



## Simultaneous Spleno-Pancreatectomy and Mini-ALPPS Approach for the Treatment of Metastatic Functional Gastrinoma

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### Abstract

**Background:** Gastrinomas are rare functional neuroendocrine tumors primarily located in the duodenum or pancreas, causing Zollinger-Ellison syndrome. At presentation, up to 25% of gastrinomas are metastasized, predominantly to the liver. The presence of liver metastases has a negative impact on the prognosis. Liver resection for neuroendocrine metastases is associated to long-term survival advantages and disease control. Nevertheless, the benefits of aggressive liver resection should be weighed against the potential risk of post-hepatectomy liver failure.

**Summary:** This report presents the case of a 41-year-old female patient who presented severe diarrhea due to a pancreatic functional gastrinoma with synchronous hepatic metastases. Preoperative assessment of future liver remnant function through a newly developed dynamic measure calculated using hepatobiliary scintigraphy -HIBA index- is described. The present case report also underlines a two-stage surgical management consisting of Mini-ALPPS procedure, distal pancreatectomy and splenectomy which allowed primary and secondary lesions to be fully resected.

**Conclusion:** Liver metastatic pancreatic neuroendocrine tumors can be approached through an aggressive R0 resection with curative intent as long as a meticulous appraisal of future liver remnant function is conducted to ensure the patient's postoperative safe and uneventful recovery.

**Keywords:** Gastrinoma; Pancreas; Liver metastases; Hepatectomy; Future liver remnant

### Abbreviations

pNETs: Pancreatic Neuroendocrine Tumors; FLR: Future Liver Remnant; ALLPS: Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy; HBS: Hepatobiliary Scintigraphy; PHLF: Posthepatectomy Liver Failure; PPT: Partial Parenchymal Transection; IPVE: Intraoperative Portal Vein Embolization

### Background

Zollinger-Ellison syndrome is a rare disease (1 to 3 cases/year per million population) characterized by gastric acid hypersecretion resulting in severe acid-related peptic disease and diarrhea. It is caused by secretion of gastrin by duodenal or Pancreatic Neuroendocrine Tumors (pNETs) called gastrinomas. Although gastrinomas are one of the most common functional pNETs, only 25% of gastrinomas arise in the pancreas [1].

Recent data suggest that 65% of gastrinomas are malignant, and up to 30% to 40% of patients will have evident metastatic disease at initial presentation. The most frequent site of metastases is the liver (40% to 93%). Because of the poor clinical outcome of patients with advanced and metastatic gastrinomas, and the overall disappointing results with systemic therapy, an aggressive management approach through hepatic resection with curative intent of metastatic NETs is encouraged [2].

Future Liver Remnant (FLR) function in patients with extensive compromise of liver parenchyma due to metastatic disease ought to be thoroughly evaluated before hepatic resective surgery is performed in order to prevent Post-Hepatectomy Liver Failure (PHLF) [3]. Therefore, whenever an insufficient FLR function is predicted, different surgical techniques can be applied to reduce morbidity and mortality due to PHLF by promoting FLR function improvement prior to a major hepatic resection. Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) constitutes one of the latest and promising technical advances among these

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**Received Date:** 15 Mar 2022

**Accepted Date:** 04 Apr 2022

**Published Date:** 08 Apr 2022

#### Citation:

Jorge C. Simultaneous Spleno-Pancreatectomy and Mini-ALPPS Approach for the Treatment of Metastatic Functional Gastrinoma. *Clin Case Rep Int.* 2022; 6: 1311.

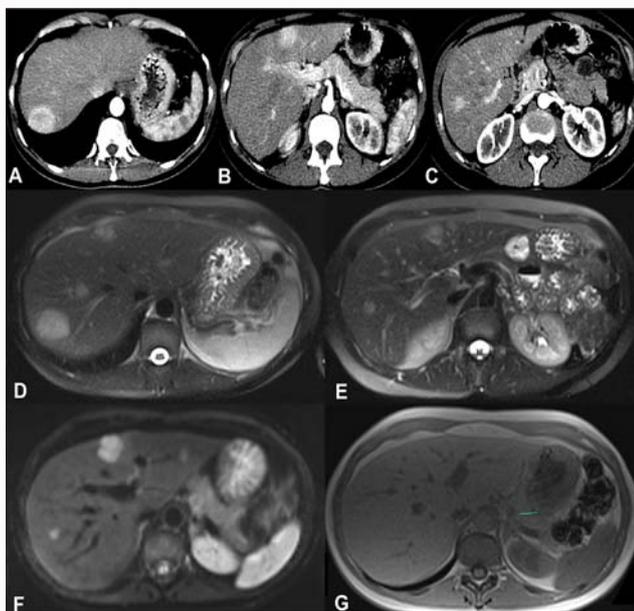
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complex groups of surgical strategies. More recently, a less invasive ALPPS variant, Mini-ALPPS, has been described by our group minimizing the first stage impact to promote rapid patient recovery and leaving the main surgical procedure for the second stage, thus decreasing morbidity and mortality.

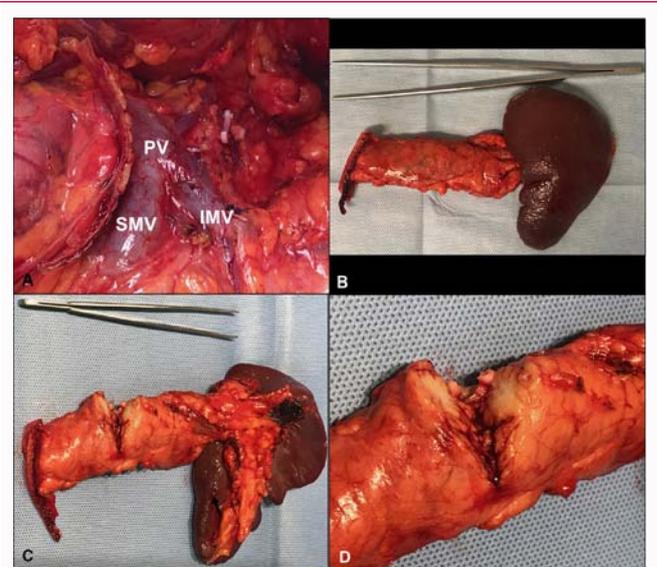
This report presents the case of a 41-year-old female patient who presented severe diarrhea due to a pancreatic functional gastrinoma with synchronic hepatic metastases. Preoperative assessment of FLR function through a newly developed dynamic measure calculated using Hepatobiliary Scintigraphy (HBS) -HIBA index- is described. The present case report underlines surgical management consisting of Mini-ALPPS procedure which allowed primary and secondary lesions to be fully resected.

## Case Presentation

Forty-one-year-old female patient without relevant prior medical history, who presented at our institution with episodic, watery, and sometimes explosive diarrhea consisting of approximately 10 to 15 bowel movements per day, that had been gradually worsening over a 30-month period. The patient had undergone several uneffective empirical and symptomatic treatments at a different center. At our institution, clinical tests were performed, ruling out celiac disease and both bacterial and parasitic infections. Upper and lower endoscopies were performed. Lower endoscopy showed no relevant findings; whereas upper endoscopy revealed a hyperplastic polyp and mild chronic gastritis. *Helicobacter pylori* were not detected in the gastric biopsy. Consequently, a proton pump inhibitor (omeprazole) was prescribed (20 mg/day). Interestingly, her severe case of diarrhea improved after the first dose of omeprazole. Afterwards, with an etiological diagnostic purpose, an abdominal ultrasound was



**Figure 1:** A-C). Multislice computed tomography. Axial view showing multiple bilateral hepatic hypodense nodular lesions with prompt brief arterial hypervascularity compatible with secondary locations of a hidden primary malignant tumor. D-F). Magnetic resonance cholangiopancreatography showing numerous hepatic nodular lesions with peak enhancement in hepatic arterial phase and peripheral rim enhancement during venous and portal phases as well as signs of restriction during diffusion-weighted images. F, G). Magnetic resonance cholangiopancreatography showing as a 12 mm nodular image in the distal section of the body of the pancreas (arrow).

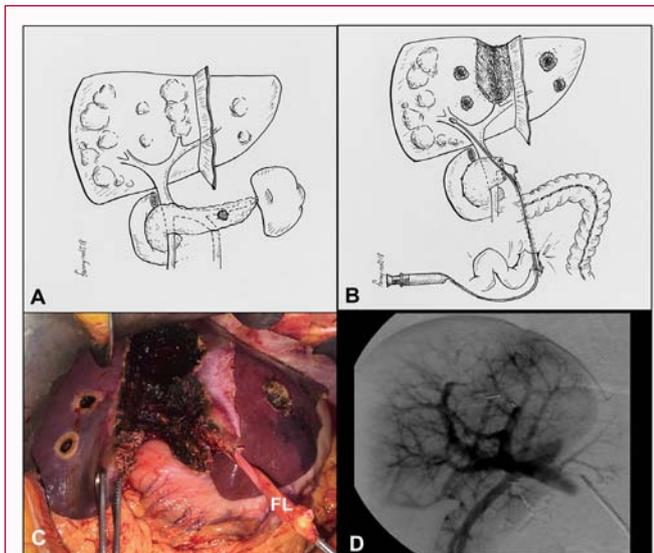


**Figure 2:** First-stage surgery. A. Distal pancreatotomy carried out with a mechanical lineal suture (Echelon Flex™ Endopath® Stapler. Ethicon, Johnson & Johnson, New Jersey, U.S.) with Gore® Seamguard® bioabsorbable staple line reinforcement (W. L. Gore & Associates, Inc., Delaware, U.S.). Suture line with duodenum-pancreas head complex on the right of the photograph (arrow). Ligated splenic vein (arrowhead). PV: Portal Vein. IMV: Inferior Mesenteric Vein. SMV: Superior Mesenteric Vein. B. Surgical specimen of distal pancreatotomy and splenectomy. C. Posterior view of surgical specimen of distal pancreatotomy and splenectomy showing transected pancreatic nodule on the body of the pancreas (asterisk). D. Enlarged posterior view of surgical specimen of distal pancreatotomy and splenectomy showing transected pancreatic nodule on the body of the pancreas (asterisk).

performed which revealed multiple solid and hypochoic liver nodules ranging from 45 mm to 20 mm in diameter. Subsequently, an abdominal multislice computed tomography was performed which confirmed numerous bilateral hepatic hypodense nodular lesions with prompt brief arterial hypervascularity and rapid wash-out during the portal venous phase. These images were compatible with secondary locations of a hidden primary malignant tumor (Figures 1A-1C). A magnetic resonance cholangiopancreatography showed the known hepatic nodules as well as a 12 mm nodular image in the distal section of the body of the pancreas (Figures 1D-1E). Routine laboratory tests, serum Chromogranin A levels, serum tumor markers (cancer antigen 19-9, alpha-fetoprotein, and carcinoembryonic antigen) and urinary excretion of 5-hydroxyindoleacetic acid were within normal parameters. However, serum gastrin was 2.100 pg/ml, with a normal reference value from 13 pg/ml to 115 pg/ml.

Based on the presumptive diagnosis of Zollinger-Ellison syndrome due to pancreatic gastrinoma with liver metastasis, a radical two-stage surgery was performed. Two weeks prior to the first-stage surgery, the patient received one dose of intramuscular octreotide long-acting release.

During the first stage a distal pancreatotomy and splenectomy were performed. Moreover, the hepatic metastatic disease was approached as well, by performing the first procedure of Mini-ALPPS technique as previously described by our group [4]. Distal pancreatotomy was carried out with a mechanical lineal suture (Echelon Flex™ Endopath® Stapler. Ethicon, Johnson & Johnson, New Jersey, U.S.) With Gore® Seamguard® bioabsorbable staple line reinforcement (W. L. Gore & Associates, Inc., Delaware, U.S.) (Figure 2). Simultaneously, the first procedure of Mini-ALPPS consisted of

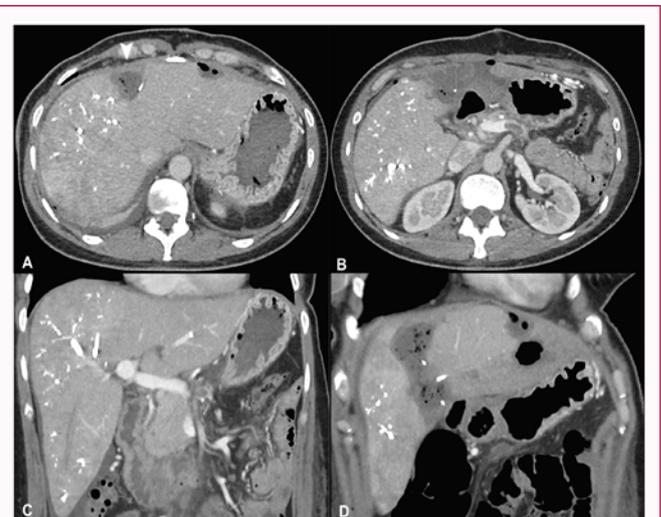


**Figure 3:** First-stage surgery. A). Graphic representation of preoperative pancreatic primary tumor and hepatic metastatic disease localization. B). Graphic representation of the first stage surgery combining the first step of Mini-ALLPS procedure and primary tumor resection. The scheme shows: partial parenchymal transection, future liver remnant clean-up, intraoperative portal vein embolization through the inferior mesenteric vein, as well as distal pancreatectomy and splenectomy. C). First step of Mini-ALLPS procedure. Partial transection of the liver parenchyma (asterisk) on the dome through a line that is marked in the proximities of the Falciform Ligament (FL) insertion up the plane anterior to the middle hepatic vein. Future liver remnant clean-up using "corkscrew technique" on segments II (arrowhead) and IV (arrows). D). Radioscopy image of intraoperative right portal vein embolization.

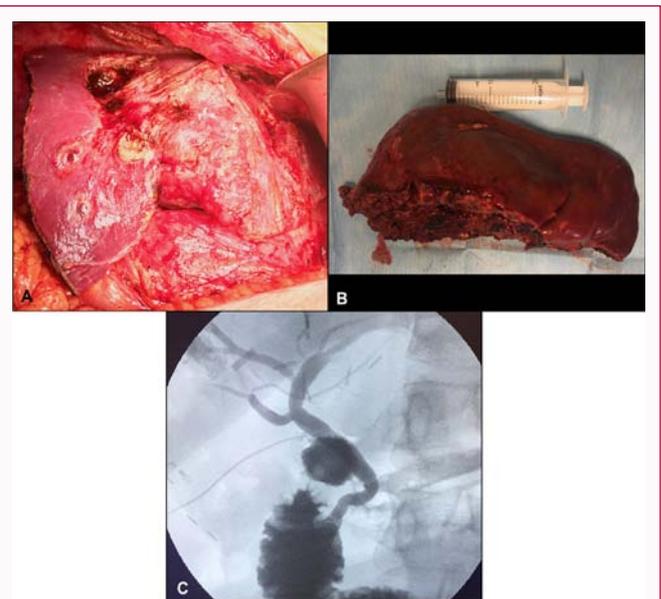
partial liver partition through a line that is marked in the proximities of the falciform ligament insertion, FLR clean-up using "corkscrew technique" by resecting 6 metastases on segments II, III, and IV and intraoperative right portal vein embolization with Histoacryl<sup>®</sup> (Braun GmbH, Kronberg im Taunus, Germany) (Figure 3). Two surgical drains were left in place and subsequently removed on postoperative day 5 after having obtained a normal amylase level in drainage fluid. Eight days after the first stage, a multislice computed tomography was performed which showed the expected postoperative modifications: Hyperdense images in the hepatic right lobe compatible with previous intraoperative right portal vein embolization. No new lesions were observed in the left liver. A hypodense image with air bubbles corresponding to partial transection of the liver parenchyma was observed (Figure 4). The patient was discharged on postoperative day 9 without complications.

In order to prevent PHLF and based on the notion that FLR volume is not equivalent and sometimes overestimates FLR function, a HBS using <sup>99m</sup>Tc-mebrofenin was performed to assess FLR function. As previously described by our group, the HIBA-index was used to estimate the risk of PHLF (being the risk higher if HIBA-index was <15%). During the first HBS performed 10 days after the first stage, functional analysis through single photon emission computed tomography revealed a FLR function/total liver function of 21%, while HIBA index was 14.76% and Amsterdam index was 0.76% min/m<sup>2</sup>. Consequently, the second stage was postponed. A second HBS was performed 30 days after the first stage revealing a FLR/total liver function of 25%, HIBA index of 17% and Amsterdam index of 0.8% min/m<sup>2</sup>.

The second stage procedure was carried out 51 days after the first stage and it consisted of a right hepatectomy (Figure 5). Once



**Figure 4:** Multislice computed tomography. A, B). Axial view showing hyperdense images in the hepatic right lobe compatible with previous intraoperative right portal vein embolization. Hypodense image corresponding to previous metastasectomy (arrowhead). No new lesions are observed in the left liver. C, D). Coronal view showing hyperdense images in the hepatic right lobe compatible with previous intraoperative right portal vein embolization. Hypodense image with air bubbles corresponding to partial transection of the liver parenchyma (arrowhead).

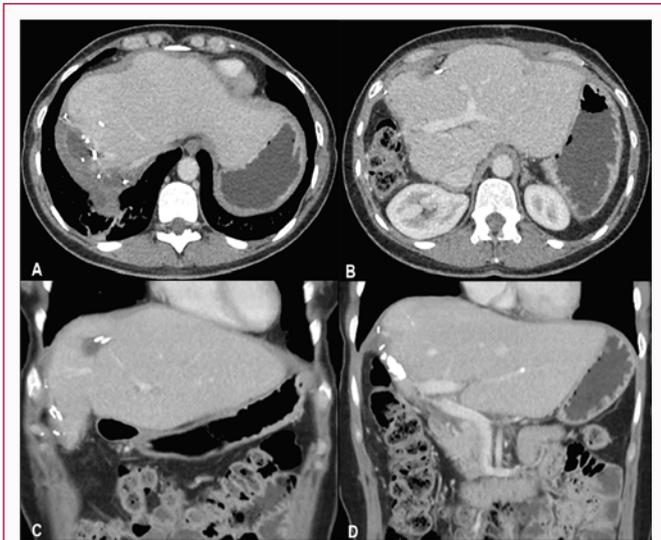


**Figure 5:** Second-stage surgery. A). Right hepatectomy. Liver remnant with healed previous partial transection of the liver parenchyma (arrow) and segment IV metastasectomies (arrowheads). B). Surgical specimen of right hepatectomy. C). Intraoperative cholangiography showing undamaged remnant left biliary tree, without leakage of contrast and adequate distal passage of contrast to the duodenum.

again, the patient was discharged on postoperative day 6 without complications or signs of PHLF.

Histopathological analysis of the surgical specimen corresponding to the first stage procedure revealed a pancreatic well differentiated pNET (G2, Ki 67 12%), 6 liver metastasis and one metastatic lymph node out of 9 resected lymph nodes. The right liver resected during the second stage presented metastatic lesions from NET as well.

One month and a half after the second stage surgery a follow-up



**Figure 6:** Multislice computed tomography. A, B). Axial view showing remnant left liver with hypodense image corresponding to previous metastasectomy (arrowhead) and without focal lesions. C, D). Coronal view showing remnant left liver with hypodense image corresponding to previous metastasectomy (arrowhead) and hyperdense images corresponding to metal clips on hepatic section line (arrows).

abdominal multislice computed tomography was performed which revealed normal postoperative changes (Figure 6).

The patient is currently receiving a monthly dose of intramuscular octreotide long-acting release. To the date, four months after her primary first-stage procedure, the patient remains with good clinical evolution without evidence of disease.

## Discussion

Gastrinomas make up 16% to 30% of functional pNETs and hyper-secrete gastrin resulting in Zollinger Ellison syndrome, the classic symptoms of which are refractory peptic ulcer disease and secretory diarrhea. Chronic diarrhea is a common problem affecting up to 5% of the population at a given time and, frequently, its etiological diagnosis entails a trying task [5]. However, when it presents associated with acid-related peptic disease and improves after prescription of proton pump inhibitors, functional NETs such as gastrinoma, must be ruled out.

Metastases are detected at diagnosis in about 40% to 80% of patients with pNETs. Surgery remains the treatment of choice in selected patients with pNETs and resectable liver metastases, because it may provide cure. Primary tumor resection combined with neuroendocrine liver metastasectomy may have either curative intent, when complete resection is possible, or palliative intent, when the majority of the tumor burden is removed to control the symptoms of the disease [2]. Liver resection for neuroendocrine metastases is associated to long-term survival advantages and disease control. Furthermore, this incremental increase in survival time has been described to have occurred regardless of tumor grade. According to guidelines and related studies, the minimum criteria for cytoreductive surgery of liver-metastatic pNETs are as follows: 1) G1/G2 liver-metastatic pNET; 2) the primary is resectable; 3) no unresectable extrahepatic disease; 4) younger patients with an acceptable morbidity and low mortality; 5) tumor volume with <25% liver involvement; 6) up to 90% or at least >70% of tumor load is thought to be resectable preoperatively; and 7) treatment decision

making requires a multidisciplinary approach; 8) either one-stage or two-stage surgery may be recommended [6].

Post-hepatectomy liver failure remains a significant cause of morbidity and mortality after major liver resection. Although the etiology of PHLF is multifactorial, an inadequate functional liver remnant is thought to be the most important modifiable predictor of PHLF. For people with a normal liver, an FLR  $\geq 25\%$  of total liver volume is adequate to avoid PHLF. Patients with chronic liver disease but without cirrhosis usually require an FLR of at least 30% while patients with cirrhosis but without portal hypertension require an FLR of at least 40%. A shift toward parenchymal-preserving operations has led to a decrease in morbidity and mortality, with excellent oncologic outcomes even in patients with significant disease burden in the liver. Parenchymal-preserving liver surgery is ideal for these well-encapsulated tumors. Non-anatomic resections in combination with ablation offer comparable oncologic results in small tumors [7]. Two-staged hepatectomies also provide a feasible resective approach for these patients. Moreover, ALPPS, a novel technique first described by Schnitzbauer et al. [8] in 2012, thoroughly accelerates FLR hypertrophy increasing the feasibility to complete both stages. As originally described, the technique consists of right portal vein ligation combined with in situ splitting of liver parenchyma during the first stage, followed by a second stage (resective procedure) performed at surgeon discretion after assessing FLR sufficiency, usually within 7 to 10 days. In 2016, our group put forward a new surgical paradigm for ALPPS called “Mini-ALLPS”, aiming to maximally reduce the aggressiveness and surgical impact of ALPPS’ first stage. The proposal incorporated the combination of Partial Parenchymal Transection (PPT) with Intraoperative Portal Vein Embolization (IPVE) as well as minimum liver mobilization, without hilar dissection [4]. This approach proves useful in cases such as the one presented in this review, where considerable bilobar hepatic disease requires FLR clean-up and functional enhancement, apart from primary pancreatic tumor resection.

FLR function assessment before indicating a mayor hepatic resection or to postpone second-step surgery until satisfactory activity has been reached, is key to the success of this complex procedure. Dynamic  $^{99m}\text{Tc}$ -mebrofenin hepatobiliary scintigraphy was developed as a quantitative method for evaluating total and regional liver function, including FRL function. In 2017, Serenari et al. [9] described inter stage assessment of FLR function in ALLPS using HBS and found that HIBA index a newly developed dynamic measure representing the proportion of radionuclide accumulated in the FLR- of <15% to best predict clinically significant PHLF in patients with an already sufficient FLR volume.

To summarize, this case comprises at least three uncommon and/or novel subjects. Firstly, the unusual diagnosis of a pNET after a two-year history of misdiagnosed diarrhea. A high level of diagnostic suspicion must be maintained when pNETs are involved, since their early diagnosis allows for the treatment of a localized disease rather than an advanced one, with the management and technical vicissitudes that this brings about, for the patient, the medical team and the health system.

Secondly, primary pancreatic tumor resection associated with two-stage hepatectomy is a challenging but feasible approach in this type of metastatic disease. Patients with advanced pNETs without extrahepatic involvement benefit greatly from R0 resection and the Mini-ALLPS technique proves a useful tool to achieve this goal; its

primary advantages being: 1) A less aggressive first stage which allows the patient to recover rapidly and uneventfully, 2) induced FLR hypertrophy through PPT and IPVE, and 3) a second stage facilitated by lesser perihepatic and hilar inflammation.

Lastly, in extended liver resections, function rather than volume alone, should dictate the minimal FLR. Preoperative or interstage measurement of  $^{99m}\text{Tc}$ -mebrofenin uptake in the FLR on functional HBS has proved more valuable than measurement of the volume of the future remnant in the assessment of the post hepatectomy risk of liver failure and liver failure-related mortality [10]. Using HIBA index, the parameter developed by our group, with a 15% cut-off value, second-stage surgery can be postponed until a safe FLR function is achieved in order to reduce the risk of PHLF.

## Conclusion

In conclusion liver metastatic pNETs can be approached through an aggressive R0 resection with curative intent as long as a meticulous appraisal of FLR function is conducted to ensure the patient's postoperative safe and uneventful recovery.

When pNETs are involved, early diagnosis allows a higher rate of respectability. Primary pancreatic tumor resection associated with two-stage hepatectomy is a feasible approach when managing metastatic pNETs. In order to prevent PHLF, using HIBA index and second-stage surgery can be postponed until a safe FLR function is achieved.

## Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. The institutional Ethics Committee for Investigative Protocols approved the study's conduct.

## Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Micaela Raíces, Cecilia Jorge, Ardiles Victoria, De santibañes Martín y De Santibañes Eduardo. The first draft of the manuscript was written by Micaela Raices and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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