

# One stage curative resection of double intestinal neuroendocrine tumors with thirty-two bilobar liver metastases.

## A case report



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## One stage curative resection of double intestinal neuroendocrine tumors with thirty-two bilobar liver metastases. A case report

Neuroendocrine tumours (NETs) of the midgut are often multifocal and have a noticeable attitude to metastasize to locoregional lymph nodes and liver. Surgery is the only curative treatment for metastatic NETs of the midgut, even though only a minority of patients are candidates to radical surgical resection.

The optimal timing for surgical resection in case of synchronous presentation of primary intestinal neoplasms and resectable LM is still controversial, especially when LM are multiple and/or involve multiple liver segments. Even though a staged approach with initial intestinal resection followed by liver resection is still preferred, recent studies have shown favourable results for simultaneous procedures, which have the striking advantage of avoiding a second laparotomy, with morbidity and mortality rates comparable to staged resections.

We report here the case of a patient with double midgut well-differentiated NET and thirty-two synchronous bilobar LM who received successful simultaneous curative right hemicolectomy and radical but conservative liver resection and radiofrequency thermal ablation with the guidance of intraoperative ultrasonography. He is alive without evidence of recurrence 48 months after surgery.

KEY WORDS: Intraoperative ultrasonography, Liver resection, Midgut neuroendocrine tumour, Neuroendocrine liver metastases

## Introduction

Neuroendocrine tumours (NETs) originate from secretory cells of the diffuse neuroendocrine system <sup>1</sup> and share the capacity of producing hormones and vasoactive substances that may give rise to different clinical syndromes.

NETs of the gastrointestinal tract are mostly non-functioning and present quite late, while functioning NETs are characterized by the occurrence of a variety of clinical syndromes caused by excess hormone secretion <sup>1,2</sup>. Gastrointestinal NETs have distinct features depending on their site of origin. NETs of the midgut are multifocal in 26-40% and have a noticeable attitude to metastasize to locoregional lymph nodes, root of the mesentery and liver <sup>1,3</sup>. Metastatic NETs of the midgut are often responsible of the classical carcinoid syndrome, characterized by flushing, diarrhoea, and valvular heart disease <sup>1,2</sup>. Surgery is the only curative treatment for gastrointestinal NETs; liver metastases (LM) occur in 50-75% of NETs of the midgut, but less than 15% are susceptible of curative liver resection and/or ablation <sup>2</sup>. The optimal timing for surgical resection in case of synchronous presentation of primary colorectal neoplasms

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and resectable LM is still controversial, especially when LM are multiple and/or involve multiple liver segments. In the past decades most investigators have recommended a staged approach with initial colorectal resection (CRR) followed by liver resection (LR) to avoid increased morbidity and mortality eventually associated with simultaneous procedures. Recently however an increasing number of studies have shown favourable results for simultaneous procedures, which have the striking advantage of avoiding a second laparotomy, with morbidity and mortality rates comparable to staged resections<sup>4</sup>. This case report describes the favourable long-term outcome of a patient who received simultaneous curative right hemicolectomy and radical LR and radiofrequency thermal ablation (RFTA) of a double midgut well-differentiated NET with thirty-two bilobar LM.

## Case Report

A 57-year-old male patient with diabetes and hypertension underwent in March 2009 routine ultrasound of the liver which revealed steatosis and 3 nodular lesions diagnosed as liver hemangiomas. A CT scan performed 6 months later was inconclusive. A Gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA)-enhanced MRI performed after further 6 months showed multiple bilobar liver lesions suggestive of metastases and the patient was referred to the oncologic unit at an outside hospital. In the meanwhile he developed symptoms of episodic flushing and diarrhea and a carcinoid syndrome was suspected. Pancolonoscopy showed a ileo-caecal mass; histological examination of the endoscopic biopsy specimens was consistent with well differentiated NET expressing both Synaptophysin and Chromogranin A. Fine-needle biopsy of a liver nodule was consistent with well differ-

entiated NET metastasis. Plasma levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within the normal range. Plasma levels of Chromogranin A (CgA) and Neuron Specific Enolase (NSE) were within the normal range.

An echocardiogram excluded specific heart valve damages as well as other cardiac disturbances. Clinical staging was concluded with a [68Ga-DOTA,1-Nal3]-octreotide (68Ga-DOTANOC) PET/CT which demonstrated two foci of intestinal hypercaptation and at least six hypercaptating hepatic lesions; no evidence of further distant metastases was present.

The patient came to our observation in September 2010 to evaluate the indication to surgical resection of the primary and of the liver metastases. A new Gd-EOB-DTPA-enhanced MRI was planned to define the number and the location of LM, the tumour-vessels relationship, the pattern of the hepatic vasculature and the presence of anatomical variations; the exam revealed at least 20 bilobar LM; the largest nodules were located in segments S6 and S7 and measured 23 and 22 mm in diameter, respectively; a small hemangioma was evident in S7. Simultaneous right hemicolectomy and liver resection plus RFTA was planned.

A midline laparotomy was initially performed. Examination of the peritoneal cavity did not show further neoplastic sites. An accurate bimanual and echographic exploration of the liver was accomplished and the operative strategy for the LM was defined on the basis of the preoperative imaging and of the intraoperative ultrasonography (IOUS) findings, according to the criteria for tumour-vessel relationship described by Torzilli et al<sup>5,6</sup>; the IOUS examination revealed 4 LM in S2, 2 LM in S4, 15 LM in S5, 5 LM in S6, 5 LM and one hemangioma in S7, 1 LM in S8, respectively; one LM in S7 was in contact with the portal vein branch

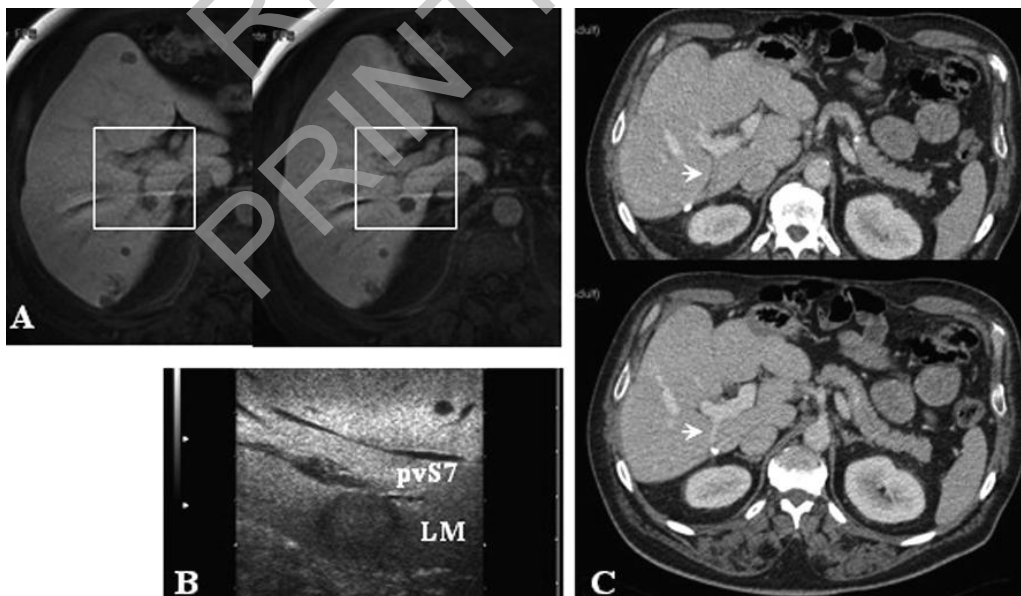


Fig. 1: The preoperative magnetic resonance imaging (A) shows a liver metastasis in contact with the portal vein branch for segment S7 (within the square). The IOUS (B) shows that the metastasis (LM) is in contact with the portal branch for segment S7 (pvS7), without evidence of vascular infiltration; the nodule was consequently detached from the vessel, which was spared. The postoperative CT scan (C) shows that the portal branch for segment S7 is patent (arrow).

for S7. Once the simultaneous resectability of the LM was established, the right hemicolectomy was performed first. Liver surgery consisted of 3 wedge resections (WR) and one RFTA in S2, 2 WRs in S4, subsegmentectomy plus 3 WRs and one RFTA in S5, 2 WRs in S6, 5 WRs in S7 and one RFTA in S8; the LM in contact with the portal vein branch for segment S7 was detached from the vessel, which was spared. Transection of the liver parenchyma was performed using intermittent hepatic pedicle clamping (IHPC) consisting of 10 minutes of ischemia followed by at least 10 minutes of reperfusion; the total duration of IHPC was 92 minutes. The dissection plane was accurately monitored with ultrasonography. RFTA was used for 3 subcentimetric, deeply located nodules. At the end of the hepatic resection, the liver was re-examined with IOUS to be certain of complete neoplasm excision and to confirm the adequate blood supply to the remnant liver. Argon beam coagulation was applied to all resected liver surfaces to achieve hemostasis and also to improve the radicality of the resection "sterilizing" another 1 to 2 mm of the remnant hepatic tissue. The length of the surgery was 680 min. Intraoperative blood transfusions were not required. The immediate postoperative course was regular.

Gross examination of the resected specimens revealed a bulging mass 25 mm in diameter in the terminal ileum and a second bulging mass 15 mm in diameter in the colic side of the ileocecal valve, respectively, and several small, whitish nodules in the resected liver parenchyma, the largest measuring 20 mm. Histopathological examination showed well differentiated (G1) NET in the terminal ileum infiltrating the perivisceral adipose tissue, well differentiated (G1) NET in the colic side of the ileocecal valve infiltrating the tunica muscularis propria, one mesenteric nodal micrometastasis, and foci of peritumoral vascular invasion; hepatic nodules were consistent with well differentiated (G1) NET metastases, along with a small hemangioma in the specimen of a wedge resection in S7.

In 7 out of 15 resected specimen the liver metastases focally reached the resection margin (R1). All the described lesions showed a positive reaction to Synaptophysin (Ventana, clone MRQ-40) and Chromogranin A (Ventana, clone LK2H10). Ki67 proliferative index (Ventana, clone 30-9) was 0,8% and 0,7% in the NET of the ileum and of the colic side of the ileocecal valve, respectively, and between 0,3% and 5,0% in the LM. According to the 2010 World Health Organization (WHO) Classification of Tumors of the Digestive System <sup>6</sup>, the final diagnosis was of well differentiated (G1) NET of the ileum and of the colic side of the ileocecal valve, with nodal and liver metastases.

The patient was discharged without complications 15 days after surgery. Nine days later he was admitted in the referring oncologic unit for persistent fever and asthenia; right basal pneumonia was diagnosed, the patient received antibiotics and supportive therapies and was dis-

charged 10 days later. A medical regimen of octreotide long-acting repeatable (LAR) was started. Forty-eight months later he is in good health, without evidence of residual or recurrent disease.

## Discussion

Although NET neoplasms of the gastrointestinal tract are usually considered quite rare, recent epidemiologic studies suggest that their incidence has significantly increased over the last decades in the United States and Europe <sup>1,2,8</sup>. NETs of the midgut develop LM in 50-75% of the cases <sup>2</sup>, with LM representing the most critical prognostic factor <sup>9</sup>. The availability of more advanced imaging techniques either for the primary or for the metastatic disease and the continuing development of more adequate treatment strategies has led to a substantial improvement of the long term survival of metastatic NETs of the midgut, from the 13-54% 5-year survival of the historical series to the 56-83% 5-year overall survival of more recent reports <sup>8</sup>.

Even though various treatment strategies have been recently proposed for NETs liver metastases, surgery still represents the only chance for potential cure <sup>8</sup>. Resection of the primary tumour along with locoregional lymph node metastases and LM is usually thought to have a favourable impact on the long-term prognosis and quality of life. Although the benefits of surgical resection of liver metastases have been questioned by recent systematic reviews <sup>10</sup>, several non-randomised series substantiate the advantages of liver surgery, from resection to transplantation, either potentially curative or cytoreductive, compared with alternative treatments <sup>9</sup>. The overall survival after LR is 46-86% at 5 years and 35-79% at 10 years, even though complete resections are reported in only 20-57% and local recurrence develop in up to 94% within 5 years <sup>8</sup>. Definite candidates for LR include grade 1 or 2 tumours without evidence of unresectable extrahepatic disease, where potentially curative resection can be obtained leaving an adequate volume of hepatic parenchyma with uncompromised vascularisation and biliary drainage, whatever the extension of the resection margin; LR with microscopically positive margins (R1) is not considered a negative prognostic factor, even though discordant results have been reported <sup>8,10</sup>. At present, LM of grade 3 NETs are usually not considered for surgery, since they are often multifocal or bilobar and high recurrence rates are reported after LR. Cytoreductive LR has also been advocated for selected patients where more than 90% of hepatic disease can be resected or ablated, with the aim of reducing the secretion of hormones and the related symptoms and also to ameliorate the long-term prognosis <sup>1,8</sup>. Intraoperative locally ablative treatments may integrate LR in selected patients to achieve potentially curative surgery.

Different therapies are presently available for metastatic NETs of the midgut, which in selected cases might contribute to a favourable outcome<sup>1</sup>. Somatostatin analogues octreotide and lanreotide are effectively used to palliate the carcinoid syndrome and to inhibit tumour growth<sup>1</sup>; systemic treatments include also interferon-alfa, inhibitors of the mammalian target of rapamycin, such as Everolimus, angiogenesis inhibitors such as Bevacizumab and Sunitinib, cytotoxic chemotherapeutic agents, radio-labeled somatostatin analogues<sup>1,8</sup>. Different angiographic liver-directed therapies are also available for patients with unresectable NETs LM, including transarterial embolisation (TAE), transarterial chemoembolisation (TACE), and selective internal radiotherapy (SIRT) with yttrium-90 (<sup>90</sup>Y)-microspheres<sup>8</sup>. Systemic therapies as well as angiographic liver-directed treatments, alone or in combination, have been shown to be potentially effective to downstage NETs LM, which might result in enhanced tumour resectability in selected cases.

In candidates to simultaneous intestinal and potentially curative liver resection, patient selection should be very accurate, based on general status and operative risk<sup>4</sup>. A precise planning of the LR and of the future liver remnant is of paramount importance to avoid severe post-operative complications. In selected cases, intraoperative RFTA or staged procedures allow potentially radical resection with low mortality rates<sup>9</sup>. It should be noted however that LM are often far more numerous than suggested by preoperative imaging. In a small series of 11 patients undergoing right or left hepatectomy for metastatic NETs, Elias et al found that less than 50% of the LM were detected preoperatively: the accuracy was 24% for somatostatin receptor scintigraphy, 38% for computed tomography and US, and 49% for magnetic resonance imaging<sup>11</sup>. For this reason extensive preoperative work-up should be routinely indicated, especially in case of multiple LM. At the time of surgical exploration, IOUS should be routinely used to define the final strategy of the LR, since it is useful to detect millimetric LM missed at preoperative imaging, to evaluate the tumour-vessels relationship, and to guide hepatic resection and also RFTA, when indicated.

Major hepatectomies seem to represent a key prognostic factor in the perioperative clinical outcome of simultaneous colorectal and liver resections<sup>4</sup>. We thereby believe that conservative IOUS-guided liver surgery should be taken into account whenever possible for patients with multiple bilobar LM, also considering that liver metastases may recur and further liver resections can be selectively indicated. The systematic use of intraoperative ultrasonography has been demonstrated to decrease the need for major hepatectomy both for primary and metastatic liver tumours without prejudice on oncological and surgical radicality<sup>5,6</sup>. Torzilli et al have recently reaffirmed that the extensive use of IOUS guidance during liver surgery permits to minimize the resection margins, to avoid the need for strict anatomic approach-

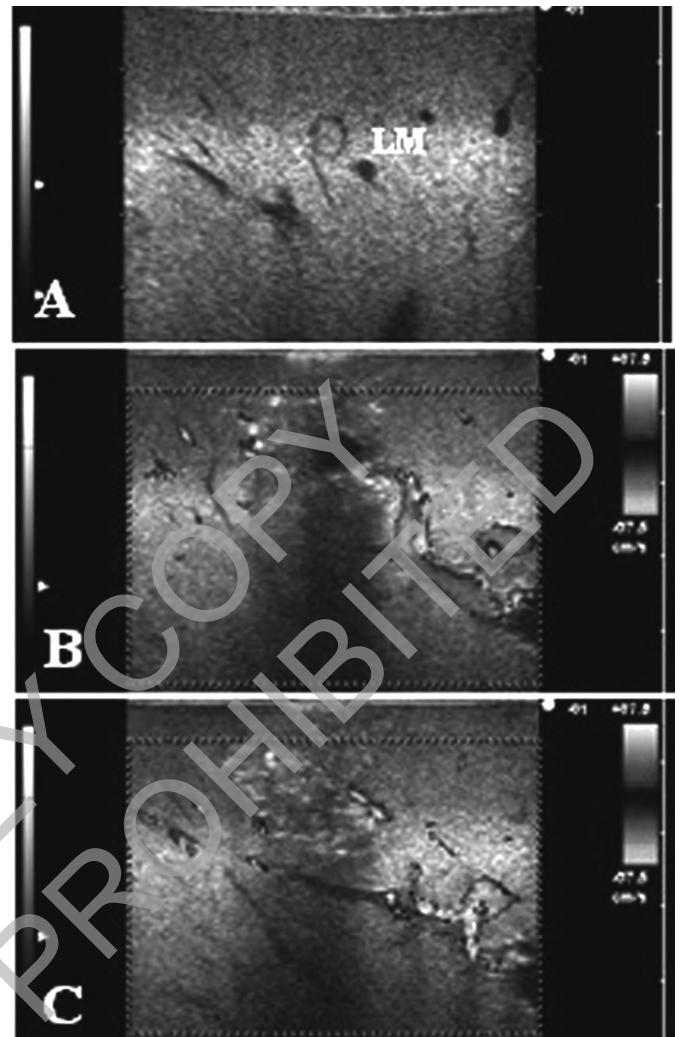


Fig. 2: The IOUS shows a subcentimetric liver metastasis (LM) missed at preoperative imaging (A), treated with intraoperative echo-guided RFTA. After the procedure the liver metastasis is necrosed, with adequate blood perfusion of the surrounding liver tissue (B, C).

es and to reduce the rate of major hepatectomies and also of two-stage hepatectomies, without increase of local recurrence rates in the long-term follow-up<sup>5,12</sup>. In our patient extensive ultrasonographic examination at surgical exploration documented the presence of 12 adjunctive LM missed at preoperative imaging; the accuracy of IOUS is somehow validated in this case by the absence of intrahepatic recurrence 48 months from the operation. Moreover, ultrasonographic guidance during hepatectomy permitted to perform a potentially radical but conservative liver resection of multiple bilobar liver metastases, avoiding the risks of major hepatectomy when it is combined with colic resection and also avoiding a two-stage hepatectomy.

In conclusion, simultaneous intestinal and liver resection can be considered in selected patients with intestinal

NETs and multiple bilobar liver metastases. IOUS guided, radical but conservative liver resection should be considered in these cases, to limit the occurrence of severe postoperative complications without prejudice on long-term oncological results.

## Riassunto

I tumori neuroendocrini (NETs) dell'intestino (midgut) sono spesso multifocali ed hanno l'attitudine a dare metastasi ai linfonodi locoregionali ed al fegato. La chirurgia rappresenta attualmente l'unico trattamento ad intento curativo per i NETs dell'intestino con metastasi a distanza, sebbene solo una minoranza di pazienti possa essere di fatto candidata ad un intervento chirurgico ad intento curativo. La strategia chirurgica ottimale nel caso di una neoplasia dell'intestino con metastasi epatiche sincrone resecabili è tuttora controversa, specie nel caso in cui le metastasi epatiche siano multiple e/o coinvolgano multipli segmenti epatici. Sebbene nella maggioranza dei casi si preferisca procedere ad un intervento chirurgico in due tempi, di regola alla resezione intestinale seguita a distanza variabile di tempo dalla resezione epatica, alcuni recenti studi stanno ad indicare che un intervento simultaneo di resezione intestinale ed epatica è possibile in casi selezionati, con risultati clinici paragonabili a quelli descritti per gli interventi chirurgici in due tempi; il notevole vantaggio degli interventi simultanei è tuttavia rappresentato dalla possibilità di eseguire in un unico tempo un intervento potenzialmente radicale evitando una seconda laparotomia.

Riportiamo il caso clinico di un paziente giunto alla nostra osservazione con una doppia neoplasia neuroendocrina dell'ileo terminale e del colon ascendente, rispettivamente, con multiple metastasi epatiche bilobar, sintomatica per la presenza di rush cutanei e diarrea.

Una pancolonscopia aveva evidenziato un NET ben differenziato dell'intestino esprimente Sinaptofisina e Cromogranina A. La biopsia di una delle metastasi epatiche confermava che anche la neoplasia metastatica era ben differenziata. L'imaging preoperatorio escludeva la presenza di metastasi extraepatiche. Il paziente veniva pertanto sottoposto ad un intervento chirurgico simultaneo di emicolectomia destra e resezione epatica ecoguidata "radicale ma conservativa"; nel complesso 32 metastasi epatiche bilobar venivano individuate e resecate in maniera radicale mediante l'impiego dell'ecografia intraoperatoria; un nodulo subcentimetrico posto nella profondità del parenchima epatico veniva sottoposto a termocoagulazione con radiofrequenza. La resezione epatica veniva condotta a termine con clampaggio intermittente dell'ilo epatico, della durata complessiva di 92 minuti. La durata complessiva dell'intervento chirurgico era di 680 minuti. Non si erano tuttavia rese necessarie emotrasfusioni intraoperatorie. Il paziente veniva dimesso in 15a giornata p.o. senza complicanze; il successivo decorso era

complicato dalla comparsa, in 24a giornata postoperatoria, di una polmonite basale destra, regredita con terapia antibiotica. Successivamente il paziente veniva sottoposto a terapia con octreotide acetato (Sandostatina LAR). A distanza di 48 mesi dall'intervento chirurgico il paziente è in eccellenti condizioni cliniche e senza evidenza di recidive neoplastiche.

Il caso descritto dimostra che, in casi selezionati di tumore neuroendocrino intestinale con metastasi limitate al fegato, una resezione simultanea intestinale ed epatica è possibile anche in presenza di metastasi epatiche multiple bilobar, a patto di eseguire una resezione epatica conservativa eco-guidata, ovvero con l'obiettivo di massimizzare il risparmio di parenchima epatico sano. Tale strategia chirurgica può consentire di ottenere risultati oncologici soddisfacenti anche a distanza.

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