CHALLENGES IN METASTATIC GASTROENTERO-PANCREATIC NEUROENDOCRINE NEOPLASMS (GEP-NENs) IN WELL-DIFFERENTIATED G1 PRIMITIVE TUMORS

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Learning objectives

Metastatic gastroenteropancreatic(GEP)-neuroendocrine neoplasms(-NENs) classified as G1 define heterogeneous clinical scenarios with a wide possibility of treatments, which are debated in the multi-disciplinary meetings dedicated to NEN at our hospital. Our work focuses on the importance of laboratory tests, anamnestic and histopathological data and the relevant imaging findings found.

Background

NENs derive from cells of the diffuse neuroendocrine system, specialized in the production of hormones and neuropeptides [1] 5% of NENs arise in hereditary syndromes like MEN1. 25% of NENs produce hormone with biological effect, determining specific syndromes [2]. In 60% of cases these tumors originate from the gastroenteropancreatic tract (GEP-NENs) [1]. Nowadays the incidence of NENs is increasing and their prognosis are getting better. The survival depends on primary tumor site, proliferation rate, histological differentiation and stage. The Ki-67 is a nuclear antigen, related to cellular proliferation and prognosis, that differentiates these tumors in 3 groups labeled as G1, G2 and G3. The WHO classification of GEP-NEN differentiates G1-G2 well-differentiated tumor (NET) from G3 poorly differentiated neuroendocrine neoplasm according to their Ki-67. Mostly of low-grade tumors NENs express somatostatin receptors (SSTR) [2]. Around 60% of diagnosed GEP-NETs onset are metastatic and the hepatic involvement occurs in most of patients. The hepatic tumor burden is a key prognostic factor since liver failure due to tumor metastases is fatal up to 80% of cases [3, 4, 5]. Biochemical analysis and multiple imaging techniques (Computed Tomography, Magnetic Resonance Imaging and Ultrasounds) allow to identify the lesions, usually detected with Somatostatin receptor imaging. G1 tumors tend to have high and homogeneous vascularization. Although metastases are more frequent in undifferentiated tumors, it is not rare to find G1 metastatic NENs. According to ENETS guidelines the patients' assessment should include:

- Primary tumor site
- Tumor stage
- Functional or not functional neoplasia, therefore, laboratory tests: Urinary 5-hydroxyindoleacetic acid (5-HIAA) in 24-hours in any case and others depending upon clinical symptoms
- Tumor markers, especially Chromogranin A (CgA) in well-differentiated NETs
- Histopathological report including Ki-67 and general neuroendocrine markers, i.e. Chromogranin A, Synaptophysin and Neuron-specific enolase (NSE) and specific markers (insulin, glucagon, etc.) if clinically indicated

Imaging is based on:

- Somatostatin receptor imaging: ^{68}Gallium-DOTA-TOC/-NOC/-TATE positron emission tomography (PET) or somatostatin receptor scintigraphy (SRS or Octreoscan)
- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI) [2]

CT shows details important for a surgical evaluation, most of all the vascular invasion and lymph node involvement. Tumoural mesenteric deposits and lymph node

metastases may be surrounded by massive fibrotic reaction. The presence of deposits is associated with a worse prognosis. ^{68}Ga-DOTATOC-PET preoperatively allows a better staging for occult metastases and extra-abdominal disease, not less a prognostic role [2]. MRI either in T2 and DWI sequences is highly reliable to detect hepatic disease [6]. Localization of neuroendocrine liver metastases, especially the number and the involvement of both lobes, matter to determine the therapeutic strategy. [18F]-fluorodeoxyglucose(^{18}FDG)-avidity increases with proliferative grade, showing an adverse prognosis with conventional therapies. [7]

CARCINOID SYNDROME

In 20#30% of patients with liver metastases occurs the carcinoid syndrome, mostly in the small intestine primary NET(siNET). Patients who need surgery should undergo preoperative evaluation by a cardiologist because of carcinoid heart disease. Treatment with long-acting somatostatin analogs (SSAs) allows to prevent the risk of crisis either in invasive and not invasive surgery [8].

THERAPEUTIC STRATEGIES

Several options are available to treat G1 metastatic NEN:

Surgery

- **Complete resection** is the first choice in metastatic disease. No adjuvant therapy is recommended after complete resection of well-differentiated (G1/ G2) NETs or in selected cases with endoscopic procedures [2]. Mesenteric metastases are treatable until the mesenteric vessel root is not completely surrounded or the mass extends retroperitoneally. Localized siNETs require an adequate lymphadenectomy irrespective if there are no signs of lymphadenopathy or mesenteric involvement. The presence of extra-abdominal disease needs to be preoperatively assessed.
- **Palliative surgery** is considered when hormonal syndrome is refractory to medical therapy and siNET to prevent intestinal occlusions [9].

Locoregional therapy

Extravascular techniques such as radiofrequency or laser ablation and cryotherapy are used for control of liver metastases in patient where surgery is not possible or as alternative to systemic therapies, especially for patients with functioning tumor. Intravascular techniques commonly used are the embolization by particles with or without cytotoxic agents (TACE/TAE) or radioactive microspheres (TARE). Portal-vein thrombosis, liver insufficiency, biliary obstruction or prior Whipple procedure are contraindications to this treatment [2, 10].

Liver transplantation

It is an alternative option for patients with unresectable neuroendocrine liver metastases, reserved to well-differentiated NEN with no extra-hepatic disease [10].

Drugs

The SSAs are recommended in carcinoid syndrome for their antisecretory effect, but also in all GEP-NENs thanks to the antiproliferative action [11].

PRRT (peptide receptor radionuclide therapy)

It is indicated in patients with well-differentiated, metastatic, unresectable midgut NETs, in progression to SSA and with positive somatostatin receptors. PRRT is based on two radioisotopes, yttrium-90(^{90}Y) or lutetium-177(^{177}Lu), linked to a SSA molecule. The absolute contraindications are pregnancy and lactation, severe hepatic or cardiac impairment, whereas relative ones are renal failure, hematological dysfunction, right heart valvular disease (the valve replacement should be considered before starting the treatment). A palliative treatment in uncontrolled symptoms can overwhelm contraindications [7].

Targeted agents

Everolimus (mTOR inhibitor) and Sunitinib (multitargeted receptor tyrosine-kinases inhibitor) are approved for the treatment of advanced well-moderately differentiated NETs [10].

Chemotherapy

Chemotherapeutic agents are generally reserved for patients with G1 NEN in rapidly progressive disease and/or after failure of other strategies [12].

Findings and procedure details

This paper reports in form of sheet the clinical history of patients with metastatic G1 primitive GEP-NEN, describing the case onset, including histopathological record and laboratory tests if positive. Their management is chronologically listed and centered on imaging data, laboratory results and treatments. In the end, the work-up established and the doubtful imaging findings are discussed.

CASE1

ONSET

AGE:31yo

SYMPTOMS: worsening dyspnea

PRIMARY TUMOR:

- LOCATION: ileum
- HISTOLOGY: well-differentiated
- Ki-67<1%
- HORMONE PRODUCTION: Carcinoid Syndrome

METASTASIS DIAGNOSED: at the onset, with hepatic biopsy positive for metastasis with Ki-67<1%

CLINICAL HISTORY

2018:

Surgery

Tumour progression

^{68}Ga-DOTATOC-PET/CT: significant hepatic uptake

^{18}F-FDG-PET/CT: weak hepatic uptake

SIGNIFICANT COMORBIDITY:

Carcinoid syndrome with massive tricuspid insufficiency

MEDICAL THERAPY:

Octreotide LAR 30mg, Furosemide 25mg

PITFALLS OF TREATMENT:

· Potential carcinoid crisis risk

· Cardiac function impairment

These conditions represent a contraindication to PRRT as first-line treatment.

CHOICE OF TREATMENT:

Fractioned embolization with Contrast-Enhanced Ultrasonography (CEUS) to reduce the hepatic involvement and carcinoid crisis risk prior to start PRRT(Fig.1).

CURRENT CONDITION: good response to treatments

CASE2

ONSET

AGE:62yo

PRIMARY TUMOR:

- LOCATION: ileum
- HISTOLOGY: well-differentiated neuroendocrine neoplasm positive for Chromogranin A and NSE. Full-thickness infiltration of the ileal wall and the serosa. Lymph node metastasis.
- Ki-67<2%
- NOT HORMONE SECRETING

METASTASIS DIAGNOSED: 11years later, with hepatic biopsy positive for metastasis with Ki-67<2%

CLINICAL HISTORY

2002:

Tumor resection

2013:

Watery diarrhea with weight loss and increased values of CgA(170ng/ml) and CEA(4.6ng/ml)

CT shows multiple hypervascularized hepatic lesions (>10) with central necrosis (up to 27mm) that were compatible with metastasis and mesenteric lymphadenomegalies

^{68}Ga-DOTATOC-PET/CT confirmed hepatic lesions uptake

Chemoembolization(Fig.2) and thermoablation of hepatic lesions

Starting to Lanreotide 90mg therapy

2014:

CT reports recurrence on treated nodule, confirmed with the ^{68}Ga-DOTATOC-PET/CT

Chemoembolization of hepatic lesions

CT presents a suspicious colon-NEN(actually diverticulum)

2015:

Increased CgA levels(145ng/ml)

CT shows other two hepatic metastasis and progression of an untreatable sub-diaphragmatic lesion(Fig.3)

2016:

^{18}F-FDG-PET/CT negative

^{68}Ga-DOTATOC-PET/CT shows lymph nodal, hepatic, peritoneal, bone, pulmonary and skin uptake

2017:

Hepatic biopsy confirms metastasis (Ki-67<2%).

^{177}Lu-DOTATOC radio-metabolic therapy with reduction of urinary 5-HIAA and plasmatic CgA levels

CT and CEUS report progression of liver disease, carcinosis and ascites

2018:

^{68}Ga-DOTATOC-PET/CT and CT confirm disease progression

Increased Urinary 5-HIAA(15.30mg/die) and plasmatic CgA(650ng/ml)

SIGNIFICANT COMORBIDITY: diabetes mellitus, diverticulosis

MEDICAL THERAPY: Lanreotide 120mg

CURRENT CONDITION:died of NET complications

NOTES: Diverticulosis represented a pitfall (Fig.4), but the integration of imaging techniques with clinic and laboratory data permitted to not miss the diagnosis.

CASE3

ONSET

AGE:52yo

PRIMARY TUMOR:

- LOCATION: ileum
- HISTOLOGY: well-differentiated neuroendocrine neoplasm G1, Stage IIIb (T4N1M0). Endophytic and plurifocal development. Full-thickness infiltration of the intestinal wall and of perivisceral adipose tissue and serosa. Lymph nodes metastasis. Positive for CgA, NSE and Synaptophysin.
- Ki-67<1%
- NOT HORMONE SECRETING

METASTASIS DIAGNOSED: 8 years later

CLINICAL HISTORY

2009:

CT images show a mesenteric lymph node cluster of 55x45mm

Ileal resection and SSA therapy

2014:

SSA therapy interrupted

2017:

68Ga-DOTATOC-PET/CT shows hepatic uptake

CT images show two hyper-vascularized lesions

Hepatic lesions chemoembolization

2018:

CT images show a new hyper-vascularized lesion

MRI negative

Radiologic stability based on CT images

SSA therapy started

^{68}Ga-DOTATOC PET/CT hepatic uptake

MEDICAL THERAPY: Octreotide LAR 20mg

CHOICE OF TREATMENT: Chemoembolization and SSA therapy

NOTES: MRI was not diagnostic to characterize the hepatic metastasis underlined by CT and ^{68}Ga-DOTATOC PET/CT, probably because of spatial resolution.

CASE4

ONSET

AGE:45yo

PRIMARY TUMOR:

- LOCATION: ileum
- HISTOLOGY: well-differentiated neuroendocrine neoplasm G1, Stage IV (T4N1M1). Full-thickness infiltration of the ileal wall and serosa. Lymph node and hepatic metastasis.
- Ki-67<1%
- NOT HORMONE SECRETING

CgA=116.60 ng/mL

METASTASIS DIAGNOSED: 4 months later

CLINICAL HISTORY

2006:

Ileocolic resection

Octreoscan: positive lesions in the liver, in mediastinal area and right retro-orbitary area

Hepatic lesions intravascular embolization

Octreoscan: lesions increased in size and fixation

2007-2009:

^{90}Y-DOTATOC radiometabolic therapy

2009:

^{68}Ga-DOTATOC PET/CT: vertebral (D7 and D9), mediastinal lymph nodes, pancreatic and hepatic uptake

Hepatic lesions embolization

MRI of dorsal spine shows stability of vertebral lesions

2010:

^{68}Ga-DOTATOC PET/CT confirms previous lesions and new hepatic lesions

2011:

Hepatic metastasis thermoablation

MR images show doubtful residual disease

2012:

Abdominal MRI not shows new signs of hepatic metastasis

2013:

CEUS shows lightly hypo-echogenic hepatic areas evocative for metastasis

2014:

^{68}Ga-DOTATOC PET/CT and abdominal MRI shows disease stability

2018:

^{68}Ga-DOTATOC PET/CT stable

MEDICAL THERAPY: Octreotide LAR 30mg

NOTES: CEUS was contradicted by ^{68}Ga-DOTATOC PET/CT and MRI

CASE5

ONSET

AGE:42yo

PRIMITIVE TUMOR:

- LOCATION: ileum(Fig.5)
- HISTOLOGY: neuroendocrine G1 tumor, Stage IV (pT4N1M1), infiltrating the entire thickness of the intestinal wall and serosa with metastases in 10/30 of the nodes and two tumor deposits.
- Ki-67<2%
- NOT HORMONE SECRETING

METASTASIS DIAGNOSED: AT THE ONSET

CLINICAL HISTORY

2016:

Ileal resection and hepatic segmentectomy

Therapy with Lanreotide LAR 60mg

2017:

CT shows the presence of 3 hypervascularized nodules (about 1cm) of possible substitutive meaning and 2 areas of dubious hypodensity in the portal phase

CEUS confirms hypervascular malignant lesions, but not portal hypodensities

Therapy with thermoablation and alcoholization (PEI) of lesions with CEUS

Slight increase in CgA and 5-HIAA

Increased posology of Lanreotide LAR to 120mg

CEUS and ^{68}Ga-DOTATOC-PET/CT negative for new lesions

CT increasing of the dubious hypodensity of 15mm

MRI with hepatospecific contrast media does not confirm the malignant nature

2018:

CT points out further dimensional increase of the hypodense formation (18mm)

CEUS and ^{68}Ga-DOTATOC PET/CT negative for new uptakes

MEDICAL THERAPY: Lanreotide 120mg

NOTES: Nuclear medicine and MRI have solved doubts of the CT (Fig 6-7-8)

CASE6

ONSET

AGE:68yo

PRIMITIVE TUMOR:

- LOCATION: ileum
- HISTOLOGY: G1, Stage IV (T4N1M1), infiltrating the wall, the mesenteric adipose tissue and the serosa with endovasal and perineural carcinosis. Positive for Chromogranin A, Synaptophysin and NSE. Node metastasis (19/22).
- Ki-67<1%
- NOT HORMONE SECRETING

METASTASIS DIAGNOSED: AT THE ONSET

CLINICAL HISTORY

2011:

CT shows nodular thickening of the ileus and locoregional lymphadenomegalia (55mm)

SPECT with Octeotride shows hyperfissation of retroperitoneal, mesentery, pelvic lymph nodes

Ileal and nodes resection

2011-2014:

Medical therapy with Octreotide LAR 30mg

Therapy with Octreotide LAR 30mg and radiometabolic therapy with ^{90}Y- DOTATATE

2015-2016:

stable CT

2017:

^{68}Ga-DOTATOC-PET/CT shows laterocervical, retroperitoneal and mesenteric node hypercaptations

2018:

^{68}Ga-DOTATOC-PET/CT stable

COMORBIDITY: diabetes, chronic kidney failure III

MEDICAL THERAPY: Octreotide LAR 30mg

CURRENT CONDITION: : Stationary with pharmacological therapy

CASE7

ONSET

AGE:50yo

PRIMITIVE TUMOR:

- LOCATION: ileum
- HISTOLOGY: G1(T3N1Mx); full-thickness infiltrating tumor up to the serosa
- Ki-67<2%
- NOT HORMONE SECRETING

CgA = 109.0 ng/ml

METASTASIS DIAGNOSED: 1 year later

CLINICAL HISTORY

2017:

^{68}Ga-DOTATOC-PET/CT shows hyper-fixation on ileal tract and lymph nodes

Therapy with Octreotide

Ileal resection

CT shows 4 subcentrimetric hyper-vascularized with poor wash-out of doubt interpretation confirmed with CEUS

^{68}Ga-DOTATOC-PET/CT negative

MRI negative

2018:

CT stable with high flow angiomas hypothesized(Fig.9)

^{68}Ga-DOTATOC-PET/CT points out a mesenteric and hepatic hypercaptations

CEUS negative

CgA elevated, but normal after 20days and 6month

MEDICAL THERAPY: Lanreotide 90mg

NOTES:^{68}Ga-DOTATOC-PET/CT and CgA found false positive lesions(Fig.10)

Images for this section:

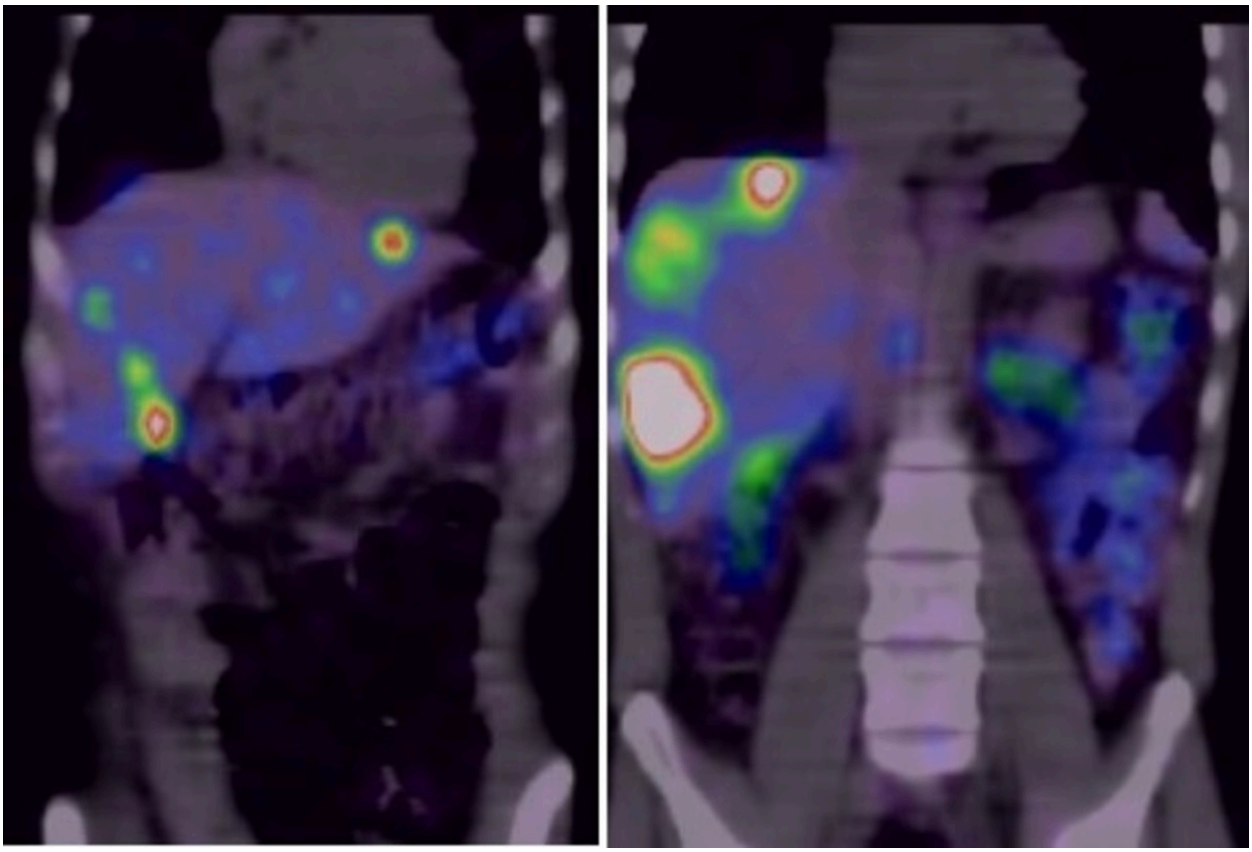

Fig. 1: Fig1

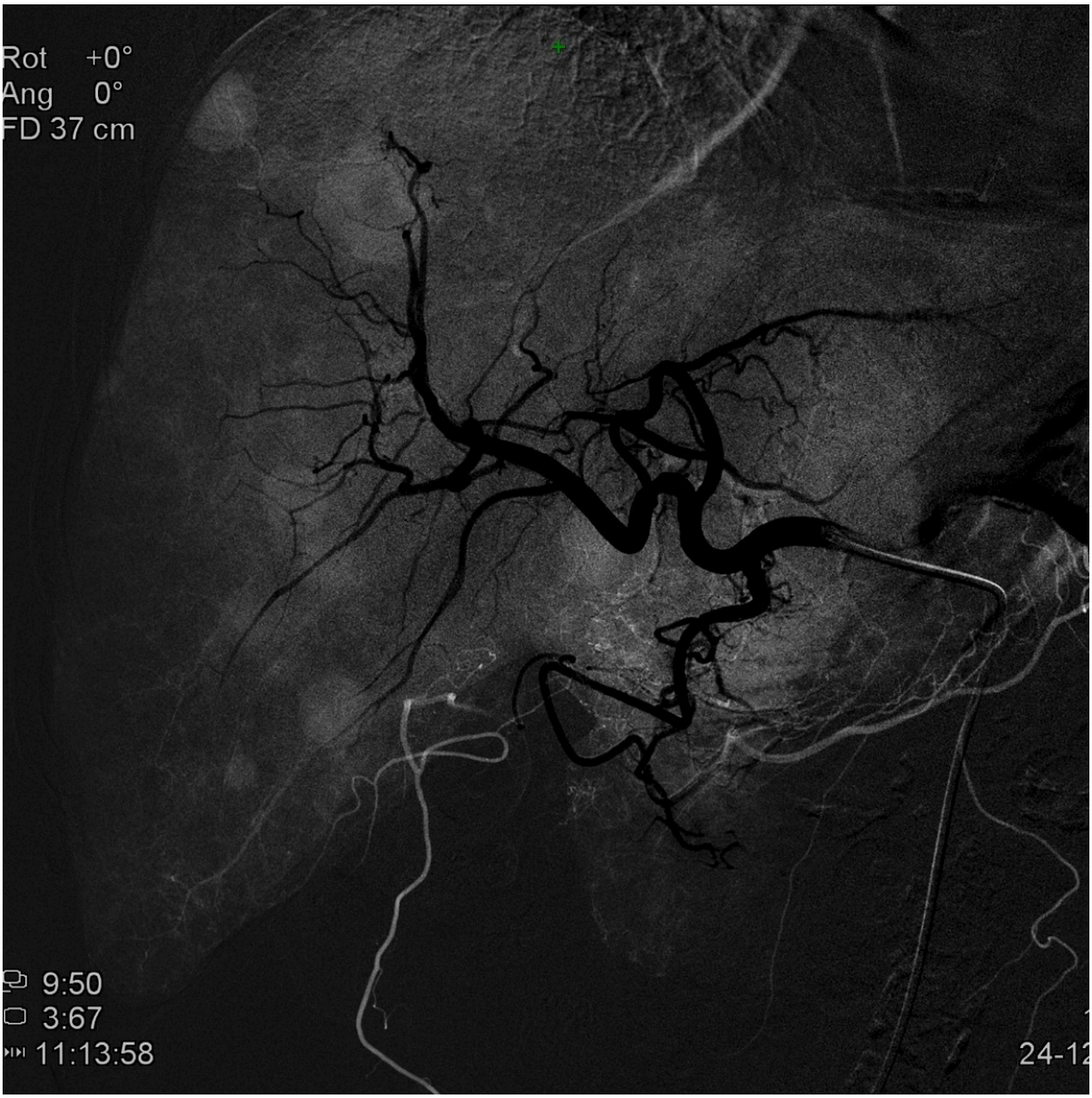

Fig. 2: Fig2

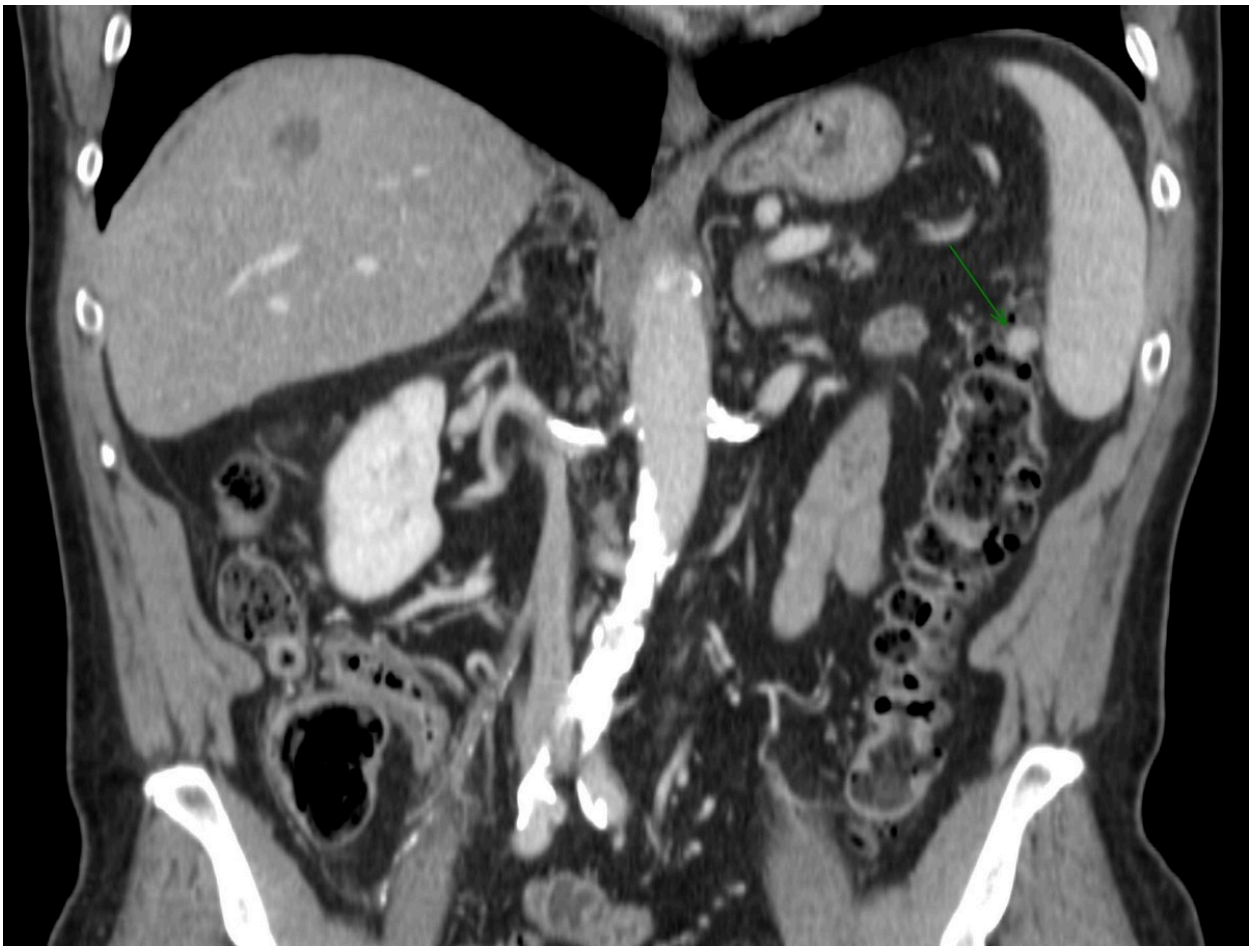

Fig. 3: Fig3

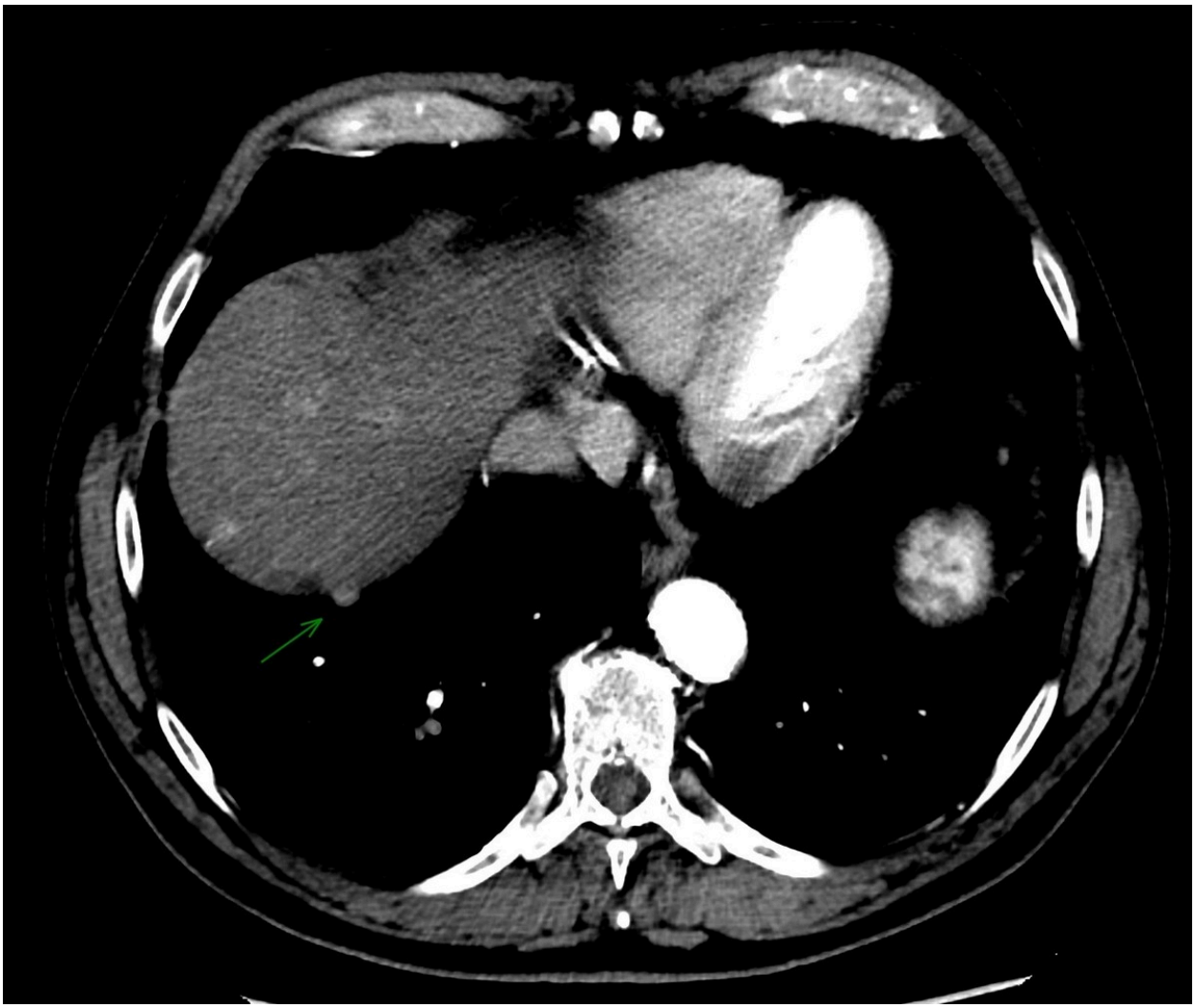

Fig. 4: Fig4

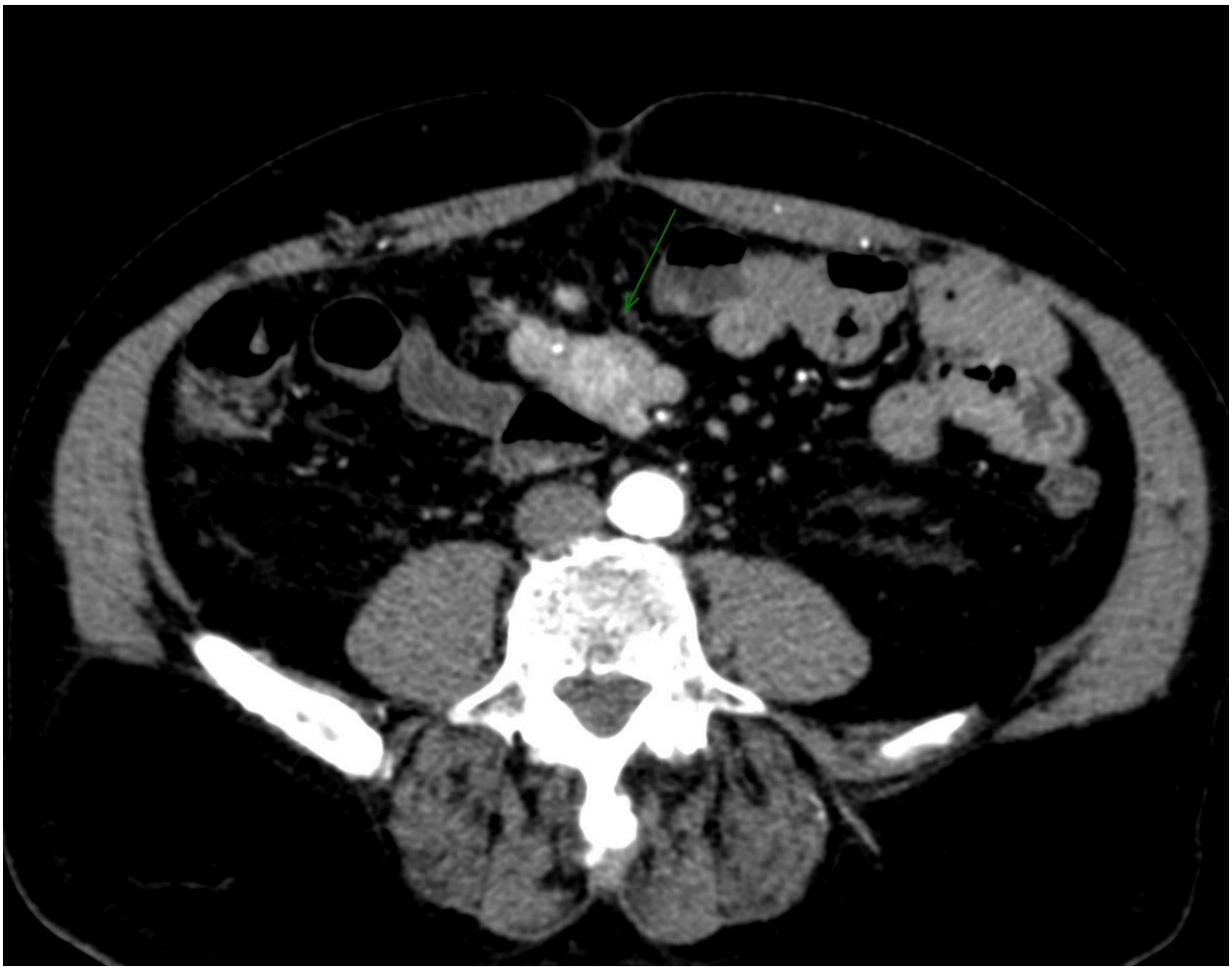

Fig. 5: Fig5

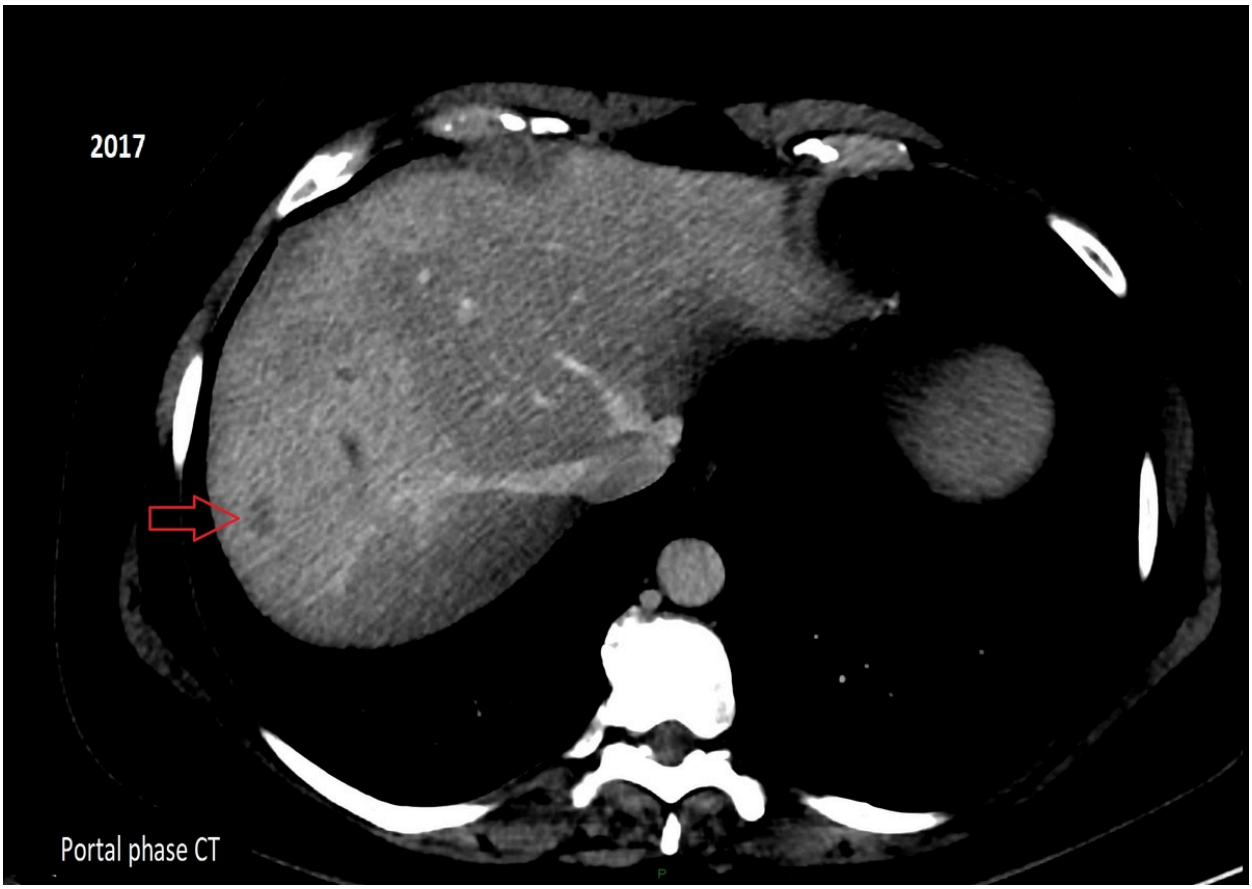

Fig. 6: Fig6

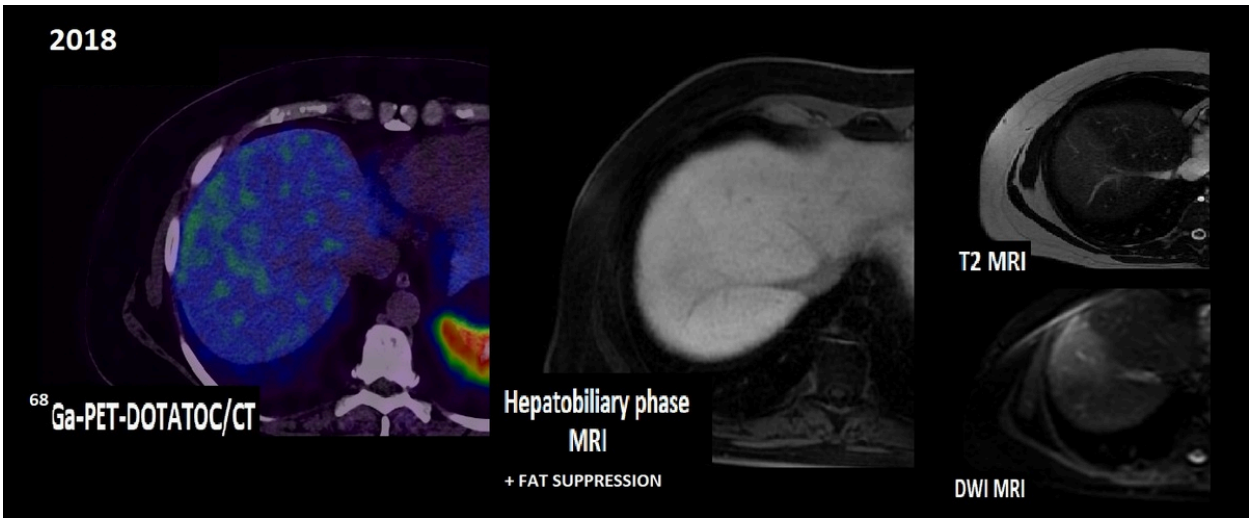

Fig. 7: Fig7

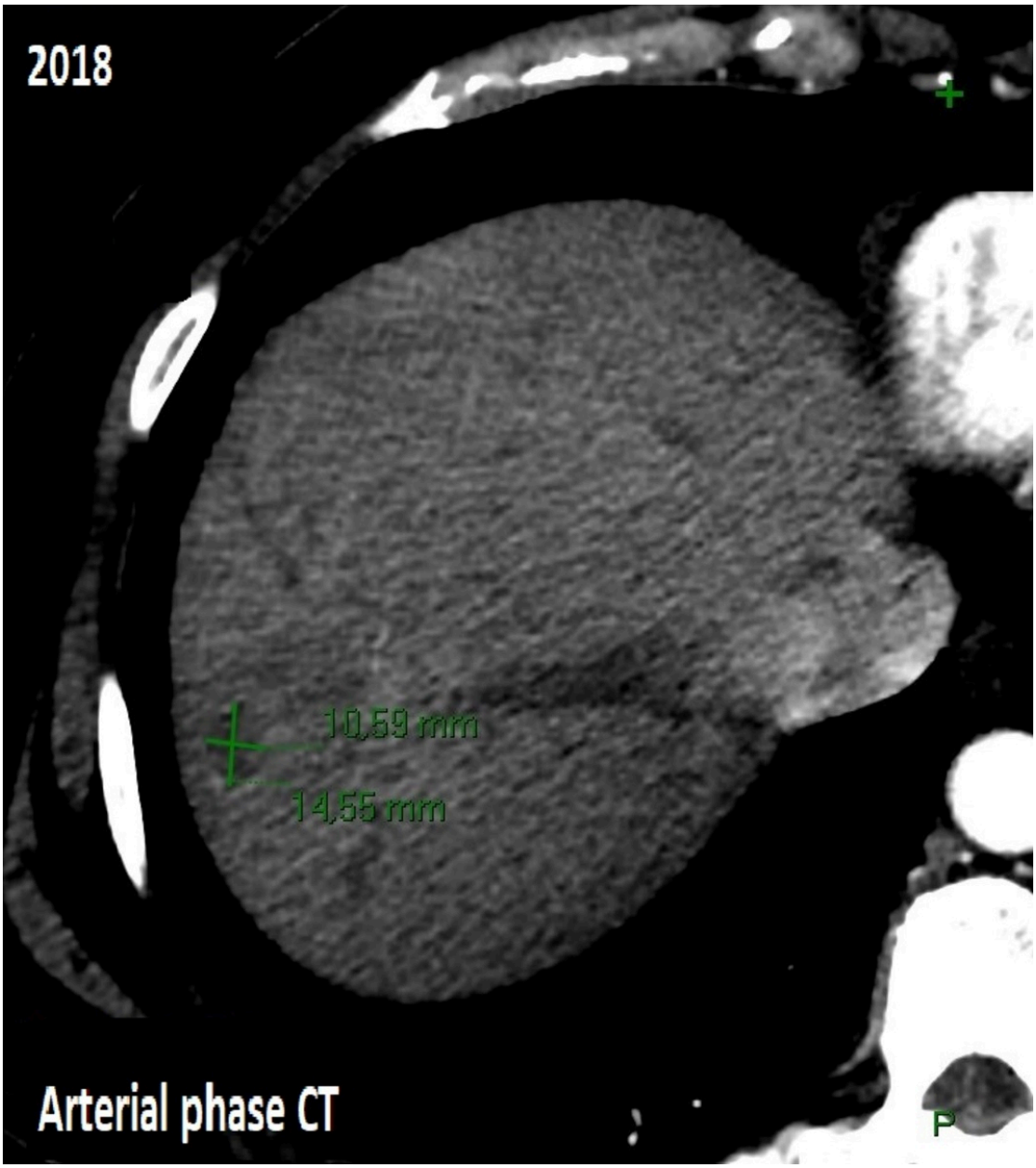

Fig. 8: Fig8

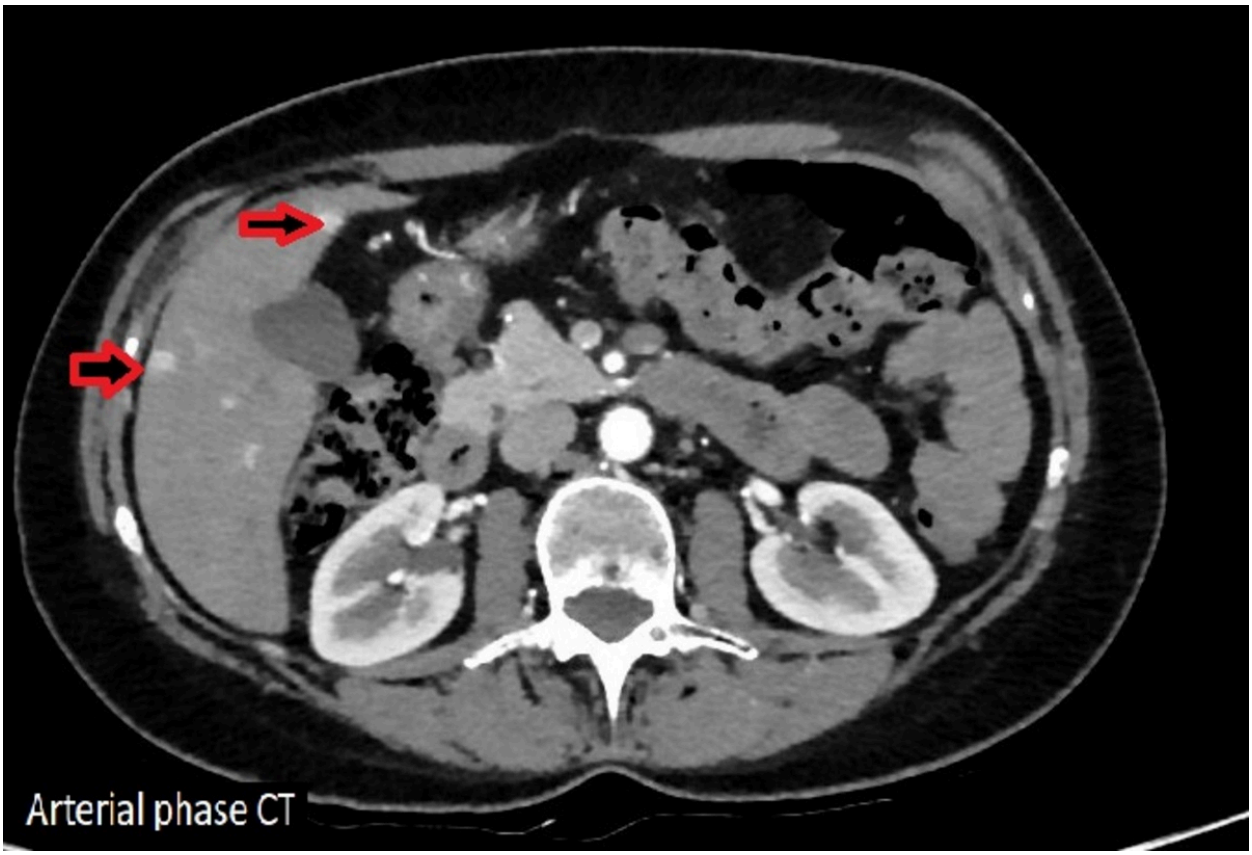

Fig. 9: Fig9

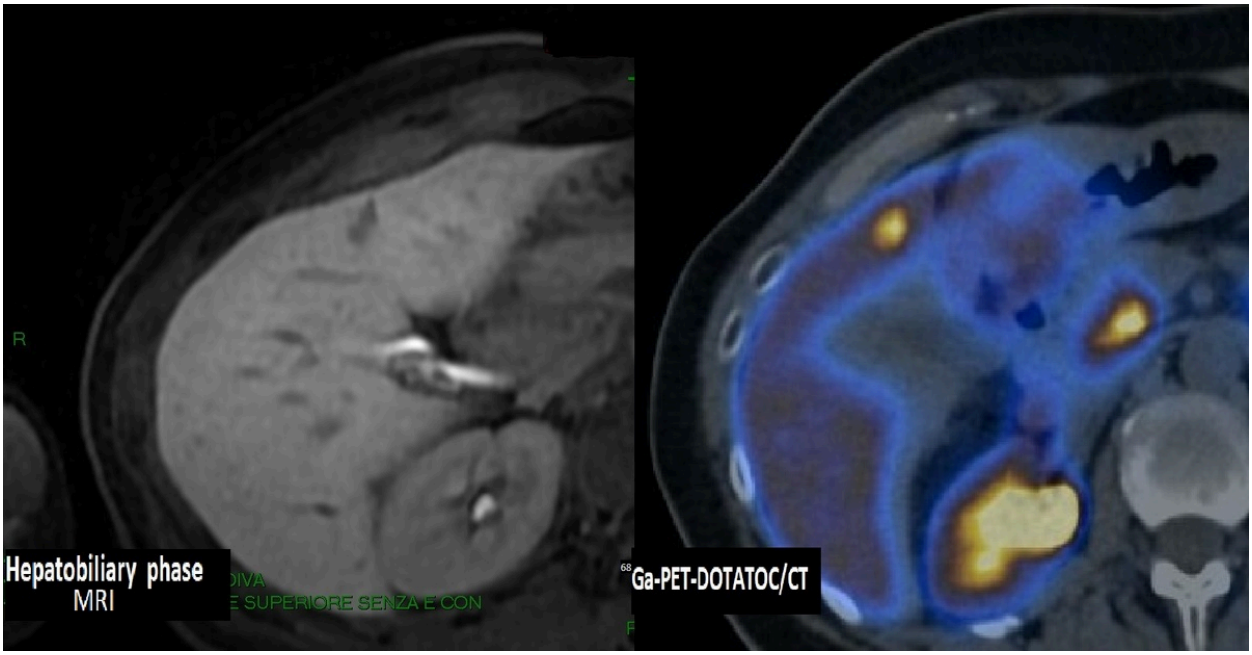

Fig. 10: Fig10

Conclusion

The multidisciplinary group allows a better management of the patient's diagnostic-therapeutic path in terms of effectiveness, efficiency, safety and saving of resources integrating the knowledge among the various specialists through:

- a better diagnosis and study of patient condition, also integrating information not always present in the hospital information system;

- planning of different therapeutic strategies;

- shortening of the management time;

- reduction of the costs, also avoiding unnecessary examinations.

In our experience, the ^{68}PET-GaDOTATOC is conclusive because the metastases of G1 tumors are generally characterized by considerable uptake, while CT, US, MRI and the use of contrast media provide more information able to improve the clinical evaluation. No imaging technique therefore seems to be able to replace the other. When ^{18}FDG-PET was performed, it did not add any relevant information. Nuclear medicine appears superior in detecting the replicative lesions, but also prone to false positives.

A collective evaluation of the images allow every specialist (in particular the clinician and the surgeon) to discuss on the report and images, while the radiologist and nuclear medicine physician can integrate information for a better interpretation of the images that led to an accurate comprehension of the case.

Metastatic G1 GEP-NENs have a long-term prognosis and disease control is the key point. The progression of disease is associated with the interruption of somatostatin analogs therapy, because of its antiproliferative effect. Not all patients have the same treatment responses and all clinical conditions are heterogeneous.

The radiologist must know contraindications to treatments, provide the data that integrate the nuclear imaging and not overlook the complications typical of this condition such as Carcinoid Syndrome or intestinal obstruction.

Personal information

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