ORIGINAL ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2021.2021-15
Cyprus J Med Sci 2022;7(4):541-545

Neuroendocrine Tumors Presenting with Liver Metastasis, is it Necessary to Find the Primary Site for a Better Outcome?

Ayşe Demirci[1], Hasret Cengiz[2], Ceyhun Varım[3]

[1]Department of Medical Oncology, Sakarya University Faculty of Medicine, Sakarya, Turkey
[2]Department of Endocrinology, Sakarya University Faculty of Medicine, Sakarya, Turkey
[3]Department of Internal Medicine, Sakarya University Faculty of Medicine, Sakarya, Turkey

Abstract

BACKGROUND/AIMS: Neuroendocrine tumors (NET) presenting with multiple liver metastasis are a heterogeneous group of tumors and their prognosis differs greatly from each other according to their differentiation, grade, and possibly to their primary site of origin.

MATERIALS AND METHODS: Seven patients diagnosed with NET who presented with multiple liver metastases between October 2014 and November 2018 were included in this retrospective study. The patients' details, their tumor characteristics, the local and systemic treatments administered, the response evaluation and their survival data were collected from the hospital files and analyzed.

RESULTS: The median age of the 7 patients was 50 (range: 27-64) years. Carcinoid syndrome was present in two patients. The histopathology of all the patients were consistent with well-differentiated NET. As an initial treatment, one patient underwent right hepatectomy. All patients received somatostatin analog for a median of 20.7 months (range: 6-48 months) as an initial systemic treatment. One patient received radionuclide therapy and palliative radiotherapy for bone metastasis, one patient received trans arterial chemo embolization to the liver and one patient received capecitabine and temozolamide treatment after progression to somatostatin analog treatment. The median progression free survival and median overall survival (follow-up) was 15 months (range: 6-48 months) and 17 months (range: 8-48 months) respectively. All patients were still alive at the end of this study.

CONCLUSION: Primary unknown well-differentiated NETs presenting with liver metastasis have different clinical and survival characteristics than primary known metastatic NETs. Treating these patients as the same disease may not be appropriate.

Keywords: Neuroendocrine tumor, liver metastasis, prognosis

INTRODUCTION

Neuroendocrine tumors (NETs) constitute less than 5% of all cancers of unknown primary sites.[1] NETs of unknown primary site are seen 10 to 13% of all NETs.[2,3] Their prognosis differs greatly from each other according to their differentiation, grade, and possibly to their primary site of origin. Survival is lower in unknown primary NETs compared to patients with liver metastasis whose primary of NETs is known so it may be important to find the primary site.[4]

The distant metastasis rates are around 40 to 45% in small intestine, colon and pancreas, 15% in stomach, 6% in rectum and 3% in appendix primaries. The five-year-survival rate is lower with distant metastatic

To cite this article: Demirci A, Cengiz H, Varım C. Neuroendocrine Tumors Presenting with Liver Metastasis, is it Necessary to Find the Primary Site for a Better Outcome? Cyprus J Med Sci 2022;7(4):541-545

ORCID IDs of the authors: A.D. 0000-0002-6291-7573; H.C. 0000-0002-5216-3368; C.V. 0000-0002-8369-0857.

Address for Correspondence: Ceyhun Varım
E-mail: ceyhunvarim@sakaryaedu.tr
ORCID ID: orcid.org/0000-0002-8369-0857

Received: 02.02.2021
Accepted: 29.05.2021

NETs including the liver (about 30 to 60%).[5] Clinical symptoms may help to detect the primary site of NETs. Carcinoid syndrome is present in 17% of cases and this suggests a small intestinal primary.[6] Immunohistochemistry (IHC) is used to find the primary site of liver metastatic NETs. Thyroid transcription factor 1 (TTF-1) is positive in poorly differentiated neuroendocrine carcinomas (NECs) and some well-differentiated NETs of lung origin but caudal-type homeobox-2 (CD-X2) is positive in well-differentiated NETs of intestinal origin.[6] Mesenteric masses also indicate a primary located in the small intestine. Pancreatic primaries are usually larger than both small and large bowel primary tumors (7.5 cm vs. 1.7 cm and 3.8 cm respectively).[7]

Resection of the primary tumor, locoregional lymph node, and liver metastasis prolongs survival and improves the quality of life in NETs.[8] Somatostatin analogue therapy is beneficial mostly in all functional NETs and small intestinal grade G1 and G2 primaries. Everolimus and sunitinib are approved for pancreatic NETs.[9] Pancreatic NET are also sensitive to chemotherapy such as temozolamide alone or in combination with capecitabine.[9] For patients with advanced poorly differentiated NECs, the prognosis is poor and determining the primary site may not alter the treatment which is usually platinum based chemotherapies but treatment for patients with metastatic well-differentiated NETs depends on the primary site.[10]

The aim of this study was to answer the question of whether the primary site is important for the management of well-differentiated liver metastatic NETs whose primary site is not known after routine screening. For this, we have retrospectively analyzed seven unknown primary NET cases.

MATERIALS AND METHODS

Seven patients diagnosed with NET who presented with multiple liver metastases between October 2014 and November 2018 were included in this retrospective study. The patients' characteristics, the pathological characteristics of their tumors, the local and systemic treatments administered, their response evaluations and survival data were collected from the hospital files and analyzed. NET was defined as well-differentiated if the Ki-67 index was equal to or below 20%. Well-differentiated, low-grade (G1) tumors have a mitotic count of less than 2/2 mm^2 [10 high-power field (HPF)] and/or a Ki-67 index of less than 3% while well-differentiated, intermediate-G2 tumors usually have a mitotic count of 2 to 20/2 mm^2 (10 HPF) and/or a Ki-67 index of 3% to 20%.[11] Progression free survival (PFS) was calculated as the time in months from the date of diagnosis to either the date of progression or the date of last follow-up for those patients without progression. Overall survival (OS) was calculated as the time in months from the date of diagnosis to the date of death or the last follow-up date.

The protocol for this retrospective study was compatible with the local ethical guidelines.

The study protocol was approved by the Ethics Committee of Sakarya University Training and Research Hospital and was conducted in accordance with the principles of the Declaration of Helsinki (approval number: 714522473/050.01.04/464).

Statistical Analysis

Statistical analysis was performed by SPSS 15.0 software, (SPSS Inc, Chicago, Illinois, USA). Data are expressed as median, mean and proportion. Survival analysis was estimated using the Kaplan-Meier method. Significance was defined as $p<0.05$.

RESULTS

Five of the patients were men and two were women. The median age of the 7 patients was 50 (range: 27-64) years. Abdominal pain was the leading symptom. Carcinoid syndrome was present in two patients. There was no sign of multiple endocrine neoplasia. One only patient was resectable. Basal serum chromogranin A (CgA) and urine 5-hydroxyindoleacetic acid (5HIAA) were elevated in four and three patients respectively (Table 1). The histopathology of all the patients were consistent with well-differentiated NET. IHC staining showed CgA and synaptophysin positivity in all cases. According to the mitotic count and Ki-67 index, four tumors were G2 and three tumors were G1. Three tumors were also positive for CD-X2 but TTF-1 was negative in all cases (Table 2). As an initial treatment, one patient underwent right hepatectomy. All patients received somatostatin analogue for a median of 20.7 months (range: 6-48 months) as an initial systemic treatment. One patient received radionuclide therapy and palliative radiotherapy for bone metastasis, one patient received trans-arterial chemo-embolization to the liver and one patient received capecitabine and temozolamide treatment after progression of somatostatin analog treatment. Median PFS and median OS (follow up) were 15 months (range: 6-48 months) and 17 months (range: 8-48 months) respectively. All patients were still alive at the end of this study (Table 3).

DISCUSSION

In addition to routine computed tomography (CT), magnetic resonance imaging, somatostatin receptor scintigraphy (SRS, Octreoscan), upper and lower endoscopies, endoscopic ultrasound (EUS), and capsule endoscopy may be needed in order to find small primaries.[7] We did

Table 1. Characteristics of patients with primary unknown neuroendocrine tumor presenting with liver involvement

Patient no	Age	Gender	Symptom	Co-morbidity	Resectable	CgA	5HIAA	Carcinoid syndrome
1	27	M	Gastric pain	None	No	High	High	Yes
2	64	M	Dyspnea	CAD	No	N	N	No
3	50	F	Abd. pain	DM, HT, COPD	No	High	N/A	No
4	50	M	RUQ pain	None	Yes	N	N	No
5	64	M	None	GI bleeding	No	High	High	No
6	54	F	Abd. pain	HT	No	N	N	No
7	39	M	Abd. pain	Appendectomy	No	High	High	Yes

G: gender, M: male, F: female, Abd: abdominal, RUQ: right upper quadrant, CAD: coronary artery disease, DM: diabetes mellitus, COPD: chronic obstructive lung disease, GI: gastrointestinal, HT: hypertension, CgA: serum cromogranin A, 5HIAA: urine 5- hydroxyindoleacetic acid, N: normal, N/A: not available.

Table 2. Pathological characteristics of patients with primary unknown well-differentiated neuroendocrine tumors presenting with liver metastasis

Patient no	Pathology	Diff.	Tumor grade	Mitotic count*	Ki-67 index	CgA	Synaptophysin	CD-X2	TTF-1
1	NET	Well	G2	>2	10	+	+	+	-
2	NET	Well	G1	<2	1	+	+	-	-
3	NET	Well	G2	>2	4	+	+	-	-
4	NET	Well	G2	>2	11	+	+	-	-
5	NET	Well	G2	>2	3	+	+	-	-
6	NET	Well	G1	<2	1	+	+	+	-
7	NET	Well	G1	<2	1	+	+	+	-

Diff: differentiation, NET: neuroendocrine tumor, CgA: chromogranin A, CD-X2: caudal-type homeobox, intestine-specific transcription factor, TTF-1: thyroid transcription factor 1, *mitotic count: counted in 10 high power fields, at 400x magnification evaluated in area of highest mitotic density. Cut-offs PER American Joint Commission on Cancer Stating Manual, 7th edition.

Table 3. Treatment characteristics of patients with primary unknown neuroendocrine tumor presenting with liver metastasis

Patient no	Initial Tx	Somatostatin analogue Tx	Dose (mg)	Somatostatin time (m)	Response	Secondary Tx	PFS (m)	OS* (m)
1	Palliative Rt (bone)	Octreotide LAR	10-30	48	Stable*	Radionuclide Tx (2 times)	48	48
2	-	Octreotide LAR	20	39	Stable	-	39	39
3	-	Octreotide LAR	30	6	Progression	Capecitabine-temozolamide (4 m)	6	17
4	Right hepatectomy	Octreotide LAR	30	15	Stable	-	15	15
5	TACE (liver)	Octreotide LAR	30	12	Stable	-	12	12
6	-	Octreotide LAR	30	17	Stable	-	17	17
7	-	Lanreotide	90	8	Stable	-	8	8

Tx: treatment, Rt: radiotherapy, TACE: transarterial chemo-embolisation, LAR: long acting release, M: month, PFS: progression free survival, OS: overall survival, *After 15 months' treatment with octreotide LAR, there was a progression of liver lesions, and patient one received radionuclide treatment 2 times in two months interval, then the disease remained stable with octreotide LAR 30 mg treatment until now. *All patients are alive at the end of the study.

not find the primary sites in our 7 liver metastatic NETs after routine workup. We did not use either EUS or capsule endoscopy because of the unavailability of these procedures in our hospital. Identification of the primary site may influence the surgical management of resectable metastatic NETs.[10] There was only one resectable liver metastasis in our primary unknown cases. If the primary site was the small intestine, the primary tumor would be so small that it would be extremely hard to find the primary site. However, this small primary NET can metastasize to regional lymph nodes causing mesenteric fibrosis and can be detected as multiple liver metastasis, which is not suitable for metastasectomy. In this case, resection of the primary intestinal tumors and regional lymph nodes or fibrosis is accepted as unresectable but stable liver metastasis.[10] This knowledge would have been beneficial in our cases if we had found the primaries of our cases to be in the small intestine.

When their primary cannot be found, well-differentiated tumors usually present with unresectable liver metastasis.[6] The presence of mesenteric mass, CD-X2 positivity and the presence of carcinoid syndrome may be the clues of intestinal primary and TTF-1 positivity may be positive in poorly-differentiated NECs and some well-differentiated NETs of lung origin.[6] In our primary unknown NET cases, they all presented as multiple liver metastasis. Our cases were all well-differentiated NETs. Four of them were G2 and three of them were G1 disease. Patients no: 1, 6 and 7 had CD-X2 positivity and patients no: 1 and 7 had carcinoid syndrome. There was no TTF-1 positivity in our cases. Treatment for well-differentiated NETs depends on the primary site. Pancreatic NETs are more sensitive to chemotherapy than other NETs from other sites. Everolimus and sunitinib are approved for those patients with advanced pancreatic NETs. Octreotide acetate improves the outcomes for those patients with advanced midgut (lower jejunum, ileum, cecum and appendix) NETs. We used octreotid acetate or lanreotide in all primary unknown cases. All patients responded to octreotid acetate or lanreotid treatment except for patient no: 3. Further treatment with capecitabine and temozolamide was also not effective in patient no: 3. The median duration of octreotid acetate treatment was 20.7 months (range: 6-48 months). This may show that our cases were sensitive to octreotid acetate similar to a midgut tumor.

Is it appropriate to treat primary unknown well-differentiated NETs as if they are a single entity? There are some clues that these tumors are different from each other. Gene expression analysis of C-type lectin domain family 13 member A (CD302) and peptidylprolyl isomerase domain and WD repeat containing 1 (PPWD1) in NET metastasis correctly identifies the primary in the ileum or in the pancreas in 80% of cases.[12] Even by using sensitive somatostatin receptor positron emission tomography/CT, the primary of one third of NET patients could not be determined.[13] Genetic signatures of primary and liver metastasis may explain the survival difference and somatostatin receptor agonist response as seen in our cases. Alternative lengthening of telomeres was also found to be a useful biomarker in patients with NET liver metastasis. This marker is positive in pancreatic origin in 56% of pancreatic NETs and positive only in 4% in gastrointestinal carcinoid tumors ($p<0.001$).[14,15] This may explain the treatment response differences of pancreatic and intestinal NETs to certain chemotherapies and targeted therapies such as everolimus and sunitinib. We did not use everolimus or sunitinib in our patients. Since patient no: 3 was not sensitive to somatostatin analogue, we tried capecitabine and temozolamide but she did not respond to chemotherapy at all. We have speculated that

patient no: 3 would not respond to everolimus or sunitinib as her tumor was not symptomatic. These targeted drugs are also approved for use in pancreatic functioning tumors. We managed all unknown primary cases like those with metastatic non-pancreatic well-differentiated tumors. We could control the carcinoid symptoms with somatostatin analogue treatment in patients no: 1 and 7. After treatment of somatostatin analogue, the high levels of CgA in the serum and 5-HIAA in the urine also decreased to normal levels in patients 3 and 5. In these patients, there was no overt carcinoid syndrome signs.

Depending on the patient's clinic and metastasis extend, local therapies may be used such as resection of the metastasis, hepatic arterial embolization or radionuclide therapies if the metastasis are somatostatin receptor positive in SRS. Curative resection is associated with better survival in all series and survival rates of 60 to 80% can be achieved in liver metastasis. In well-differentiated unresectable liver metastatic NETs, liver transplantation is a valid option in selected patients. The 5-year-survival and disease specific survival rates are 52% and 30% respectively. Although post-operative mortality is still high.[16] New surgical methods and liver parenchymal preserving surgical and radionuclide treatments may give better results in the future. In our patient no: 1, we achieved 4-year-survival in this multiple liver and bone metastatic patient with radionuclide therapy and somatostatin analogue treatment.

Study Limitations

This study was conducted on patients in a single university hospital, and this was accepted as a limitation. The limitations of this study include its small sample size and recruitment from a single center. Since NETs are one of the rare cancers, the number of cases in our study is low. This is another limitation.

CONCLUSION

Primary unknown well-differentiated NETs presenting with liver metastasis have different clinical and survival characteristics than primary known metastatic NETs. Treating these patients as if they are the same disease may not be appropriate. Well-designed prospective randomized studies about unknown primary NETs are needed.

MAIN POINTS

- Primary unknown well-differentiated NETs presenting with liver metastasis have different clinical and survival characteristics than primary known metastatic NETs. Treating these patients as if they are the same disease may not be appropriate.
- Gene expression analysis may guide us to identify the primary origin, the survival difference and somatostatin receptor agonist response.
- Depending on the patient's clinic and metastasis extend, local therapies may be used, such as resection of the metastasis, hepatic arterial embolization or radionuclide therapies.
- New surgical methods and liver parenchymal preserving surgical and radionuclide treatments may give better results in the future.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Sakarya University Training and Research Hospital and was conducted in accordance with the principles of the Declaration of Helsinki (approval number: 714522473/050.01.04/464).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: A.D., Design: A.D., Materials: H.C., C.V., Data Collection and/or Processing: H.C., C.V., Analysis and/or Interpretation: A.D., H.C., C.V., Literature Search: A.D., H.C., C.V., Writing: A.D., Critical Review: A.D., C.V.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study had received no financial support.

REFERENCES

1. Spigel DR, Hainsworth JD, Greco FA. Neuroendocrine carcinoma of unknown primary site. Semin Oncol. 2009; 36(1): 52-9.
2. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008; 26(18): 3063-72.
3. Catena L, Bichisao E, Milione M, Valente M, Platania M, Pusceddu S, et al. Neuroendocrine tumors of unknown primary site: Gold dust or misdiagnosed neoplasms? Tumori. 2011; 97(5): 564-7.
4. Grimaldi F, Fazio N, Attanasio R, Frasoldati A, Papini E, Angelini F, et al. Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. J Endocrinol Invest. 2014; 37(9): 875-909.
5. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am. 2011; 40(1): 1-18.
6. Oien KA. Pathologic evaluation of unknown primary cancer. Semin Oncol. 2009; 36(1): 8-37.
7. Wang SC, Wang SC, Parekh JR, Zuraek MB, Venook AP, Bergsland EK, Warren RS, et al. Identification of unknown primary tumors in patients with neuroendocrine liver metastases. Arch Surg. 2010; 145(3): 276-80.
8. Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al; Working Group on Neuroendocrine Liver Metastases. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol. 2014; 15(1): 8-21.
9. Öberg K, Knigge U, Kwekkeboom D, Perren A; ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23(Suppl7): vii124-30.
10. Bergsland EK, Nakakura EK. Neuroendocrine tumors of unknown primary: is the primary site really not known? JAMA Surg 2014; 149(9): 889-90.
11. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas. 2010; 39(6): 707-12.
12. Kyriakopoulos G, Mavroeidi V, Chatzellis E, Kaltsas GA, Alexandraki KI. H. Alexandraki. Histopathological, immunohistochemical, genetic and molecular markers of neuroendocrine neoplasms. Ann Transl Med. 2018; 6(12): 252.

13. Kaemmerer D, Posorski N, von Eggeling F, Ernst G, Hörsch D, Baum RP, et al. The search for the primary tumor in metastasized gastroenteropancreatic neuroendocrine neoplasm. Clin Exp Metastasis 2014; 31(7): 817-27.

14. Dogeas E, Karagkounis G, Heaphy CM, Hirose K, Pawlik TM, Wolfgang CL, et al. Alternative lengthening of telomeres predicts site of origin in neuroendocrine tumor liver metastases. J Am Coll Surg. 2014; 218(4): 628-35.

15. Bocchini M, Nicolini F, Severi S, Bongiovanni A, Ibrahim T, Simonetti G, et al. Biomarkers for Pancreatic Neuroendocrine Neoplasms (PanNENs) Management-An Updated Review. Front Oncol 2020; 10: 831.

16. Partelli S, Maurizi A, Tamburrino D, Baldoni A, Polenta V, Crippa S, et al. GEP-NETS update: Surgery of Neuroendocrine Tumors. Eur J Endocrinol. 2014; 171(4): R153-62.