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One stage surgery for synchronous liver metastasis from a neuroendocrine tumor of the colon. A case report.

INTRODUCTION: *Neuroendocrine tumors (NETs) are a heterogeneous group of tumors. NET of colon represent less than 1% of colonic tumors. Synchronous liver metastases, present in 75-80%, are considered significant adverse prognostic indicators. Liver is the second commonest site for metastasis in patients with colorectal neuroendocrine tumors. Available treatment options include surgical resection, chemotherapy, biotherapy. Surgery is the gold standard for curative therapy and it is strictly related to the localization, the grade of tumor, and the stage of disease.*
CASE REPORT: *We present a 64-year-old man with clinical carcinoid syndrome. Colonoscopy revealed ileocecal valve vegetating mass with negative biopsy. CT scans of thorax and abdomen showed a voluminous lesion (10 cm of diameter) of right liver. CEA, CA 19.9 and aFP were all normal. Only urinary 5HIAASerum 5-hydroxyindoleactic acid and blood Chromogranin A were positive. Surgical strategy was to treat the primary tumor and the liver synchronous metastasis in one stage surgery.*
DISCUSSION: *Management of NETs liver metastases is challenging and requires aggressive therapy. Currently, there are many therapeutic options for metastatic NETs. Although complete surgical resection remains the optimal therapy and aggressive surgical resection increases the 5-year survival of NETs with solitary liver metastasis to 100%. In this case, clinical status with doubt of carcinoid syndrome was essential for diagnosis and for subsequent surgical strategy with one stage surgery.*
CONCLUSION: *Resection of the primary tumor, liver metastases, and local mesenteric lymph node metastases is thought to strictly promote long-term survival and quality of life. Typically, a multidisciplinary approach is a cornerstone for decision making while dealing with this aggressive disease.*

KEY WORDS: Carcinoid syndrome, Liver surgery, NETs, Neuroendocrine tumor, One stage surgery, Synchronous liver metastasis

Introduction

Neuroendocrine tumors (NETs) are epithelial neoplasms with predominant neuroendocrine differentiation that can arise in most body organs and share common pathologic features. NET of colon represent less than 1% of colonic tumors, and only 4% of all carcinoid tumors [1] This group of heterogeneous neoplasms defined as either non-functioning tumors or functioning tumors that secrete peptide hormones [2] . These hormones could cause characteristic patterns of symptoms, like flushing, diarrhea, and palpitation. NETs can be classified by extent of disease as having either local, regional, or distant involvement. After the lymph nodes, the liver is the pre-

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dominant site for NETs metastases. Synchronous liver metastases present in 75-80% [3,4] of patients, which is a key adverse prognostic factor. Morbidity and mortality, are the results of hormonal or hormone-related symptoms, but can also be the consequence of problems caused by tumor expansion. Different treatment options of metastatic NETs including surgery, regional and systemic biological therapy, and ablation with a variety of interventional radiology procedures have been proposed. Despite to different complex management strategies for neuroendocrine liver metastases, surgery remains the only potentially curative option. Surgical resectability is a primary concern, as neuroendocrine liver metastases are frequently numerous and bulky, and it can be confirmed based on anatomical feasibility and volumetric tolerance.

Case Report

A 64-year-old man was admitted in to our Department, presenting worsening diarrhea from 4 months and several episodes of flushing. Personal and familiar history was negative for tumors, Crohn's disease and others. Routine laboratory investigations, including liver and renal function tests and bleeding profile, such as the tumor markers (α-fetoprotein, carcinoembryonal antigen and carbohydrate antigen 19-9) were all normal. At colonoscopy, a vegetating mass of the ileocecal valve and multiple diverticula were. Biopsy were negative for tumors. CT scans of thorax and abdomen showed a voluminous lesion (10 cm of diameter) of right liver, largely hypodense, with areas of fluid attenuation, septations, irregular margins and peripheral nuclei satellites (Fig. 1). In addition to this, there was a locoregional lymph-node involvement and an irregular thickening of caecum and ileocecal valve.
So, with a strong suspect of metastatic NETs of cecum, biopsy endoscopic of cecal lesion was remade with

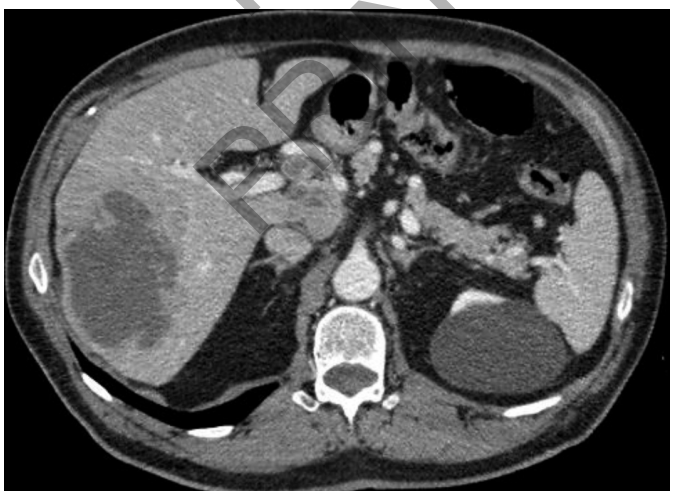

Fig. 1: CT scan illustrating right liver metastasis (left renal cyst).

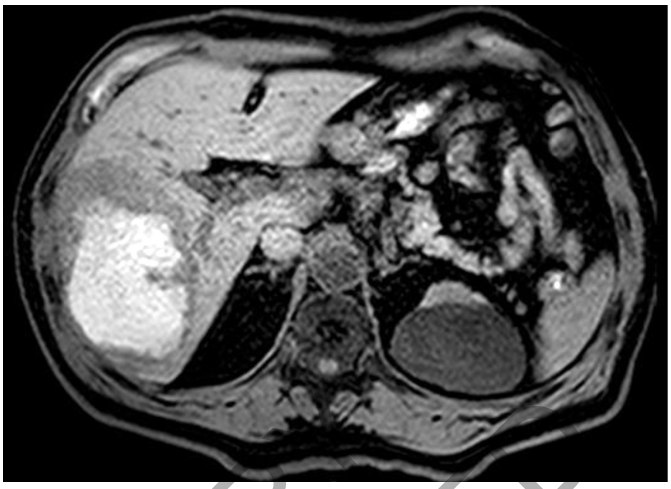

Fig. 2: MRI scan of the liver metastasis.

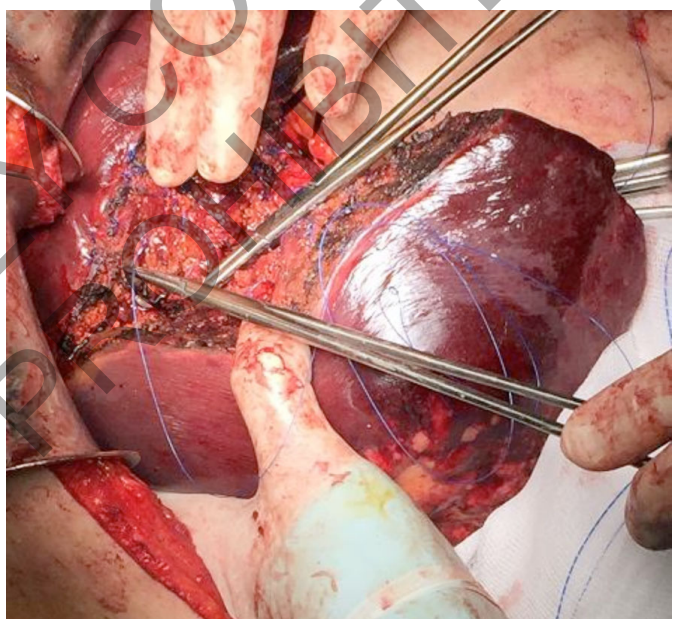

Fig. 3: Intraoperative phase: liver parenchymal transection.

immune-histochemical study for the Chromogranin A, that turned negative again.
Instead, urinary 5HIAASerum 5-hydroxyindoleactic acid (250,9 mg/24h) and blood Chromogranin A (>50 nmol/L) were much elevated. The transesophageal echocardiogram showed a severe stenosis of tricuspid valve, completing so the clinical pattern of the carcinoid syndrome.
MRI of liver was performed to better characterize the liver lesion, that involved the hepatic segments 5-6-7-8, with the dimension of 12x9x10 cm, widely heterogeneous, with solid and fluid areas (Fig. 2).
A therapy with somatostatin analogues (SSAs) was promptly started to control symptoms.
The patient was eligible for surgery and a liver volumetry was made to confirm a sufficient volume of

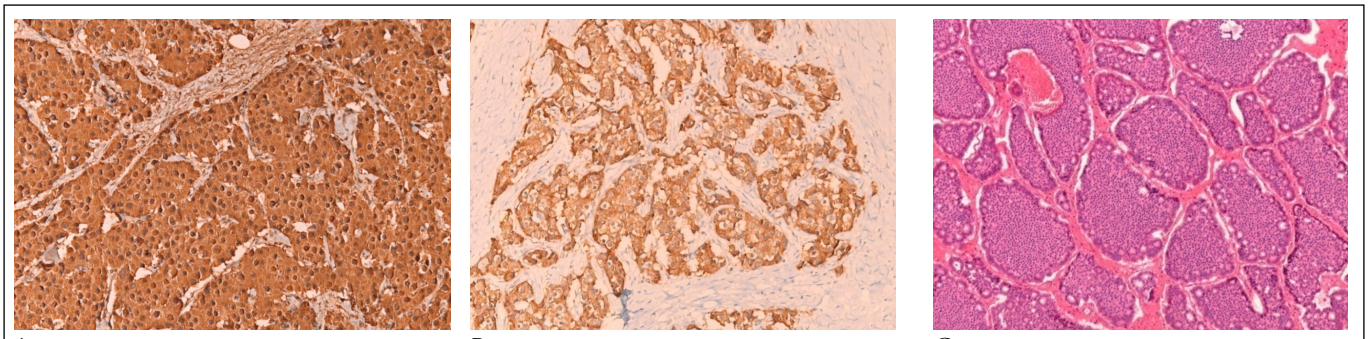

Fig. 4: The tumor was mainly composed by islands of round cells with uniform nulei (A: hematoxylin & eosin, original magnification 100X); the cells showed diffuse and intense expression of neuroendocrine markers chromogranin A (B)and synapthophysin (C).

effective remnant liver. The patient underwent to right hemicolectomy with oncological resection of the lymph drainage, right hepatectomy, wedge resection of metastasis of fourth liver segment unknown to CT and RMI scans and asportation of a diaphragmatic nodule.

The surgery time was 4 hours, with single right subcostal incision. After a careful abdominal exploration, a metastatic diaphragmatic nodule was found in continuity with the liver metastasis.

An intraoperative echography of liver was made in order to evaluate the left liver, that showed a single metastatic nodule of fourth hepatic segment,subcapsular, of about 1 cm of diameter.

So, the first phase of the surgery was completed with a right hepatectomy, while the second step was the right hemicolectomy (Fig. 3). Two abdominal drain was placed, and removed in third and sixth postoperative days. Discharge was in 8 postoperative day without any complication.

The pathological result has proved a neuroendocrine tumor, ulcerated, of the ileocecal valve, with typical cellular elements and large cytoplasm. The tumour was mainly composed by islands of round cells with uniform nuclei; the cells showed diffuse and intense expression of neuroendocrine markers Chromogranin A and Synapthophysin (Fig. 4). Ki67 index was 12%, with an intermediate grade of differentiation G2 (WHO 2010). Metastatic cells were confirmed in liver metastasis, diaphragmatic nodule, and in two lymph nodes of intestinal drainage. The immune-histochemical study showed that tumor cells expressed Chromogranin A, Synaptophysin, NSE and CD56. Pathological TNM (TNM/AJCC 2010) was pT4N1M1.

After surgery, treatment with an Octreotide LAR was started. Follow-up was programmed every 4 months with clinical, biological, oncological and imaging evaluation. one year after the patient's follow-up is negative for disease recurrence.

Discussion

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors that arise in different anatomic locations and have a shared capacity for production of peptides, neuroamines and other and vasoactives substances which give rise to a variety of clinical syndromes.

In the gastrointestinal tract tumors can originate from enterochromaffin or klutishcky cells whilst those in the distal colon and rectum arise from L cells [5].

There is a gradual move away from the term carcinoid in favor of the term neuroendocrine neoplasm, which is further classified according to site of origin, histological grade and differentiation [6].

Grade refers to the proliferative activity of the tumors, commonly measured by the mitotic rate (number of mitotic figures per 10 high-powered fields) and Ki-67 index.

Differentiation refers to the extent to which neoplastic cells resemble normal endocrine tissue.

The most recent nomenclature proposed by WHO 2010 guidelines distinguishes between well-differentiated tumors (low-grade G1 and intermediate grade G2) and poorly differentiated ones (G3) [7].

NETs typically fall into Grade 1 or 2, being well differentiated neoplasms expressing neuroendocrine markers such as low molecular weight [8] and glicentin/PYY from those derived from L cells [9].

In one large series, only 1% of jejunal and ileocaecal (midgut) tumors were poorly differentiated [10]. The 5-years survival rates for low and intermediate grade tumors were 79% and 74% respectively, whereas high-grade NETs had a 5-year survival rate of only 40% [10].

Until recent years, neuroendocrine tumors lacked a formal TNM staging classification.

In 2007, The European Neuroendocrine Tumor Society (ENETS) proposed a formal TNM staging system for tumors of the lower jejunum and ileum, a system that

was subsequently adopted by American Joint Committee on cancer [11,12].

A validation analysis of 270 NETs (which included a combination of midgut and hindgut tumors) showed this classification is statistically significantly able by univariate analysis to discriminate in a prognostically relevant manner between NET with only local (stage I and II) or loco-regional (stage I, II, III) spread and more extensive tumor disease (stage IV).

In fact, this study reported a 5-years disease-specific survival rate of 100% for patients with stage I and II tumors vs. 97% for stage III and 83% for stage IV tumors [13].

In according to the site, within the gastrointestinal tract, a plurality of NETs arose in the small intestine (42%), followed by rectum (27%), stomach (20%), colon (20%) and appendix (18%) [14].

In the right colon, most tumors arise in the caecum, followed by the ileo-caecal region and ascending colon. The majority of NETs are asymptomatic at the time of diagnosis; due to the high capacitance of the right colon, patients only become symptomatic once they reach a large size (>2 cm), with pain, bleeding, altered bowel habits, weight loss and anorexia.

Carcinoid tumors present a slow growth, rarely evolves for clinically evident mass [15].

With advanced disease they may present with symptoms of bowel obstruction, anemia or a palpable liver. Bowel obstruction is more typical of ileum [16], that in some case described in the literature could cause multiple synchronous stenosis of the same tract [17].

Presentation is usually in the 7th decade with mean age of diagnosis 65. Less than 5% of these patients will have carcinoid syndrome and only then in the presence of liver metastases, such as our case [18].

Napolitano et al. [19] described a case of right colon carcinoid tumour with single hepatic metastasis, underwent right hemicolectomy and hepatic wedge resection, whose diagnosis was postoperative, with histological exam, because it was a non-functioning tumor with an unfavorable prognosis; the patient died after 12 months from surgery despite the therapy with Octreotide and 5-Fluorouracil.

In caecal tumors the rate of localized disease only has been reported as low as 16% [20].

Metastases are usually to lymph nodes, liver, peritoneum. The carcinoid syndrome includes diarrhea, cutaneous vasomotor symptoms and right heart valvular disease. Serotonin was identified as the primary hormonal factor responsible for the carcinoid syndrome [21-23].

Other vasoactive substance elaborated [24] by intestinal NET include biogenic amines (histamine, dopamine), tachykinins and prostaglandins. The carcinoid syndrome is associated in nearly all cases with metastatic NETs because of the serotonin was secreted from liver metastases directly into systemic (rather than portal) circulation.

In an analysis of 91 patients with the carcinoid syndrome, diarrhea and flushing were the most commonly observed phenomena, occurring in 73% and 65% of patients respectively; carcinoid heart disease was detected in 10% of cases [25]. These substances act to stimulate peristalsis [26] and to determine vasodilatation. The flushing typically involves the face, neck and upper torso and may be precipitated by exercise, stress, alcohol [27].

Massive releases of vasoactive substances may occur during surgery leading to a "carcinoid crisis" characterized by severe hypotension [28]. Operative management with SSAs is indicated to avoid intra and post-operative carcinoid crisis [29,30].

The majority of colonic NETs will be diagnosed at routine endoscopy and this is likely to rise with the increase in colonoscopies resulting from screening programs.

Endoscopic investigation remains the gold standard for the detection and characterization of these lesions, CT scans, MRI and somatostatin-receptor scintigraphy (SRS) are the primary imaging modalities used to identify and follow metastatic NETs of the colon. At CT scans, NETs are typically vascular and may enhance with iodinated contrast during early arterial phases of imaging, or with washout during the portal venous imaging phase. MRI scans represent a sensitive method for detection of liver metastases, particularly useful when evaluating potential candidates for hepatic surgery.

SRS images the entire body enabling detection of metastases outside of the abdominopelvic region. It remains the gold standard for diagnosis and localization of most NET's however its utility in colonic NETs has not been validated due to the sparse data available.

On the other hand, SRS is useful to determine somatostatin receptor expression and thereby guide the use of somatostatine analogues as well as radionuclide therapy.

Although not widely available, several positron emission tomography (PET) radiotracers for functional imaging have emerged, including ^{18}F-dihydroxy-phenyl-alanine (^{18}F-DOPA), ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP), and ^{68} Ga-DOTA-octreotide. These novel PET modalities offer higher spatial resolution than conventional SRS and improved sensitivity for detection of small lesions.

Urinary 5HIAA and is typically normal among patients with localized tumors, and is usually elevated in patients with liver metastases. Patients with carcinoid heart disease have levels exceeding 5-10 times upper limits of normal. Chromogranin A may be elevated in metastatic disease, and it may be used in surveillance, in order to assess response to therapy or recurrence after surgery.

Liver metastases occur in 75% to 80% of patients with neuroendocrine tumors (NETs) [1,2], and are considered significant adverse prognostic indicators. Management of NETs liver metastases is challenging and requires aggressive therapy. Currently, there are many therapeutic options for metastatic NETs.

Although complete surgical resection remains the optimal therapy, a variety of other minimally invasive surgical and medical optionsare available; this includes thermal ablative techniques (e.g., radiofrequency ablation [31]

, microwave ablation, cryotherapy), embolization using transcatheter embolization, [32] or radioembolization [33], andmedical therapy (e.g., chemotherapy [34], biotherapy with somatostatin analogues [35] and interferon [36].
Liver transplantation might be considered in carefully selected patients [37, 38] who fail to respond to other treatment options [39,40].
Currently there is no evidence-based data directly comparing surgical versus alternative liver-directed treatment options. However, numerous studies have confirmed complete hepatic resection for liver metastases has significantly improved long-term [42], surgical resection can be considered with curative intent when a debulking threshold of ≥ 90% is achieved, in patients without extrahepatic disease. This cutoff has been adopted by many centers, even if the recent use of expanded criteria for debulking (debulking threshold of > 70%) resulted in 90% 5-year disease-specific survival in selected patients [43].
Aggressive surgical resection increases the 5-year survival of NETs with solitary liver metastasis to 100%, where disseminated metastatic NETs suffer a 51% 5-year survival rate after surgical resection [44].
Surgical treatment of NETs liver metastases plays a central role in the multimodal management of these tumors. Before planning surgical approach, tumor characteristic symptoms, distribution of the metastases, and the histological features should be always considered along with patients' co morbidities and expectations. An aggressive surgical approach can lead to long-term survival with a good quality of life.
In fact, when it is feasible, aggressive surgical management of both the primary tumor and the liver metastases improve overall survival rates extensively [45] but multiple factors including primary tumor site, histological grade and metastatic sites other than liver play a major role in the overall survival [46].
The surgical approach used depends firstly on the distribution of metastases, because non-pathological liver has an excellent regeneration capacity after resection, and a remnant functional amount of 20% to 25% normal liver tissue may be adequate.
Furthermore, saving a liver remnant with sufficient function for life maintenance, low peri operative morbidity and mortality, and acceptable long-term survival is one of the major challenges facing surgeons. In unilobar metastasis, resection of the primary tumor and liver metastasis can be completed synchronously; this was our surgical strategy.

Conclusion

Resection of the primary tumor, liver metastases, and local mesenteric lymph node metastases is thought to strictly promote long-term survival and quality of life.
Optimal patient care should be directed by a multidisciplinary team to assure that all treatment options are explored for decision-making while treating this aggressive disease.

Riassunto

I tumori neuroendocrini (NETs) rappresentano un gruppo eterogeneo di neoplasie. I NET del colon costituiscono meno dell'1% dei casi di neoplasie coliche. Le metastasi epatiche sincrone, presenti nel 75-80% dei casi, sono considerate un indice prognostico sfavorevole. Le opzioni terapeutiche disponibili includono la resezione chirurgica, la chemioterapia, e la bioterapia. La chirurgia rappresenta il gold standard della terapia curativa ed è fortemente condizionata dalla localizzazione, il grading e la stadiazione della neoplasia.
Il caso clinico preso in oggetto è un uomo di 64 anni che presentava la sindrome da carcinoide. La colonscopia rilevò una massa vegetante della valvola ileocecale con biopsia negativa. La TC stadiativa mostrò una voluminosa lesione del fegato di destra con un diametro massimo di 10 cm. I markers tumorali erano negativi; mentre risultarono positivi i dosaggi urinari dell'acido 5-idrossiindolacetico e i valori plasmatici della Cromogranina A. Il trattamento chirurgico prevedeva l'asportazione del tumore primitivo e della sincrona metastasi epatica in un unico tempo chirurgico.
Il management delle metastasi epatiche dei NETs resta controverso e richiede una strategia terapeutica multidisciplinare aggressiva. Al momento, molte sono le opzioni terapeutiche proposte, sebbene la completa resezione chirurgica della neoplasia resta la terapia di scelta poiché associata ad un aumento della sopravvivenza a 5 anni del 100% nei pazienti con singola metastasi epatica.
La resezione del tumore primitivo con associata linfadenectomia e delle metastasi epatiche, in un unico tempo operatorio come presentato nel nostro caso, è fortemente indicato poiché migliora la qualità di vita e la sopravvivenza in questi pazienti.

References

1. Cheek RC, Wilson Hz: *Carcinoid tumors*. Curr Probl Surg, 1970; 4-31[PMID:4921098].

2. Ballantyne GH, Savoca PE, Flannery JT, Ahlman MH, Modlin IM: *Incidence and mortality of carcinoids of the colon. Data from the Connecticut Tumor Registry.* Cancer, 1992; 69(10):2400-5.

3. Chambers AJ, Pasieka JL, Dixon E, Rorstad O: *The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors.* Surgery, 2008; 144(4):645-51. doi:10.1016/j.surg.2008.06.008.

4. Saeed A, Buell JF, Kandil E: *Surgical treatment of liver metastases in patients with neuroendocrine tumors*. Ann Transl Med, 2013; 1:6. doi: 10.3978/j.issn.2227-684X.2015.04.10.

5. Klöppel G, Perren A, Heitz PU: *The gastroenteropancreatic neuroendocrine cell system and its tumors: The WHO classification*. Ann N Y Acad Sci, 2004; 1014:13-27. PMID: 15153416.

6. Niederle MB, Hackl M, Kaserer K, Niederle B: *Gastroenteropancreatic neuroendocrine tumours: The current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters*. Endocr Relat Cancer, 2010; 17(4):909-18.

7. 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. PMID: 20664470 DOI: 10.1097/MPA.0b013e3181ec124e

8. Caplin M, Sundin A, Nillson O, Baum RP, Klose KJ, Kelestimur F, Plöckinger U, Papotti M, Salazar R, Pascher A: Barcelona Consensus Conference participants. *ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: Colorectal neuroendocrine neoplasms*. Neuroendocrinology, 2012; 95(2):88-97.

9. Fiocca R, Rindi G, Capella C, Grimelius L, Polak JM, Schwartz TW, Yanaihara N, Solcia E: *Glucagon, glicentin, proglucagon, PYY, PP and proPP-icosapeptide immunoreactivities of rectal carcinoid tumors and related non-tumor cells.* Regul Pep, 1987; 17(1):9-29. PMID: 2882565.

10. Strosberg JR, Weber JM, Feldman M, Coppola D, Meredith K, Kvols LK: *Prognostic validity of the american joint committee on cancer staging classification for midgut neuroendocrine tumors.* J Clin Oncol, 2013; 31(4):420-25.

11. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B: *TNM staging of midgut and hindgut (neuro) endocrine tumors: A consensus proposal including a grading system*. Virchows Arch, 2007; 451(4):757-62. PMID: 17674042DOI: 10.1007/s00428-007-04521.

12. *AJCC cancer staging manual.* 7th ed. Chicago: Springer; 2010.

13. Jann H, Roll S, Couvelard A, Hentic O, Pavel M, Müller-Nordhorn J, Koch M, Röcken C, Rindi G, Ruszniewski P, Wiedenmann B, Pape UF: *Neuroendocrine tumors of midgut and hindgut origin: Tumor-node-metastasis classification determines clinical outcome*. Cancer, 2011; 117(15):3332-41. PMID: 21246527 DOI: 10.1002/cncr.25855.

14. Modlin IM, Lye KD, Kidd M: *A 5-decade analysis of 13,715 carcinoid tumors.* Cancer, 2003; 97(4):934-59. PMID: 12569593 DOI: 10.1002/cncr.11105

15. Nacchiero ML, Marzaioli R, Campanile L, Incantalupo F, Loverre G, Bonomo GM: *Right abdominal colonic masses. Recent diagnostic and therapeutic advances: personal experience*. Ann Ital Chir, 2002; 73(1):47-57.

16. Marzocca GL, Caputo E, Varrone F, Lo Gatto M, Rocchi B, Polito S, Sorbellini F: *Intestinal occlusion by ileal carcinoid.* Ann Ital Chi, 2008; 79(6):457-61.

17. Zuccon WL, D'Angelo C, Giorgetta C, Tagliabue F, Balduzzi V, Bonandrini L: *A rare case of intestinal carcinoid tumour. Clinical considerations and therapeutic approach.* Ann Ital Chir, 2007; 78(4):311-14.

18. Ramage JK, Goretzki PE, Manfredi R, Komminoth P, Ferone D, Hyrdel R, Kaltsas G, Kelestimur F, Kvols L, Scoazec JY, Garcia MI, Caplin ME: Frascati Consensus Conference participants. *Consensus guidelines for the management of patients with digestive neuroendocrine tumord: Well-differentiated colon and rectum tumot/carcinoma.* Neuroendocrine, 2008; 87(1):31-9.

19. Napolitano L, Francomano F, Gargano E, Francione T, Angelucci D, Napolitano AM: *Our experience regarding biologically inactive gastroenteropancreatic neuroendocrine tumors*. Ann Ital Chir, 2001; 72(1):61-4.

20. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, Nutting C, Bushnell DL, Caplin ME, Yao JC; North American Neuroendocrine Tumor Society (NANETS*). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: Well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum*. Pancreas., 2010;39(6):753-66 PMID: 20664473 DOI: 10.1097/MPA.0b013e3181ebb2a5

21. Lembeck F: *Detection of 5-hydroxytryptamine in carcinoid metastases*. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol, 1954; 221(1):50-66.

22. Neri V, Ambrosi A, Fersini A, Tartaglia N, Lapolla F, Forlano I: *Severe acute pancreatitis: Clinical forms of different gravity*. Ann Ital Chir, 2013; 84(1):47-53.

23. Erspamer V, Asero B: *Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine.*Nature. 1952 z, 10; 169(4306):800-01. PMID: 14941051.

24. Vinik AIL, Silva MP, Woltering EA, Go VL, Warner R, Caplin M: *Biochemical testing for neuroendocrine tumors.* Pancreas, 2009; 38(8):876-89. PMID: 19855234 DOI: 10.1097/MPA. 0b013e3181 bc0e77.

25. Davis Z, Moertel CG, McIlrath DC: *The malignant carcinoid syndrome.* Surg Gynecol Obstet, 1973; 137(4):637-44. PMID: 4730072.

26. von der Ohe MR, Camilleri M, Kvols LK, Thomforde GM: *Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea.* N Engl J Med. 1993; 329(15):1073-8. PMID: 8371728 DOI: 10.1056/NEJM 199310073291503.

27. KvolsLK: *Metastatic carcinoid tumors and the malignant carcinoid syndrome.* Ann NY Acad Sci, 1994; 733:464-70. PMID: 7978896.

28. Kahil ME, Brown H, Fred HL: *The carcinoid crisi*s. Arch Intern Med, 1964; 114:26-8. PMID: 14156067.

29. Kvols LK, Martin JK, Marsh HM, Moertel CG: *Rapid reversal of carcinoid crisis with a somatostatin analogue.* N Engl J Med, 1985; 313(19):1229-230. PMID: 2865675 DOI: 10.1056/NEJM 198511073131915.

30. Oberg K, Kvols L, Caplin M, et al.: *Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic syste*m. Ann Oncol, 2004; 15:966-73. PMID: 15151956.

31. Henn AR, Levine EA, McNulty W, Zagoria RJ: *Percutaneous radiofrequency ablation of hepatic metastases for symptomatic relief of neuroendocrine syndromes.* AJR Am J Roentgenol, 2003; 181(4):1005-10. PMID: 14500219 DOI: 10.2214/ajr. 181.4. 1811005.

32. Gupta S, Yao JC, Ahrar K, Wallace MJ, Morello FA, Madoff DC, Murthy R, Hicks ME, Ajani JA: *Hepatic artery embolization*

and chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J, 2003; 9(4):261-7. PMID:12967136.

33. Rhee TKL, Lewandowski RJ, Liu DM, Mulcahy MF, Takahashi G, Hansen PD, Benson AB 3rd, Kennedy AS, Omary RA, Salem R.90Y: *Radioembolization for metastatic neuroendocrine liver tumors: preliminary results from a multi-institutional experience.* Ann Surg, 2008; 247(6):1029-35PMID: 18520231 DOI: 10.1097/SLA.0b013 e3181728a45.

34. Chan JA, Stuart K, Earle CC, Clark JW, Bhargava P, Miksad R, Blaszkowsky L, Enzinger PC, Meyerhardt JA, Zheng H, Fuchs CS, Kulke MH: *Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors.* J Clin Oncol; 2012; 30(24):2963-896. PMID: 22778320 DOI: 10.1200/JCO. 2011. 40.3147.

35. Oberg K, Kvols L, Caplin M, DelleFave G, de Herder W, Rindi G, Ruszniewski P, Woltering EA, Wiedenmann B: *Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system.* Ann Oncol, 2004; 15(6):966-73. PMID:15151956.

36. Kölby LL, Persson G, Franzén S, Ahrén B: *Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours*. Br J Surg, 2003; 90(6):687-93. PMID: 12808615 DOI: 10.1002/bjs.4149.

37. Mazzaferro V, Pulvirenti A, Coppa J: *Neuroendocrine tumors metastatic to the liver: How to select patients for liver transplantation?* J Hepatol, 2007; 47(4):460-66. PMID: 17697723 DOI: 10.1016/j. jhep.2007.07.004

38. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R: Barcelona Consensus Conference participants. ENET: *Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary*. Neuroendocrinology, 2012; 95(2):157-76. PMID: 22262022 DOI: 10.1159/000335597

39. Chan G, Kocha W, Reid R, Taqi A, Wall W, Quan D: *Liver transplantation for symptomatic liver metastases of neuroendocrine tumours*. Curr Oncol, 2012; 19(4):217-21. PMID: 22876148 PMCID: DOI: 10.3747/co.19.950

40. Le Treut YP1, Grégoire E, Belghiti J, Boillot O, Soubrane O, Mantion G, Cherqui D, Castaing D, Ruszniewski P, Wolf P, Paye F, Salame E, Muscari F, Pruvot FR, Baulieux J: *Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report*. Am J Transplant, 2008 J; 8(6):1205-213. PMID: 18444921 DOI: 10.1111/j.1600-6143. 2008.02233.x

41. Frilling A, Sotiropoulos GC, Li J, et al.: *Multimodal management of neuroendocrine liver metastases.* HPB (Oxford), 2010; 12:361-79. PMID: 20662787 PMCID: DOI: 10.1111/j.1477-2574.2010. 00175.x

42. Sarmiento JM, Heywood G, Rubin J, et al.: 10*cal treatment of neuroendocrine metastases to the liver: aplea for resection to increase survival*. Surgi. J Am Coll, Surg, 2003; 197: 29-37. PMID: 12831921 DOI: 1016/S1072-7515(03)00230-8

43. Graff-Baker AN, Sauer DA, Pommier SJ, Pommier RF: *surExpanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients*. Surgery, 2014;156(6):1369-376; discussion 1376-377. PMID: 25456912 DOI: 10.1016/j..2014.08.009

44. Frilling A, Li J, Malamutmann E, et al.: *Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease*. Br J Surg, 2009; 96: 175-84. PMID: 19160361

45. Basuroy R, Srirajaskanthan R, Ramage JK: A *multimodal approach to the management of neuroendocrine tumour liver metastases*. Int J Hepatol, 2012; 2012:819193. PMID: 22518323

46. Saxena A, Chua TC, Sarkar A, et al.: *Progression and survival results after radical hepatic metastasectomy of indolent advanced neuroendocrine neoplasms (NENs)supports an aggressive surgical approach.* Surgery, 2011; 149:209-20.