

Liver Metastases: Incidence and Clinicopathological Data

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Aim: To investigate the clinicopathological features of liver metastases diagnosed in Mureş County, Romania.

Material and method: We performed a retrospective study based on data collected from histopathological reports stored in the archives of the Pathology Laboratories of Emergency Mures County Hospital, Romania. We selected those patients' data that were diagnosed with liver metastases during January 2004 – August 2011. The acquired data were collected and processed statistically by using the GraphPad InStat Demo 3 statistical software.

Results: We identified 748 liver tumours out of which 484 were liver metastases. The liver metastases: primary liver tumours ratio was 1.833:1. In cases of liver metastases, the male:female ratio was 1.45:1. The mean age of male patients was 62.13 (± 10.79 years) as for female patients it was 61.61 (± 10.82 years). In most of the cases (34.71%) the primary tumor was colorectal carcinoma followed by pancreatic carcinomas (16.52%).

Conclusions: Most cases of liver metastases are carcinomas, whereof the most frequent ones originate from the digestive area, respectively gastrointestinal tract and pancreas. Independently by the primary tumour, liver metastases occur more frequent in males, in their 7th decade of life.

Keywords: liver tumours, liver metastases, colorectal cancer

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Introduction

Liver cancer is the seventh most commonly diagnosed cancer in adults [1]. Hepatocellular carcinoma is the most common type of malignant primary liver tumour (85–90%) [2], which occurs in most cases as a complication of cirrhosis. Metastases present an incidence 20 times higher than primary malignant liver tumours.

The most common metastases provides from colorectal carcinoma, followed by lung carcinoma, breast carcinoma, oesophageal and urogenital tumours [3].

In the year 2000, there were an estimated 564,000 new cases of liver cancer globally and a similar number of patients died as a result of this disease [4].

Regarding the localization of secondary tumours the most frequent site is the liver, followed by the lungs [5].

15–25% of patients with colorectal cancer present liver metastases when diagnosed and a similar proportion of patients develop metachronous metastases after colorectal resection [6].

The aim of our study was to analyze the incidence and the origins of the liver metastases in patients diagnosed in Mureş County hospitals, Romania.

Material and methods

We performed a retrospective analysis of liver tumour cases

diagnosed in the County Emergency Clinical Hospital, Târgu Mureş, Romania, between January 2004 – August 2011.

We assessed the histopathological diagnosis, histological type of metastasis, age, gender and the diameter of metastases. In cases of cancers of the gastrointestinal tract which produced liver metastases, we also reported the degree of differentiation of the primary tumour.

We selected patients' data diagnosed with liver metastases, registered them by using a Microsoft Office Excel worksheet and then processed them statistically by using the GraphPad InStat Demo 3 statistical software. For the univariate analysis of data we used the Student test for independent variables (continuous variables with normal distribution in the Kolmogorov-Smirnov test). We calculated mean values and standard deviation (SD). Differences were considered statistically significant when the p-value was less than 0.05.

Results

Clinico-pathological data

In the studied material we identified 748 cases of liver tumours out of which 484 cases (64.71%) were metastases, 287 male patients and 197 females (Figure 1).

The mean age of male patients was 62.13 (± 10.79 years), between the ages of 25 and 83 years and the mean age of female patients was 61.61 (± 10.82 years), between the ages of 28 and 86 years, with no statistically significant difference ($p=0.45$).

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Table I. Frequency of cardiovascular diseases and diabetes in the studied population of hypertensive patients

Hepatic metastases	Number (%)	Men	Age range men	Mean age men (\pm SD)	Women	Age range women	Mean age women (\pm SD)	Tumor diameter range (mm)
Colorectal adenocarcinoma	168 (22.45%)	99	25–83	61.87 (\pm 10.83)	69	43–78	61.21 (\pm 9.51)	2–142
Pancreatic carcinoma	80 (10.69%)	45	40–79	62.33 (\pm 9.04)	35	31–82	58.8 (\pm 13.04)	3–30
Gastric adenocarcinoma	64 (8.55%)	54	30–83	63.5 (\pm 12.07)	10	57–81	68.6 (\pm 7.6)	3–170
Undifferentiated carcinoma	47 (6.28%)	32	37–82	59.78 (\pm 10.1)	15	52–76	63.6 (\pm 7.36)	2–70
Adenocarcinoma of unknown origin	46 (6.14%)	25	40–80	66.28 (\pm 10.29)	21	28–83	64.8 (\pm 11.41)	2–140
Gallbladder adenocarcinoma	25 (3.34%)	5	45–71	53.6 (\pm 11.01)	20	52–86	65.3 (\pm 9.44)	3–75
Squamous cell carcinoma of the oesophagus	9 (1.2%)	8	35–70	56.37 (\pm 10.94)	1	57	–	9–20
Squamous cell carcinoma of unknown origin	8 (1.06%)	6	56–76	–	2	57, 64	–	8–45
Neuroendocrine carcinoma	8 (1.06%)	2	55, 73	–	6	33–66	52.5 (\pm 13.15)	6–100
Breast carcinoma	7 (0.93%)	–	–	–	7	30–62	53.71 (\pm 11.29)	7–70
Determination of non-Hodgkin's lymphoma	5 (0.66%)	1	70	–	4	29–75	–	3–50
Malignant melanoma	4 (0.53%)	3	54–73	–	1	76	–	2–13
Extrahepatic bile duct adenocarcinoma	4 (0.53%)	1	69	–	3	56–74	–	2–15
Clear cell renal cell carcinoma	3 (0.4%)	3	64–70	–	–	–	–	5–60
GIST	2	1	46	–	1	52	–	5, 60
Determination of Hodgkin's lymphoma	2	1	48	–	1	59	–	9, 18
Squamous cell carcinoma of the cervix	1	–	–	–	1	42	–	12
Squamous cell carcinoma of the anus	1	1	73	–	–	–	–	15

The histological types of liver metastases and clinicopathological data obtained as a result of our study are summarized in Table I.

Most cases of liver metastases were carcinomas, Hodgkin's and non-Hodgkin's lymphomas, representing only 0.93% of liver tumours. Although in both males and females the primary tumour was mainly a colorectal carcinoma, the second place was held by pancreatic tumors in females and gastric carcinomas in males, respectively (Figure 2).

Characteristics of metastases according to their origin

1. Liver metastases from colorectal adenocarcinoma

Out of the total 748 cases of liver tumours, 168 cases of liver metastases spread from colorectal adenocarcinoma. They represented 22.45% of the total 748 cases of primary and secondary liver tumours. Ninety-nine were identified in male patients with a mean age of 61.87 (\pm 10.83) years (between the ages of 25 and 83) and 69 were identified in females with a mean age of 61.21 (\pm 9.51) years (between the ages of 43 and 78), with no statistically significant difference ($p=0.68$). 31.54 % of the cases presented multiple liver metastases.

Regarding the histological grade of the primary tumour we could assess the following: there were 2 well differentiated, 90 moderately differentiated and 14 poorly differentiated tumours (Figure 3). The diameter of the liver metastases ranged between 2 mm and 142 mm.

2. Liver metastases from pancreatic carcinoma

Out of the total of 748 cases of liver tumours, 80 cases of liver metastases spread from pancreatic carcinoma, representing 10.69%. Forty-five were identified in male patients with a mean age of 62.33 (\pm 9.04) years (between the

ages of 40 and 79) and 35 were identified in female patients with a mean age of 58.8 (\pm 13.04) years (between the ages of 31 and 82), with no statistically significant difference ($p=0.15$). The diameter of the liver metastases ranged between 3 mm and 30 mm.

3. Liver metastases from gastric adenocarcinoma

We identified 64 liver metastases spread from gastric adenocarcinoma, representing 8.55% of the total 748 cases of primary and secondary liver tumours. Out of these 54 were identified in male patients with a mean age of 63.5 (\pm 12.07) years (between the ages of 30 and 83) and 10 were identified in female patients with a mean age of 68.6 (\pm 7.6) years (between the ages of 57 and 81), with no statistically significant difference ($p=0.20$). 12.5% presented multiple liver metastases. The diameter of the liver metastases ranged between 3 mm and 170 mm.

Regarding the histological grade of the primary tumour we could assess the followings: there were 1 well differentiated, 13 moderately differentiated and 15 poorly differentiated tumours (Figure 4).

4. Liver metastases from undifferentiated carcinomas

We identified a total of 47 liver metastases from undifferentiated carcinomas, out of which 32 were identified in male patients with a mean age of 59.78 (\pm 10.1) years (between the ages of 37 and 82) and 15 identified in female patients with a mean age of 63.6 (\pm 7.36) years (between the ages of 52 and 76), with no statistically significant difference ($p=0.19$). The diameter of the liver metastases ranged between 2 mm and 70 mm.

5. Liver metastases from adenocarcinoma of unknown origin

Out of the total 46 cases of liver metastases spread from adenocarcinoma of unknown origin, representing 6.14%

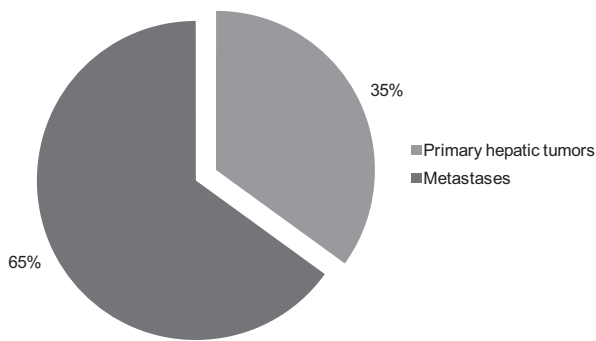


Fig. 1. Liver metastases vs. primary tumours

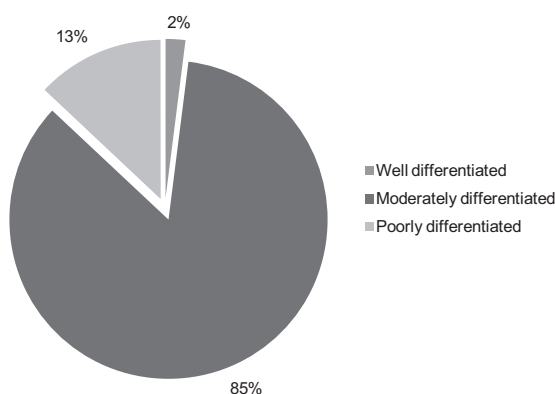


Fig. 3. Degree of differentiation of colorectal adenocarcinoma

of the total 748 cases of primary and secondary liver tumors, 25 were identified in male patients with a mean age of 66.28 (± 10.29) years, (between the ages of 40 and 80) and 21 were identified in female patients with a mean age of 64.8 (± 11.41) years, (between the ages of 28 and 83) with no statistically significant difference ($p=0.64$ Student test). The diameter of the liver metastases ranged between 2 mm and 140 mm.

6. Liver metastases from adenocarcinoma of the gallbladder
 Out of the total 46 cases of liver metastases spread from gallbladder adenocarcinoma, 5 were identified in male patients with a mean age of 53.6 (± 11.01) years, (between the ages of 45 and 71) and 20 were identified in female patients with a mean age of 65.3 (± 9.44) years, (between the ages of 52 and 86). Applying the Student test for mean ages by gender, we found a statistically significant difference ($p=0.02$). The diameter of liver metastases was between 3 and 75 mm.

Discussions

By performing this study we wanted to reveal the proportional structure of the histological types of liver metastases, and a series of characters influencing their prognosis, such as size, multiple metastases, distribution by gender and age range found in Mureş County medical units.

In a study performed in England and Wales on randomly selected liver biopsies, the most common histologi-

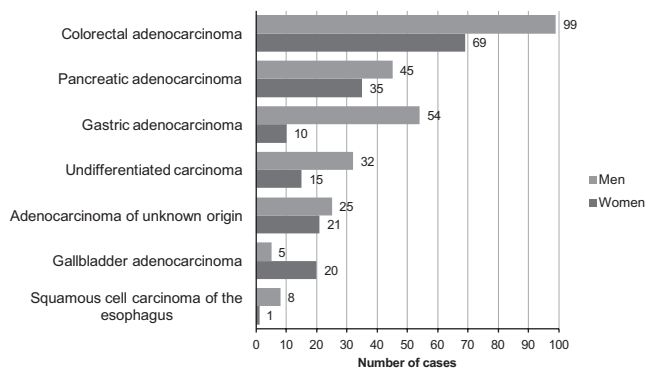


Fig. 2. Gender based distribution of the main types of cancer that produced liver metastases

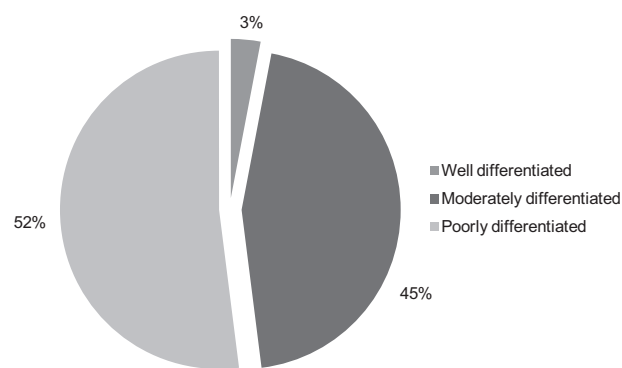


Fig. 4. Degree of differentiation of gastric adenocarcinoma

cal type of metastases was adenocarcinoma (39%) followed by not otherwise specified (NOS) carcinoma (36%), the rest being small cell undifferentiated carcinoma, other special types of carcinomas and lymphomas [7]. Frequency according to primary location of cancer in Western population is: upper gastrointestinal tract (stomach, gall bladder, pancreas): 44–78%, colon 56–58%, lung: 42–43%, breast: 52–53% esophagus: 30–32%, genitourinary organs: 24–38% [8]. Ovarian, endometrial, prostate and urothelial carcinoma are uncommon sources of liver metastases, each representing 4% or less. Clear cell renal cell carcinoma rarely produces liver metastasis, representing only 3% [8]. The liver is the most affected organ by metastases arising from neuroendocrine tumours, followed by bone and lung tumours. 85% of neuroendocrine tumours originate from the gastrointestinal tract, most patients presenting liver metastases when diagnosed [9,10]. Liver metastases of malignant melanoma are rare, their incidence representing only 2.2% of all cases [8]. Primary hepatic lymphomas are extremely rare, representing 0.016% of all cases of non-Hodgkin's lymphoma and even less in case of Hodgkin lymphoma, unlike secondary hepatic lymphomas, which are more common [11]. Hodgkin and non-Hodgkin lymphomas affect the liver in up to 20% when first diagnosed and 55% of autopsied cases [12]. Sarcomas are less frequent, but 6% present liver metastases when first diagnosed, which are mostly intra-abdominal leiomyosar-

comas [13]. In a study performed on 69 cases of gastrointestinal stromal tumours, 15.9% had liver metastases [14].

In a recently performed study on 1021 patients diagnosed with liver metastases in Denmark, between 1998–2009, they found 52.99% cases of colorectal cancer out of which 14.10% originated from the pancreas, 12.73% from the lung, 3.72% from the stomach, 2.12% from the breast, 2.06% from the esophagus, 1.86% from the kidney and 1.57% from the gall bladder. The mean age of patients was 67.7 for cases of liver metastases arising from colorectal cancer and 66.2 for other types [15].

Cirrhosis provides a relative protection against secondary tumours [16]. It was also suggested that metastases are rare in fatty liver, but heavy drinking apparently increases liver metastases [17,18].

Globally, half of about one million patients diagnosed annually with colorectal cancer will develop liver metastases during the progression of the disease [19,20]. In other types of cancers, liver metastases are the manifestations of disseminated systemic diseases, surgical excision not always being a curative option [21]. Although in case of colorectal adenocarcinomas and neuroendocrine tumours portal circulation favours the emergence of liver metastases, sometimes being unique, without systemic dissemination [21]. Therefore surgical excision is a potentially curative therapeutic option for patients with resectable liver metastases, in contrast with palliative chemotherapy for patients with unresectable metastases [22].

Recently, hepatic resection has been accepted as the most effective therapy for patients with various cancer types that metastasize to the liver, especially those arising from the digestive tract [23], the survival rate at 5 years after resection reaching to 60% [24].

In addition to these, systemic chemotherapy has proved to be useful in case of decreasing secondary liver tumour stage, initially unresectable stage, allowing a potentially curative surgical treatment [25]. Thus, the preoperative administration of cetuximab or bevacizumab, although not yet fully evaluated, does not cause increased mortality or an exacerbation of chemotherapy-induced hepatotoxicity [26,27], such as steatosis produced by the administration of 5-fluorouracil, steatohepatitis due to irinotecan or sinus congestion caused by oxaliplatin [28].

Early detection of liver metastases in patients diagnosed with malignant tumours is important for determining therapeutic strategy and prognosis, and survival possibilities. In some patients with preoperative detection of hepatic metastases treatment is possible at the same time with that of the primary tumour [6].

Conclusions

The number of liver metastases remains greater than primary liver tumours. Most cases originate from tumours located in the digestive system. Independently of the primary tumor, the liver tumors are the most common in males, in their 7th decade of life.

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References

1. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr>, accessed on 05/12/2011.
2. Blonski W, Kotlyar DS, Forde KA. Non-viral causes of hepatocellular carcinoma. *World J Gastroenterol*. 2010;16(29):3603-3615.
3. Albrecht T. Sonography of Liver Metastases, in Lencioni R, Cioni D, Bartolozzi C (eds): Focal Liver Lesions. Detection, Characterization, Ablation. Springer-Verlag Berlin Heidelberg. 2005;261-274.
4. Bosch FX, Ribes J, Diaz M, Cléries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology*. 2004;127:S5-S16.
5. Khan AN. Liver, Metastases: eMedicine Radiology. 2009. Available from: URL: <http://emedicine.medscape.com/article/369936-overview>
6. Larsen LPS. Role of contrast enhanced ultrasonography in the assessment of hepatic metastases: A review. *World J Hepatol*. 2010;2(1):8-15.
7. Jenkins D, Gilmore IT, Doel C, Gallivan S. Liver biopsy in the diagnosis of malignancy. *QJM*. 1995;88:819-825.
8. Shak K, Goodman Z, Stocker J, eds. Tumors of the Liver and Intrahepatic Bile Ducts. 3rd series. Vol 31. Washington, DC: AFIP; 2001.
9. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *Journal of Hepatology*. 2007;47(4):460-466.
10. Oberg K, Eriksson B. Endocrine tumours of the pancreas. *Best Practice and Research: Clinical Gastroenterology*. 2005;19(5):753-781.
11. Noronha V, Shafi NQ, Obando JA, Kummar S. Primary non-Hodgkin's lymphoma of the liver. *Crit Rev Oncol Hematol*. 2005;53:199-207.
12. Jaffe ES. Malignant lymphomas: pathology of hepatic involvement. *Semin Liver Dis*. 1987;7:257-268.
13. Jaques DP, Coit DG, Casper ES, Brennan MF. Hepatic metastases from soft-tissue sarcoma. *Ann Surg*. 1995;221:392-397.
14. Tateishi U, Hasegawa T, Satake M, Moriyama N. Gastrointestinal stromal tumor correlation of computed tomography findings with tumor grade and mortality. *J Comput Assist Tomogr*. 2003;27:792-8.
15. Høyer M, Erichsen R, Gandrup P, Norgaard M, Jacobsen JB. Survival in patients with synchronous liver metastases in central and northern Denmark, 1998 to 2009. *Clinical Epidemiology*. 2011;3(Suppl 1):11-17.
16. Uetsuji S, Yamamura M, Yamamichi K, et al. Absence of colorectal cancer metastasis to the cirrhotic liver. *Am J Surg*. 1992;164:176-177.
17. Hayashi S, Masuda H, Shigematsu M. Liver metastasis rare in colorectal cancer patients with fatty liver. *Hepatogastroenterology*. 1997;44:1069-1075.
18. Maeda M, Nagawa H, Maeda T, Koike H, Kasai H. Alcohol consumption enhances liver metastasis in colorectal carcinoma patients. *Cancer*. 1998;83:1483-1488.
19. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2004;239:818-825; discussion 825-827.
20. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40 983): a randomised controlled trial. *Lancet*. 2008;371:1007-1016.
21. Borner MM. Neoadjuvant chemotherapy for unresectable liver metastases of colorectal cancer – too good to be true? *Ann Oncol*. 1999;10:623-626.
22. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg*. 2004;240:1052-1061; discussion 1061-1064.
23. Saif MW. Secondary hepatic resection as a therapeutic goal in advanced colorectal cancer. *World J Gastroenterol*. 2009;15(31):3855-3864.
24. Nikfarjam M, Shereef S, Kimchi ET, et al. Survival outcomes of patients with colorectal liver metastases following hepatic resection or ablation in the era of effective chemotherapy. *Ann Surg Oncol*. 2009;16:1860-1867.

25. Blazer DG 3rd, Kishi Y, Maru DM, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. *J Clin Oncol.* 2008;26:5344-5351.
26. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol.* 2008;26:1830-1835.
27. Adam R, Aloia T, Levi F, et al. Hepatic resection after rescue cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic therapy. *J Clin Oncol.* 2007;25:4593-4602.
28. Ribero D, Wang H, Donadon M, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. *Cancer.* 2007;110:2761-2767.