

Moderately differentiated neuroendocrine tumor (NET G2) of the pancreatic tail - stage IV clinical case

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Abstract. The aim of this study was to determine the epidemiologic and anatomohistopathologic features of genital tract disorders in she-camels slaughtered at abattoirs in southeast Algeria. We estimated the prevalence of the disorders among a total of 740 female camels selected from different breeds and ages. Abnormalities were detected in 213 animals (28.8%) at the level of the uterus, oviducts, or vagina. Infection was the most common uterine disorder, followed by endometritis (3.2%), metritis (2.8%), and pyometra (1.1%). Other lesions with low incidence included endometrial cysts, polyps, abscesses, and adhesions. Oviduct abnormalities included pyosalpinx (0.7%), hydrosalpinx (0.1%) and catarrhal salpingitis (0.5%). Cervicitis constituted the most frequent cervical lesion (2%), followed by total obstruction of the cervix (0.3%). Vaginitis accounted for 2/3 of the vaginal pathologies detected in the present study, and vaginal adhesions for 1/3. Microscopic examination revealed the histologic modifications generally associated with the various abnormalities.

Key Words: neuroendocrine tumor, secondary hepatic malignancies, carcinoid syndrome.

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Introduction

Pancreatic neuroendocrine tumors are rare tumors that develop from cells that produce hormones. Some of these may secrete peptide hormones such as insulin, glucagon, intestinal vasoactive peptide, and cause characteristic clinical symptoms. Most neuroendocrine tumors are sporadic, but they may associate with hereditary endocrinopathies in MEN1, Von Hippel Lindau, type I neurofibromatosis or tuberous sclerosis. The purpose is to present the case of a 66-year-old female patient who presented herself to our unit accusing flushing, sweating and right and left hypochondrium pain.

Clinical case

The 66-year-old female patient with stage II hypertension, additional high risk of approximately 15 years, presented herself to our unit to investigate the cause of several liver tumors detected during an ultrasound scan performed in a local health centre. Subjectively, the patient presented periumbilical, right and left hypochondrium pain, felt as intermittent pain (stinging), symptoms that respond to minor analgesics. The patient also accused associated flushing and sweating episodes for about 1 year. Objectively, the patient had a good general condition at admission, pain on deep palpation of the right and left hypochondrium and periumbilical pain. Based on patient history and clinical examination, the diagnosis was that of abdominal pain syndrome and possible carcinoid syndrome.

Biohumoral examination showed elevated GGT levels (possibly in the presence of cholestasis) and elevated AFP levels (141.1 ng/ml). The parameters regarding renal function, serum electrolytes, transaminases, serum proteins were within the normal reference range. In order to exclude any chronic hepatopathy which could have overlapped with hepatocarcinoma, hepatitis viral markers (Ag Hbs, Ac anti HVC) and autoimmune markers (anti-ANA, anti SMA, PANCA, AMA, LKM1) were assessed and they were non-reactive.

Abdominal ultrasound performed in our unit detected (Logiq E9 Ultrasound System) liver without pathological elements of possible chronic liver disease. Both the left and the right hepatic lobes showed numerous hyperechoic focal images (some of which have a hypoechoic center indicating possible central necrosis), with a maximum diameter of up to 47 mm indicating secondary liver malignancies. The caudal part of the pancreas showed a 40/35/30 mm hypoechoic mass with possible splenic vein infiltration (Figure 1).

Ultrasound examination using contrast agent evaluated the vascular behavior of the pancreatic tumor and hepatic tumor formations. The result was contrast enhancement during the arterial phase and contrast washout during the venous phase.

CT scan using contrast media (Somaton Prospective 64- slice Multi Detector CT scanner) in the diagnosis and staging of pancreatic cancer showed the presence of numerous focal lesions in both hepatic lobes, except for segment I, ranging in size from several mm to 64 mm, hypervascular lesions in the arterial phase (Figure 2), most of them with central necrosis, that are washing

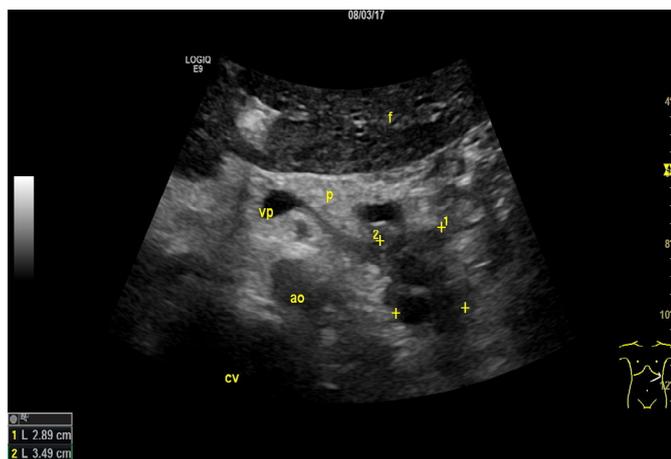


Figure 1. Abdominal ultrasound - transverse section. The caudal part of the pancreas shows a predominantly hypoechoic lesion (40/35/30 mm) with possible infiltration of the splenic vein. (F = liver, VP = portal vein, Ao = aorta)

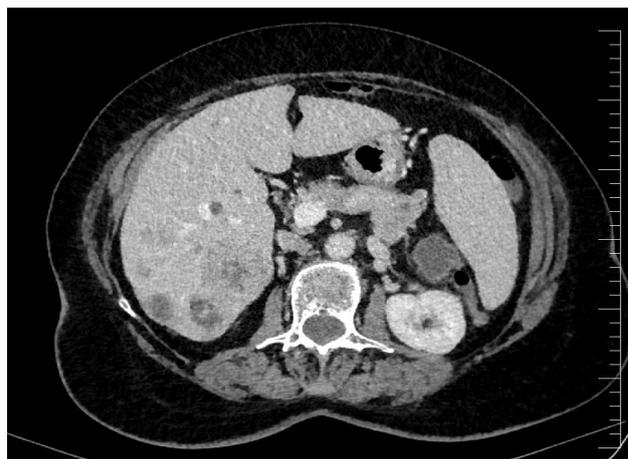


Figure 3. CT scan of the abdomen and pelvis with intravenous contrast and entero-CT protocol, axial plane - venous phase. Focal liver formations washing the contrast medium. Isodense focal caudal pancreatic formation.

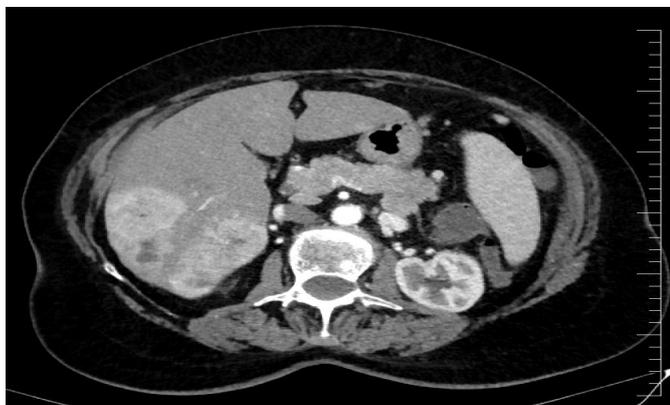


Figure 2. CT scan of the abdomen and pelvis with intravenous contrast and entero-CT protocol, axial plane - arterial phase. Liver with numerous focal lesions, hypervascular in the arterial phase, with areas of central necrosis. The tail of the pancreas shows a tumor formation with microcalcification during arterial phase hypoenhancement (≈ 26 mm in diameter), which causes the widening of the pancreatic tail. There is no intra- or retroperitoneal adenopathy.

the contrast medium in the venous phase (Figure 3). The tail of the pancreas indicated a native isodense tumor with peripheral calcification, together with the presence of hypocapture, with a diameter of about 26 mm, without the confirmation of the primary or secondary character of the formation. There was also evidence of perigastric, subcardial and intraparietal gastric varices, signs of segmental portal hypertension most likely due to tumor invasion of the splenic vein (Figure 4). Subsequently, CEA and CA19-9 tumor markers were assessed and results were within the normal reference range.

Considering the presence of segmental portal hypertension observed during the CT scan, endoscopic control was performed (Olympus Evis Exera III CLV 190) and showed two subcardial venous tracts indicating subcardial gastric varices.

In order to establish whether there is a relationship between hepatic tumor formations and caudal pancreatic tumor formation, synchronous or interdependent tumors, it was necessary to

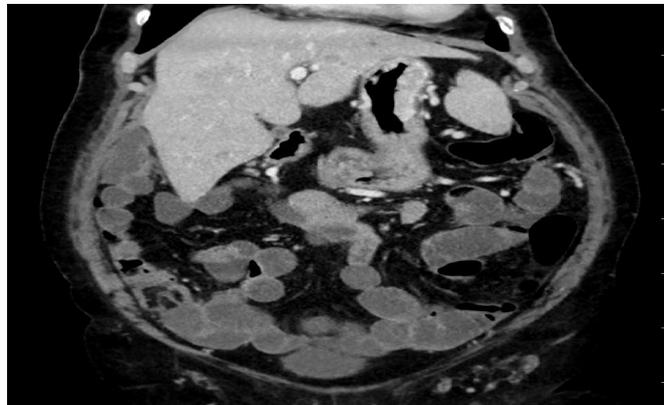


Figure 4. CT scan of the abdomen and pelvis with intravenous contrast and entero-CT protocol, coronal plane - venous phase. Perigastric varices and subcardial gastric varices

specify the histopathological substrate. Thus, both percutaneous hepatic biopsy puncture from a hepatic focal lesion in segment V and biopsy from a caudal pancreatic tumor formation were performed. The correlation with the microscopic aspect (Figure 5) and the immunohistochemical aspect (Figure 6,7,8) of the hepatic tumor formation support the presence of hepatic metastasis of moderately differentiated neuroendocrine tumor (NET G2), diffuse staining with synaptophysin and heavily positive on tumor cells.

The primary nature of the pancreatic tumor formation was demonstrated using ecoendoscopy, which describes the hypoechoic pancreatic tumor formation with calcifications invading the splenic vein without showing peripancreatic adenopathy (Figure 9). Endoscopic ultrasound with fine-needle aspiration puncture (Olympus GF Type UCT 180 echoendoscope) was performed and the microscopic aspect correlated with the immunohistochemical aspect showed a pancreatic neuroendocrine tumor (NET G2) (Figure 10,11,12).

Considering that $>80\%$ of patients with MEN I syndrome develop pancreatic neuroendocrine tumors, thyroid ultrasound was performed to exclude the presence of tumor formations at this level. The following serum and urinary markers specific to neuroendocrine tumors were measured: serum serotonin (143.8 $\mu\text{g/l}$),

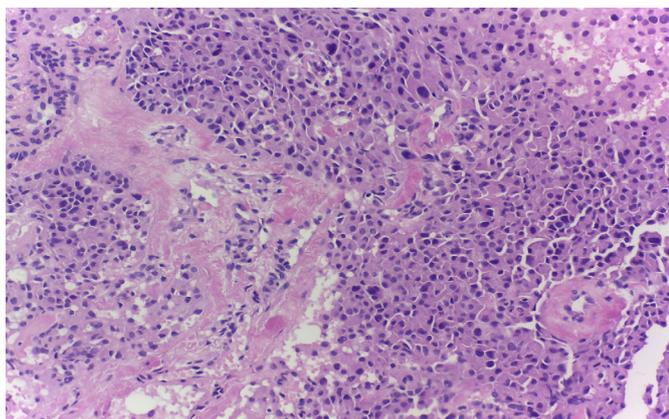


Figure 5. Anatomopathological examination of liver biopsy - tumor mass in liver segment V. Hematoxylin-eosin staining with a 20-fold magnification showed the proliferation of medium-sized, monomorphic tumor cells with poorly visible cell boundaries, round and slightly enlarged nuclei, fine chromatin, poorly visible nucleoli, amphophilic cytoplasm, disposed as solid areas. A fine fibrovascular stroma is interposed between tumor cells.

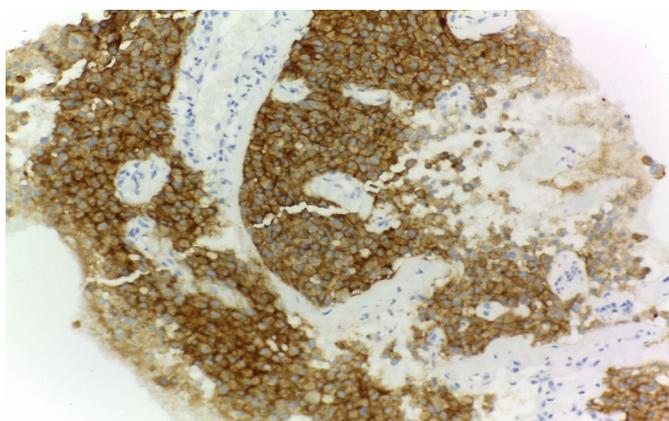


Figure 6. Anatomopathological examination of liver biopsy - tumor mass in liver segment V. Immunohistochemical staining performed using anti-synaptophysin antibody: synaptophysin - diffuse and intensely positive on tumor cells (neuroendocrine marker).

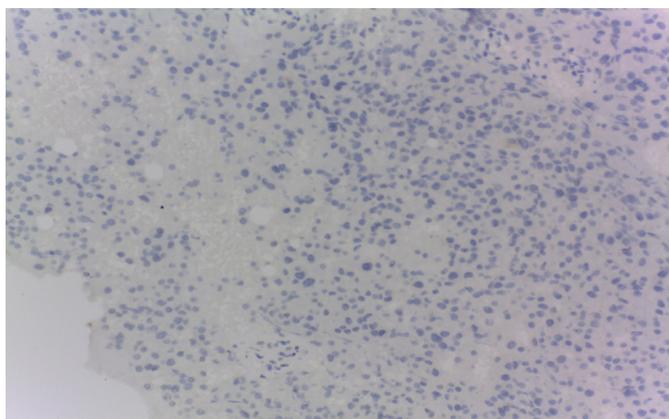


Figure 7. Anatomopathological examination of liver biopsy - tumor mass in liver segment V. Immunohistochemical staining performed using anti-HepPar1 antibody (hepatocellular differentiation marker) was negative, excluding a primary hepatic tumor (HCC).

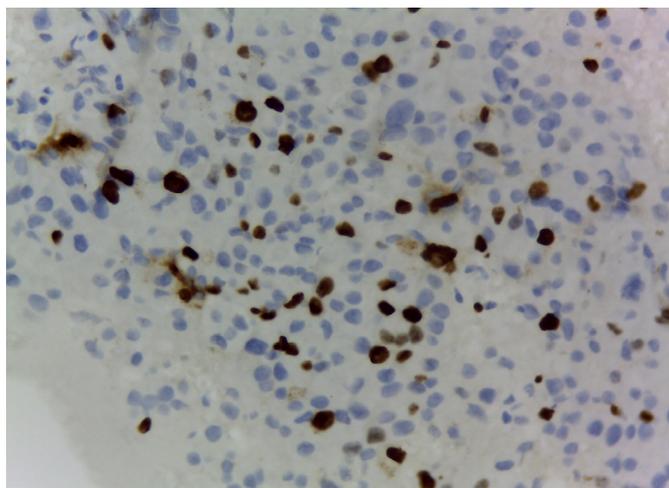


Figure 8. Anatomopathological examination of liver biopsy - tumor mass in liver segment V. Ki-67 (proliferation index) was evaluated at an index value of 10%.



Figure 9. Ecoendoscopic image showing a tumor formation of the pancreatic tail, predominantly hypoechoic, about 25 mm in size, with the presence of calcifications.

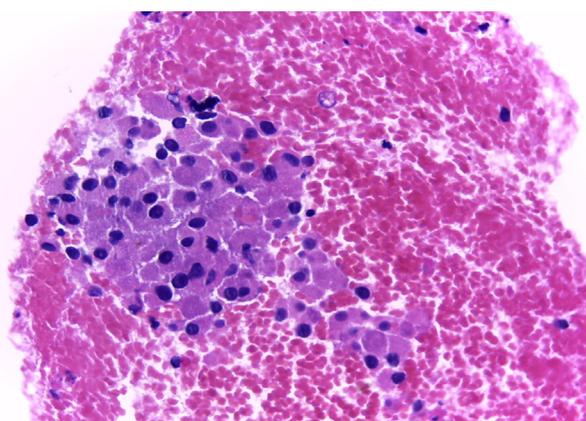


Figure 10. Hematoxylin-eosin staining: EUS-guided fine needle aspiration (EUS-FNA) consisting of fibrin-hematic masses and rare inflammatory elements with small disparate fragments originating from tumor proliferation, similar to those described by liver biopsy. The images show the monomorphic character of the cells, the amphophilic cytoplasm, round-to-oval nuclei, fine chromatin, with no visible nucleoli.

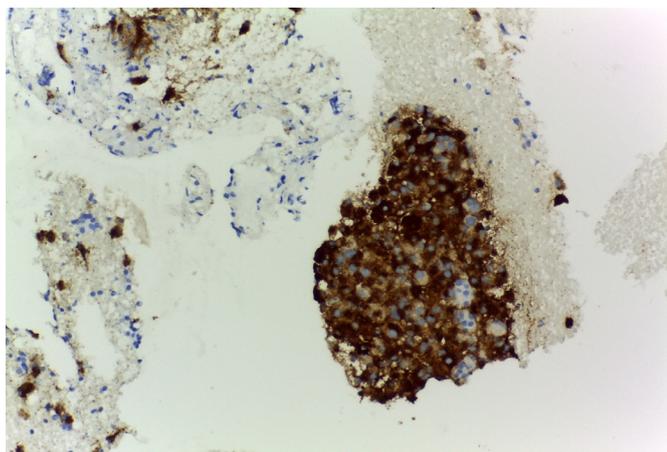


Figure 11. Fine needle aspiration specimen - tumor mass in the tail of the pancreas. Positive tumor cells during immunohistochemical staining performed using anti-Chromogranin A antibody - neuroendocrine marker.

chromogranin A (3030 ng/ml) and 5-hydroxyindoleacetic acid /24 h (12.5 mg/24 h).

Following oncology consultation, in terms of therapeutic strategy, somatostatin analogues were chosen to control the symptoms associated with carcinoid syndrome and to control tumor growth through the antiproliferative effect. Surgery was not an option as it was not possible to reduce tumor volume by >90%.

Diagnosis

Following examination, biochemistry tests and medical imaging, the diagnosis formulated was that of moderately differentiated neuroendocrine tumor (NET G2) of the pancreatic tail - stage IV, with multiple secondary hepatic malignancies and tumor invasion of the splenic vein causing secondary segmental portal hypertension and subcardial gastric varices.

Discussions

Pancreatic neuroendocrine tumors are rare tumors that develop from pancreatic endocrine cells. Their incidence is of $\leq 1/100,000$ (Hallet et al 2015). Although they may occur at any age, the maximum incidence is in the 6th decade of life, the patient in our study being diagnosed in the 7th decade of life. The vast majority of pancreatic neuroendocrine tumors are sporadic, as it was the case in our study, but they can associate with hereditary endocrinopathies (Metz et al 2008). Clinical symptoms vary depending on the type of secreted peptide hormones. Between 50 and 75% of pancreatic neuroendocrine tumors are nonfunctional - they are not associated with hormonal syndromes (Strosberg 2017, Rindi et al 2010, Halfdanarson et al 2008). In the present case there were symptoms of carcinoid syndrome. According to the World Health Organization (WHO), neuroendocrine tumors that originate in the digestive tract are divided into two major categories: well differentiated (G1-low grade and G2-intermediate grade) and poorly differentiated. In our case, the microscopic aspect correlated with the immunohistochemical aspect indicates a NET G2 pancreatic neuroendocrine tumor (Rindi et al 2010).

The diagnosis based on medical imaging using radiolabeled somatostatin analogues is useful in both identifying occult primary

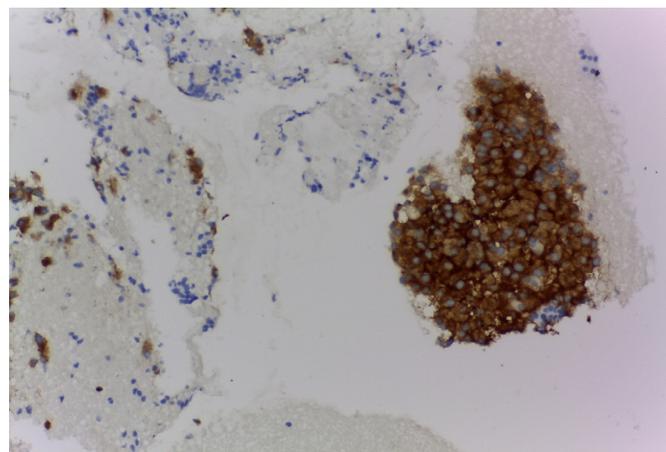


Figure 12. Fine needle aspiration specimen - tumor mass in the tail of the pancreas. Positive tumor cells during immunohistochemical staining performed using anti-Synaptophysin antibody - neuroendocrine marker.

tumors and evaluating the response to somatostatin analogue therapy (Sadowski et al 2016). Typically, during computer tomographic examination using contrast media, pancreatic neuroendocrine tumors are hypervascular, revealing intense contrast enhancement in the arterial phase and contrast washout in the venous phase (Strosberg 2017), with clear perfusion angiography nature in the case presented, and possible isodense liver metastases after contrast injection. During MRI examination, pancreatic neuroendocrine tumors typically show T1 hyposignal and T2 hypersignal (Thoeni et al 2000). Ecoendoscopy is an extremely valuable examination because it can detect lesions of up to 2-3 mm in diameter (Khashab et al 2011). It can even identify pancreatic neuroendocrine tumors like gastrinoma located in the duodenal wall and metastasis in the peripancreatic ganglia (Strosberg 2017). Another benefit is the possibility of performing EUS-guided fine needle aspiration, which was also performed in our case, resulting in a histological diagnosis of pancreatic neuroendocrine tumor (Chatzipantelis et al 2008). Diagnostic imaging using radiolabelled somatostatin analogues provides both imaging and functional information related to the expression of somatostatin receptors in the tumor. When available, because of its greater sensitivity, it is preferable to use ^{68}Ga -PSMA PET/CT instead of ^{111}In pentetreotide (OctreoScan) (Strosberg 2017). Currently, these types of examination are not available in our unit.

Curative surgery and/or locoregional therapy should be considered at the time of diagnosis and also later as an alternative to systemic therapy. In patients with functional neuroendocrine tumors, all therapies for secondary liver tumor formations should be preceded by treatment with somatostatin analogues (or other symptom control measures) (Pavel et al 2016). Cytoreductive therapy is indicated in selected cases of functional pancreatic neuroendocrine tumors with secondary liver malignancies in order to relieve symptoms even if the tumor volume can not be reduced to >90%. Liver transplantation is an option only in very well-selected cases in young patients with functional syndromes with early resistance to drug therapy (Watzka et al 2015, Mayo et al 2013).

Somatostatin analogues, octreotide and lanreotide, are used in the control of functional neuroendocrine tumors. Increasing the

dose of somatostatin analogues may be considered in the case of refractory carcinoid syndrome (Pavel et al 2016, Eriksson et al 2008). In the present case, following oncology consultation, somatostatin analogues were chosen for the antiproliferative and symptom control effect.

Everolimus and sunitinib are antiproliferative agents in progressive neuroendocrine tumors. They can be used as first-line therapy. They are usually used when there is no therapeutic response to somatostatin analogues or systemic chemotherapy (Raymond et al 2011).

The 5-year survival rate for patients with endocrine pancreatic tumors is estimated to be around 25% for metastatic disease.

Conclusions

We reported a rare type of malignant tumor of the pancreas, the neuroendocrine tumor, with multiple secondary hepatic malignancies, with clinical manifestation of the carcinoid syndrome.

References

- Chatzipantelis P, Salla C, Konstantinou P, et al. Endoscopic ultrasound-guided fine-needle aspiration cytology of pancreatic neuroendocrine tumors: a study of 48 cases. *Cancer* 2008;114:255.
- Eriksson B, Kloppel G, Krenning E Ahlman H, Plockinger U, Wiedenmann B, et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors-well differentiated jejunal-ileal tumor/carcinoma. *Neuroendocrinology* 2008;87:8-19.
- Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognostic and recent trend toward improved survival. *Ann Oncol* 2008;19:1727.
- Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015;121:589.
- Khashab MA, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, et al. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. *Gastrointest Endosc* 2011; 73:691.
- Mayo SC, Herman JM, Cosgrove D, Bhagat N, Kamel I, Geschwind JF, Pawlik TM. Emerging approaches in management of patients with neuroendocrine liver metastasis: role of liver-directed and systemic therapies. *J AM Coll Surg* 2013; 216(1):123-34.
- Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 2008;135:1469.
- Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R et al. Consensus Guidelines update for the management of distant metastatic diseases of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown site. *Neuroendocrinology* 2016;103(2):172-85.
- Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-13.
- Rindi G, Arnold R, Bosman FT, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumors of the Digestive System, 4th ed, Bosman F, Carneiro F, Hruban RH, Thiese ND, IARC Press, Lyon, France 2010. p13.
- Sadowski SM, Neychev V, Millo C, Shih J, Nilubol N, Herscovitch P, et al. Prospective Study of 68-Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Enteropancreatic Neuroendocrine Tumors and Unknown Primary site. *J Clin Oncol* 2016; 34:588.
- Strosberg JR. Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine tumors (islet-cell tumors). Nathan D, Whitcomb D, et al (ed). February 2017. www.upToDate.com, accessed in 03.06.2017.
- Thoeni RF, Muller-Lisse UG, Chan R, Do NK, Shyn PB. Detection of small, functional islet cell tumors in the pancreas: selection of RMN imaging sequences for optimal sensitivity. *Radiology* 2000;214:483.
- Watzka FM, Fottner C, Miederer M, Schad A, Weber MM, Otto G, et al. Surgical therapy of neuroendocrine neoplasm with hepatic metastasis: patient selection and prognosis. *Langenbecks Arch Surg* 2015;400(3):349-58.

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