

# Liver Metastasis of Gastrointestinal Neuroendocrine Tumors: A Single Center Experience

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## Abstract

**Background:** Gastrointestinal neuroendocrine tumors (GI-NETs) are potentially malignant tumors, and their most common location of metastasis is the liver.

**Objectives:** In this report, we will describe our experience with some clinical and pathologic findings of hepatic metastasis in a group of cases of GI-NETs at the largest referral center of GI and liver diseases in south Iran.

**Materials and Methods:** In this four-year study (2011-2014), all GI and liver NETs were extracted from the pathology files of hospitals affiliated with Shiraz University of Medical Sciences. After classification based on the world health organization guidelines, the patients were evaluated according to their location, sex, age, and proliferative index. After studying the imaging and clinical charts of liver-NET cases with an unknown primary location, a complete panel of immunohistochemical markers (TTF-1, CDX-2, CK-7, CK-2, etc.) was used to find the primary GI location. Carcinoid tumors from other sites, such as the lung, were omitted from this study.

**Results:** The most common primary site of metastatic GI-NET to the liver in our center was the small intestine, which was also the most frequent location of GI-NET without liver metastasis. No cases of appendiceal-NET were found with liver metastasis. In 8 cases (11.6%) with liver-NETs, no primary location was identified. GI-NETs with liver metastasis had a significantly higher grade and proliferative index compared with NETs without liver metastasis.

**Conclusions:** Liver metastasis of neuroendocrine tumors in Iran presents in a very similar manner as that seen in western countries. In about 89% of cases with liver-NET, complete imaging, clinical, and pathological studies can help to identify the primary origin of the liver-NET, which is very important in the patient's management.

**Keywords:** Liver, Neuroendocrine Tumor

## 1. Background

Neuroendocrine tumors (NETs), which were formerly called carcinoid tumors, have an annual incidence of 1–2,100,000. The gastrointestinal tract is the most common site of NETs and accounts for 70% of them. NETs represent 2% of all tumors in the gastrointestinal tract. The incidence of this tumor type has been increasing during the last 30 years (1).

Even with completely bland cytomorphology, NETs can be potentially malignant tumors; the most common location of metastasis is the liver (2). However, there has been no report from Iran about the common locations and clinicopathologic findings of this tumor in the liver and GI tract, except for one case involving the pancreas (3).

## 2. Objectives

The present study is the first report to describe and compare pathologic findings of GI-NET both with and without liver metastasis from Iran that lasted for four years (2011-2014) and were carried out in hospitals affiliated with Shiraz University of Medical Sciences, the largest referral center in south Iran.

## 3. Materials and Methods

In this retrospective study, 131 cases of GI and liver NETs were identified from the archives of pathology in hospitals affiliated with Shiraz University of Medical Sciences from 2011 - 2014. These tumors were reviewed by the GI and liver pathologist (BG) and classified according to the latest world health organization (WHO) classification (i.e., performing Ki-67 for determination of the grade) (4). For

liver-NETs, clinical charts were reviewed to identify the primary site, which has previously been located in about 89% of cases by surgical exploration or imaging studies. However, in those with an unknown primary location, a complete immunohistochemical (IHC) panel (TTF-1, CDX-2, Pax-8, CK-7, CK-20, etc.) was used to find the probable site of the primary tumor. This modality (IHC) helped to identify the primary location of another 9% (8 patients) of cases. In these patients, Ki-67 was performed on the metastatic tissue in the liver when the primary tumor was not available. It is worthy to note that in this study, bronchial carcinoids with or without liver metastasis were not included. The size of the primary GI-NET was also omitted from this study because we did not have the exact size in some of the primary GI-NETs.

#### 4. Results

During the study period, 131 cases of GI and liver NET (123 GI-NETs both with and without liver metastasis and 8 cases with liver-NET and no primary location) were identified. Among these cases, 62 were GI-NETs with no evidence of liver metastasis and 69 cases were liver NET, 8 of which showed no known primary NET. The age range of the GI-NET was 2 - 83 ( $43.9 \pm 17.08$ ), while that for GI-NET with no liver metastasis was 2 - 79 ( $41.69 \pm 21.43$ ) and for hepatic NET was 8 - 83 ( $46.13 \pm 15.98$ ).

Table 1 shows the overall characteristics of the patients with NET both with and without liver metastasis during the study period.

The most common site of GI-NET has been the small intestine (35.78%), including the terminal ileum and duodenum.

There was no statistically significant difference between a GI-NET with liver metastasis and a non-metastatic GI-NET in regard to sex and age; however, there were significantly more liver metastases in gastric and intestinal NETs and also no liver metastasis associated with appendiceal NET. In addition, there were significantly more grade-2 and grade-3 cases of NETs with liver metastasis.

#### 5. Discussion

GI-NETs are a heterogeneous group of tumors with potentially malignant behavior. There have been different methods of classifying this group of tumors; however, in the most recent WHO classification, this tumor type was classified according to its Ki67 positivity (proliferative index) percent. It seems that the most important prognostic value for predicting behavior of GI-NET is the degree of proliferation, which can be determined by Ki67 (3).

The most common metastatic site of involvement in this group of tumors is the liver (4). There are different reports from several parts of the world about the primary sites of GI-NET involving the liver (5-7). However, no study has been published in Iran about the epidemiology of GI-NETs with hepatic involvement so far.

According to our study, the most common site of GI-NET has been the small intestine (i.e. 35.78% of all GI-NETs during the study period in our center have been from this location, and the most common primary site of liver metastasis has been the small intestine as well (39%). Most of the reports from other parts of Europe and the United States (US) have shown the same results; the most common site of GI-NET either with or without liver metastasis has been the small intestine (terminal ileum) (8-11); however, separate reports from other countries, such as Korea, have shown that most of the metastatic liver-NETs have originated from the pancreas (5).

One of the most important issues in GI-NET is liver metastasis. It is crucial to find the primary site of liver metastasis in liver-NET because it has great impact on the patient's outcome by resection of the primary tumor (8). There are many diagnostic modalities for finding the primary GI-NET of the liver, such as upper and lower endoscopy and also imaging techniques, including computed tomography (CT), positron emission tomography (PET/CT), magnetic resonance imaging (MRI), and octreotide scans (10). However, in about 11% - 14% of liver metastases, the primary site cannot be identified (8).

In our study, in about 80% of the liver-NETs, the primary location was identified using different imaging and clinical parameters. In the remainder of the cases, thorough pathologic studies and IHC markers have helped to identify more than 10% of tumor origins of the liver-NETs (12). Overall, in 11.6% of the liver-NETs, no primary location was found. According to many previous studies, the most common site of liver-NETs with unknown primaries should be the terminal ileum because they are difficult to be identified upon imaging and endoscopic studies (8). There are also controversial reports about when to call these liver-NETs "primary liver neuroendocrine tumors." However, it seems that all the imaging (including octreotide scanning) and pathological modalities should be applied before calling a NET in the liver as the primary. Primary liver-NET is an extremely rare occurrence, and less than 150 cases have been reported in the English literature so far (13).

##### 5.1. Conclusion

The incidence of GI-NETs has been increasing during the last 10 years, which is partly due to improved diagnostic modalities. The proper pathologic diagnosis and classification of the GI-NETs is very important and should be

**Table 1.** Pathologic Characteristics of the NETs in the GI Tract Both With and Without Liver Metastasis<sup>a, b</sup>

Value	GI NET	GI-NET Without Liver Metastasis	Hepatic NET	Statistical Difference
<b>Number</b>	123	62	69	-
<b>Age, y</b>	2- 83 (43.9 ± 17.08)	2- 79 (41.69 ± 21.43)	8- 83 (46.13 ± 15.98)	Not significant
<b>Gender</b>				
M/F	64/59	31/31	36/33	Not significant
<b>Location</b>				
Stomach	22 (17.89)	5 (8)	17 (24.7)	Significant
Small intestine	44 (35.78)	17 (27.4)	27(39)	Significant
Rectum	9 (7.33)	5 (8)	4 (5.8)	Not significant
Appendix	20 (16.2)	20 (32.3)	0	Significant
Pancreas	28 (22.8)	15 (24.3)	13 (18.7)	Not significant
Unknown		-	8 (11.6)	-
<b>G1</b>	82 (66.7)	47 (75.8)	35 (50.7)	Not significant
<b>G2</b>	30 (24.4)	12 (19.3)	25 (36.2)	Significant
<b>G3</b>	11 (8.9)	3 (4.8)	9 (13.1)	Significant

Abbreviation: M, male; F, female.

<sup>a</sup>Values are expressed as mean ± SD or No. (%).

<sup>b</sup>Statistical Method: Chi Square, Significant P < 0.05.

performed according to the last WHO classification (2010) because it has the most important prognostic implication and is predictive of malignant behavior as well as distant metastasis. The most common site of metastasis in GI-NETs is the liver, and in every liver-NET, all of the diagnostic methods should be used to find their primary origin, which is very important when making therapeutic decisions.

## Footnote

**Authors' Contribution:** Bita Geramizadeh: proposal of the research, collecting the data, diagnosis and grading, writing the paper; Ali Kashkooe: collecting the data; Seyed Ali Malekhosseini: conducting surgery and finding the patients.

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