal carcinomas have a significant incidence of liver metastases. The "seed-and-soil" theory claims that some primary cancers, specifically target the liver as a site of metastatic growth. The promotion and maintenance of liver metastases are thought to involve a number of cells, including Kupffer cells, liver sinusoidal endothelial cells, hepatic stellate cells, dendritic cells, parenchymal hepatocytes, resident natural killer cells, as well as other immune cells like monocytes, macrophages, and neutrophils. In the process of liver metastasis, four crucial phases have been identified: microvascular, pre-angiogenic, angiogenic, and growth phases.<sup>6</sup>

Although liver metastases are a common site for metastatic disease, little is known about how frequently different malignancies manifest as liver metastases. This study aimed to identify the most prevalent primary tumors and assess the effects of therapy and primary tumor detection on patient survival.

## PATIENTS AND METHODS

This study comprised 42 patients initially presenting with hepatic metastases of unknown primary origin at Mosul Oncology Hospital between 2018 and 2021. All the included cases had single or multiple hepatic lesions on U/S and MRI, excluding cases with primary hepatocellular

carcinoma, no history of malignant Neoplasm, and were aged more than 18 years. All cases were followed up for at least 12 months.

This prospective study was authorized by the College of Medicine/University of Mosul, Scientific Committee and carried out in accordance with the Helsinki Declaration. After referral to the hospital, a thorough evaluation of the patient was performed including; medical history, general and systematic examination focusing on the abdominal examination, and breast examination in women, Laboratory tests were done consisting of blood electrolyte, liver function test, renal function test, and complete blood count and tumor markers in some patients like CEA (Carcinoembryonic antigen), CA19-9, CA 125 and AFP (Alpha-Fetoprotein). Medical Imaging included a Computed Tomography scan of the chest, abdomen, and pelvis, an Ultrasound of the suspected site of origin, and a PET-CT scan for selected cases. Immunohistochemical studies were done in some cases, Patients with incomplete medical records or inconsistent clinical follow-up data were excluded.

The performance status of the included patients was categorized according to the ECOG score.<sup>7</sup> The final diagnosis was made when the imaging test detected the primary tumor and was confirmed histopathologically and/or by clinical follow-up. If the workup investigations could not detect the primary tumor and it remained unknown in follow-up, the case was considered persistently unknown primary.

The patients' ultimate diagnosis and survival were prospectively analyzed, and the patients' overall survival time was calculated from the time of initial hepatic metastatic presentation until either the date of death or the date of the last visit.

## Analytical Statistics

The data management and statistical analysis were done using SPSS (Version 20; SPSS). For a survival study, the Kaplan-Meier test was employed.

## RESULTS

Of 42 patients, 23 were male (54.8%) and 19 patients were female (45.2%), their ages ranged between (22-81 years) with a mean age was 55.2 years. The primary diagnosis of liver metastasis

was diagnosed by U/S in the majority of the patients( 76.2%) while MRI of the abdomen was the imaging test used for primary diagnosis in the remaining cases (23.8%). Twenty seven cases (64.3%) had normal liver function tests at presentation, and 15 cases ( 35.7%) had mild to moderate elevation of liver enzymes.

The majority of the included patients had good performance status at the time of hepatic metastasis, as shown in Table (1).

Table 1: Performance status of the patients presented with hepatic metastasis according to ECOG score.

Performance score	Number	Percentage
0	4	9.4
1	23	54.8
2	10	23.8
3	5	11.9

Regarding the frequency of tumors that were discovered to be the origin of the included cases who presented with hepatic metastasis of unknown primary, gastrointestinal tumors (colon cancer, pancreatic cancer, gastric cancer) were the most frequent type, followed by lung origin (NSCLC, SCLC), then breast cancer as shown in Table (2)

Table 2: The frequency of primary tumors detected in patients with hepatic metastasis.

Primary tumor	Number	Percentage
GIT	18	42.9
Lung	12	28.6
Breast	8	19.0
Melanoma	3	7.1
Sarcoma	1	2.4
Total	42	100

\*GIT: Gastrointestinal Tumors

Regarding the histopathological types of tumors in the included patients with hepatic metastasis, adenocarcinoma was found to be the most frequent type, as shown in Table 3, and the majority of the patients were treated with chemotherapy as the main treatment approach.

Table 3: Histopathological subtypes of the metastatic tumors to the liver.

Histopathological type	Number	Percentages
Adenocarcinoma	30	71.4
Squamous cell carcinoma	5	12
Others	7	16.6

Table 4: Types of Treatment that have been given to the patients with hepatic metastasis.

Treatment	Number	Percentage
Chemotherapy only	17	40.5
Chemo-Biological	17	40.5
Biological only	7	16.7
Palliative only	1	2.3

Breast cancer patients have a longer overall survival with a mean survival of 21.5 months, which is significantly longer than for GIT tumors and lung cancer, with a mean survival of 16.5 months, and 13.7 months respectively as shown in Figure 1.

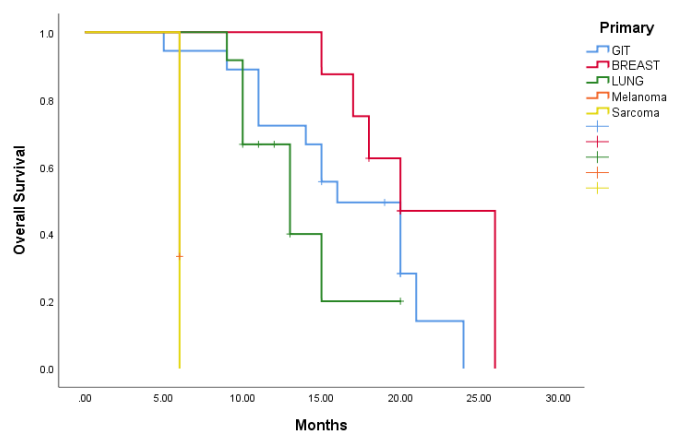


Figure 1: Overall survival of patients presented with hepatic metastasis from different primaries.

Patients who had received chemotherapy and biological therapy had significantly higher overall survival comparing with those received chemotherapy or radiotherapy alone as shown in figure (2).

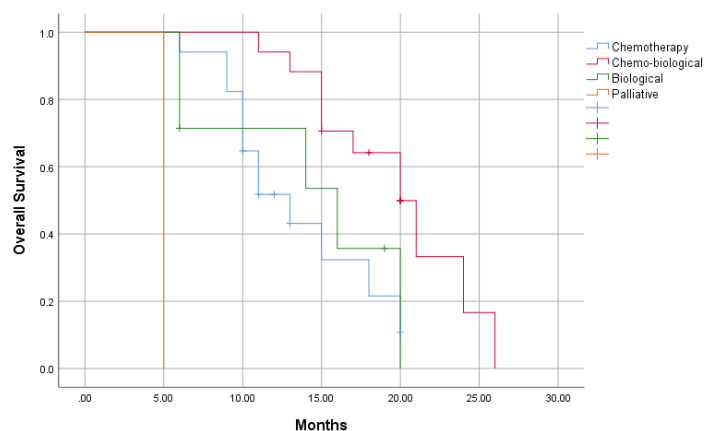


Figure (2): Overall survival of patients presented with hepatic metastasis treated with different therapeutic approaches.

## DISCUSSION

knowledge of favored metastatic sites may guide staging and surveillance plans for all types of malignancies. At the same time, in patients with an unknown underlying tumor, patterns may be utilized to predict the primary tumor site, which is crucial for therapeutic decisions. Hepatic metastasis is not rare and 25% of metastatic tumors metastasize to the liver<sup>1</sup>, liver metastasis is discovered incidentally or less frequently due to hepatic metastasis-related symptoms.<sup>8</sup>

In our study, tumors of gastrointestinal origin were the most frequent tumor in patients who present primarily with hepatic metastasis with unknown primary, and this result was similar to the results of many previous articles,<sup>3, 9-13</sup> this could be related to its anatomical position in relation to portal circulation, make the liver is the most frequent location of metastases in individuals with gastrointestinal cancer.<sup>14</sup> and it is reported that At the initial medical diagnosis, between 14 and 18% of colorectal cancer patients have metastases.

Another 20–25% of patients will go on to develop metastasis during the course of their follow and about 70% of patients with colorectal cancer will eventually develop liver metastases.<sup>15</sup> Hepatic metastasis could be developed as synchronous hepatic metastasis in one-third of cases or metachronous hepatic metastasis in two-thirds of cases.<sup>14,16</sup> Therefore, Ultrasound, liver enzymes, and tumor markers are the recommended techniques used for follow-up screening.

Interestingly, Prospective research shows that serial serum Carcinoembryonic antigen (CEA) testing is the most reliable screening method for identifying colorectal liver metastases.<sup>17</sup>

Lung cancer was the second most frequent primary tumor for patients with hepatic metastasis followed by breast cancer, this sequence is similar to the result of other studies<sup>6</sup> and different from another study<sup>18</sup>. This could be related to the difference of the incidence of these cancers in these counties.

Our study showed that adenocarcinoma is the most frequent histological subtype of the tumor that metastasized to the liver and this result is similar to the result of the previous studies.<sup>1,3,4</sup> and it is reported that the most prevalent primary sites for metastatic carcinomas to the liver are the lung, colon, pancreas, breast, and stomach, these main sites account for around 70% of all carcinomas. Interestingly, Adenocarcinomas were not only the most frequent type of carcinoma metastasizing to the liver but also regarded as the most frequent type of carcinoma presenting as unknown primary.<sup>19,20</sup>

The median survival of the included patients with hepatic metastasis in our study by primary tumors

is similar to the result of the pan-cancer study conducted in 2020, which reported a median survival of 17 months for patients with hepatic metastasis from colorectal cancer and 15 months for patients with hepatic metastasis from breast cancer<sup>21</sup>, however, Our survival results are longer than the overall survival of the patients included in the prior study on patients with hepatic metastasis that was conducted before 20 years.<sup>2,3,6,22</sup> This difference is primarily attributable to the recent advances in biological and targeted therapy, which have shown great survival advantages.<sup>23</sup>

Conclusion: The most common primary tumors that metastasize to the liver are gastrointestinal tumors, followed by lung and breast cancer. Because the prognosis of hepatic metastasis varies depending on the primary tumor, it is highly advised to undergo a thorough clinical, radiological, and pathological examination to identify the primary tumors. This will allow more tumor-specific treatment to be administered.

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