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REVIEW

Current Status of Interventional Radiology in the Management of Gastro-Entero-Pancreatic Neuroendocrine Tumours (GEP-NETs)

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Abstract Within the group of Gastro-Entero-Pancreatic Neuroendocrine tumours (GEP-NETs), several heterogeneous malignancies are included with a variety of clinical manifestations and imaging characteristics. Often these cases are inoperable and minimal invasive treatment offered by image-guided procedures appears to be the only option. Interventional radiology offers a valid solution in the management of primary and metastatic GEP-NETs. The purpose of this review article is to describe the current status of the role of Interventional Radiology in the management of GEP-NETs.

Keywords Interventional oncology · Embolization · Ablation · Neuroendocrine tumours

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Introduction

Gastro-Entero-Pancreatic Neuroendocrine tumours (GEP-NETs) are a vast and heterogeneous group of neoplasms that may involve organs of the foregut (oesophagus, stomach, proximal duodenum, liver, pancreas), the midgut (distal duodenum, ileum, jejunum, ascending colon and proximal 2/3 of the transverse colon) and the hindgut (distal 1/3 of the transverse colon, descending and sigmoid colon and rectum). Their incidence is raised from 1.09/100.000 to 5.25/100.000 in the last 30 years; the highest prevalence is in the fourth to sixth decades of life [1]. GEP-NETs may appear either as a single sporadic lesion or in the context of a more generalized genetic endocrine disorder such as Multiple Endocrine Neoplasia (MEN) type 1, Von Hippel–Lindau (VHL) disease, Neurofibromatosis (NF) type 1 or tuberous sclerosis [2].

Their clinical presentation is related to the secretion or not of "active peptides" that act distantly as hormones. The most common GEP-NETs are the carcinoids (apudomas that may be located in the small or large bowel with mainly serotonin secretion) that are usually presented with diarrhoea and heart disease. Other GEP-NETs are the insulinomas (islets of Langerhans cells of the pancreas with insulin secretion) that are presented with severe hypoglicemia, the gastrinomas (mainly pancreatic location and gastrin secretion) that are presented with acid hypersecretion and duodenal ulceration and the glucagonomas (alpha cells of the pancreas and glucagon secretion) that are presented with diabetes and necrolytic migratory erythema. More rare GEP-NETs are the Vasoactive Intestinal Peptide tumours (or VIPomas, known as Verner Morrison syndrome) and the somatostatinomas that appear with a frequency of 1/10,000,000 cases) [3]. The most frequent GEP-NETs and their clinical presentation characteristics

Table 1 The most common GEP-NETs and their clinical presentation characteristics

Type of NET	Clinical presentation	Special exams (other than CT or MRI)
Neuroendocrine tumours of the midgut	Carcinoid syndrome characterized by flushing, diarrhoea, bronchoconstriction and cardiac abnormalities	CT/MR enterography, octeotride-scan, DOTATOC-PET and colonoscopy
Gastrinoma	Typical peptic ulcer disease and severe diarrhoea	Endoscopic ultrasound, octeotride-scan or DOTATOC-PET (only for patients with normal gastrin blood level)
Insulinoma	Episodes of Hypoglycaemia and weight loss	Endoscopic ultrasound
VIPoma	Watery diarrhoea, hypokalaemia, achlorhydria (Verner Morrison Syndrome)	Octeotride-scan, DOTATOC-PET
Glucagonoma	Diabetes and Necrolytic migratory erythema	Octeotride-scan, DOTATOC-PET
Non-functioning NET, with or without liver metastases	Mass symptoms such as liver failure, obstruction (bowel and biliary), ischaemia and bleeding	Octeotride-scan, DOTATOC-PET

are shown in Table 1. GEP-NETs metastasize to the liver with a frequency between 25 and 90 % [3] (Table 2).

Accurate grading and staging permits the evaluation of clinical, pathological and prognostic features. GEP-NETs are classified according to the World Health Organization (WHO) classification, the European Neuroendocrine Tumor Society (ENETS) grading system and the Union for International Cancer Control (UICC) system. In 2010, the latest version of the WHO classification was published amending the two previously published versions of 2000 and 2004 that distinguished between well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). The GEP-NETs are now separated according to the mitotic activity found in 10 high-power fields (HPF), into G1: <2/10 HPF, G2: 2–10/10 HPF and G3: >10 HPF and the proliferative activity as expressed by the antigen KI-67 as low (<2 %), intermediate (3–20 %) and high (>20 %) [4, 5].

The American Joint Committee on Cancer (AJCC), in the 7th edition AJCC Cancer Staging Manual, and the European Neuroendocrine Tumor Society (ENETS) have published two systems of TNM staging manual; there are some differences between these systems, particularly for primary tumours of the pancreas and the appendix, but there is also a considerable overlap. Additionally, the staging criteria for both systems rely predominantly on the size of the tumour and the extent of invasion into similar landmarks as used for the staging of non-neuroendocrine carcinomas of the same sites [6].

Grading and TNM directly correlate with patients' survival. Localized, regional and metastatic disease is linked to a progressively lower survival rate. In addition, the primary tumour site, the histological type, the age, sex and race appear to influence overall survival [7].

Therapeutic approaches may either involve total surgical excision where applicable or local and symptomatic control in the cases of advanced and metastatic disease [8]. Management is specific for each type of tumour and is described in the international guidelines of the National Comprehensive Cancer Network (NCCN) with the latest version published in 2014 (NCCN 2.2014 guidelines version). Surgery is applied to approximately 10 % of the cases; the remaining of the cases are considered inoperable either due to the extensive location of the primary tumour with involvement of surrounding anatomical structures or due to the presence of extensive metastatic disease. Surgical excision of the primary GEP-NET may be curative in 75–98 % of patients [9]. Debulking resection may be also offered for primary locally advanced lesions. However, the morbidity is high and complications such as bleeding, fistula formation or tumour seeding may occur. Laparoscopic treatment of pancreatic GEP-NETs demonstrated to be correlated to slightly lower morbidity than open resection; the main advantage was the reduction of intra-abdominal collections and pleural effusion formation, postoperative fever and infection, postoperative haemorrhage, necrotizing pancreatitis and duration of hospitalization [10].

Many alternatives to surgery have been proposed for unresectable GEP-NETs with or without metastatic disease aiming to improve the median progression-free survival and to control symptoms in functional disease. Of particular interest are biological therapies (everolimus, sunitinib), Peptide Receptor Radio nucleotide Therapy (PRRT) and cytotoxic chemotherapy. However, chemotherapy does not appear to be effective for the reduction of the tumour burden whereas somatostatine analogues like octreotide do not appear to be effective for the control of symptoms [8].

Image-guided treatment in the form of percutaneous embolization; chemoembolization, trans-arterial radioembolization (TARE) or thermal ablative treatment has also offered a valid option in a variety of cases of patients with GEP-NETs and unresectable primary or metastatic disease. The role of palliation is to offer a good quality of life (QoL) and to preserve the patient as symptom-free for as long as possible [11].

Table 2 Overall survival as described in the literature post-ablation end embolization of metastatic lesions

Article	Technique	Patients	1 year OS	2 years OS	3 years OS	5 years OS	Median OS	Notes
Embolic								
Gupta et al. [44]	TAE	32	nd	nd	nd	nd	33.8 months	–
	TACE	22	nd	nd	nd	nd		
Strosberg et al. [45]	TAE	84	nd	nd	nd	45 %	36 months	–
Ruutiainen et al. [51]	TAE	23	68	nd	46	33	nd	–
	TACE	44	86	nd	67	50	nd	
Pitt et al. [52]	TAE	51	70	54	nd	13	25.7 months	–
	TACE	49	69	52	nd	13	25.5 months	
Maire et al. [53]	TAE	14	100	100	nd	nd	nd	–
	TACE	12	91	80	nd	nd	nd	
De Baere et al. [55]	DEBs-TACE	18	100	nd	nd	nd	nd	–
Kennedy et al. [59]	Y90-Radioembolization	148	nd	nd	nd	nd	70 months	–
King et al. [60]	Y90-Radioembolization	34	nd	nd	nd	nd	27.6 months (mean)	–
Cao et al. [61]	Y90-Radioembolization	58	86	58	47	nd	36 months	–
Kalinowski et al. [63]	Y90-Radioembolization	9	100	57	57	nd	nd	–
Limouris et al. [68]	In-111-DTPA-Phe^{1}-Octreotide	17	nd	nd	nd	nd	32 months	–
Ablative								
Akyildiz et al. [70]	VLS-RFA	89	nd	nd	nd	57	72 months	–
Mazzaglia et al. [71]	VLS-RFA	63	91	77	nd	48	3.9 years	Not only neuroendocrine
Martin et al. [72]	MW	11	nd	nd	nd	nd	18 months	–
Shapiro et al. [74]	Cryoablation	5	60	40	nd	nd	nd	–
Bilchik et al. [76]	Cryoablation	19	nd	nd	nd	nd	49 months	–

OS overall survival, *TAE* trans-arterial embolization, *TACE* trans-arterial chemioembolization, *DEBs-TACE* drug-eluting beads TACE, *VLS-RFA* videolaparoscopic radiofrequency ablation, *MW* microwaves, *nd* not defined

In the multidisciplinary tumour board, the choice of which image-guided procedure to use depends on the local expertise and availability; there are no randomized clinical trials comparing the efficacy loco-regional therapies and palliative liver surgery [12, 13].

The purpose of this review article is to describe the current status on the use of image-guided treatment in the management of Gastro-Entero-Pancreatic GEP-NETs.

Primary GEP-NETS

Detection and Imaging Characteristics

The detection of primary GEP-NETs usually requires the multimodality approach according to recent published guidelines [14], combining Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and somatostatin receptor scintigraphy (SSRS). Endoscopic ultrasound (EUS) is also utilized in case of suspected GEP-NETs, while Gallium-68 Positron Emission Tomography (PET)/CT (DOTATOC, DOTATATE) is recommended for detection of unknown primaries. In their majority, GEP-NETs are small, thus the sensitivity is rather low for primary detection, with primary tumour revealed through the presence of mesenteric disease, enlarged lymph nodes and liver metastases. CT or MR Enteroclysis, allowing for multiplanar reformats certainly increase reported sensitivity and specificity for small bowel NETs.

Functional, usually smaller, pancreatic NETs demonstrate avid contrast enhancement during arterial phase CT/MRI. Combined with EUS, multidetector CT may reach 100 % sensitivity [15]. Larger, malignant, non-functioning pancreatic tumours demonstrate necrosis, calcification and invasion of adjacent structures. Pancreatic NETs show high signal intensity on T2 weighted and low signal intensity on T1-weighted sequences. On post-intravenous contrast administration, MR images lesions may be isointense to surrounding pancreatic parenchyma.

Imaging plays a key role also during follow-up. The ENETS recommends the use of all available imaging techniques. However, the technique of choice depends on the local expertise; CT or MR is recognized as the gold standard during follow-up, allowing the evaluation of progression and/or spread of the tumour. Also octreoscan is widely used, however, DOTATOC-PET demonstrated high diagnostic accuracy and probably is going to replace octreoscan in the future [16]. Chromogranin A (CgA) samples are useful for both diagnosis and follow-up with a sensitivity and specificity of 75.3 and 84.2 %, respectively [17]. The CgA levels at diagnosis are also linked with the overall survival of the patient [18].

Image-guided treatment

The first-line treatment for primary GEP-NETs is surgical resection according to the International Guidelines [12]. However, image-guided interventions play a significant role in complicated cases or in cases that cannot undergo surgical resection. The percutaneous treatment of primary GEP-NETs either with embolization or thermal ablation is described by several authors in the literature [12, 13, 19].

Embolization

Percutaneous embolization is mainly used for the control of inoperable functional insulinomas or gastrinomas. Both appear to be suitable for treatment with embolization, as they are nourished by a rich blood supply, receiving about 10–15 % of the pancreatic blood flow [20]. A blush of contrast is visible in the angiographic pictures. The lesion is usually receiving supply from the dorsal pancreatic artery, however, other arteries like branches of the colic artery may also supply the area.

The first reported case was described by Moore et al., where embolization was performed with microfibrillar collagen, in a young patient with recurrent insulinoma 1 year after surgical resection [21]. The authors reported control in the blood glucose levels in the 11 months follow-up. Uflacker et al., in 1992, reported two other cases with insulinoma, one in a patient who denied surgery and the other who underwent emergency embolization. PVA particles (150–300 nm) were used in both cases [22]. Rott et al. presented the case of an 84-year-old woman with a symptomatic insulinoma, who refused surgery and underwent successful embolization with 300–500 nm trisacryl gelatin microspheres [23]. Peppa et al. presented a 30-year-old patient with MEN1 and recurrent insulinoma with severe hypoglycaemic episodes who could not be surgically treated due to the adherence of the tumour to large blood vessels and to prior multiple surgical operations. He was treated by repeated embolization using non-spherical polyvinyl alcohol particles (100–300 nm), resulting in shrinkage of the tumour, decrease of the severity and the frequency of the hypoglycaemic episodes, and improvement of the quality of life [20]. Embolization may also be used in some cases for the reduction of blood supply prior to surgical resection. Ben-Ishay et al. [24] described preoperative embolization of an extremely hypervascular NET located at the head of the pancreas, which was successfully embolized and then excised, and Whipple operation followed.

A relevant technical question, regarding the embolization of pancreatic NETs, is what might be the most suitable embolic material. Considering the size, there are no data regarding the precise diameter of the arteries that supply the NETs, so the choice of particle size is purely empirical.

Most of the operators used microparticles (100–300 nm) and there are no reports in the literature of failed embolization. Particles are usually used because an acute ischaemic effect is desirable. Potential complications of pancreatic NET embolization include exudative pancreatitis and a form of type 2 diabetes in insulinomas [23].

Thermal ablations

Radiofrequency ablation of the pancreas is nowadays a feasible method of tumour control [25]. It was initially applied to animal models. Goldberg et al. studied the safety and efficacy of RFA in experimental models and concluded that RFA can be used in small neuroendocrine tumours [26]. Date et al. [27] demonstrated the safety and efficacy of RFA in the normal pancreas of a porcine model. Matsui et al. [28] published the first clinical study of 20 patients in the year 2000. In the literature, the use of this technique for the treatment of NETs was described in just few cases and was mainly indicated in patients with functional tumours, not candidate to surgery and where the medical therapy failed.

The first case report was published in 2009 by Limmera et al. and describes the case of CT-guided RFA of an insulinoma localized at the tail of the pancreas in an elderly patient with high surgical risk and where the medical therapy was not satisfactory [29]. After the procedure, the patient was free of symptoms and no complications occurred. Akhlaghpoor et al. described a case of a 48-year-old man with a functional insulinoma of the tail of the pancreas that after surgery and medical therapy continued to be symptomatic due to the presence of residual functional tumour [30]. The patient underwent a CT Fluoroscopy–guided transcaval radiofrequency ablation, which was clinically successful and no complication occurred. Pei-Hong et al. reported a case of a percutaneous radiofrequency ablation approach through the spleen for a pancreatic gastrinoma [31]. Hlavsa et al. presented the first case report of a patient with locally advanced pancreatic neuroendocrine tumour successfully treated with intraoperative RFA [32].

However, due to the delicate structure of the organ and the central location, pancreatic RFA may lead to severe complication [29]. Rates of overall complications, in patients with locally advanced pancreatic tumours, ranged from 10 to 43 % [33]. The types of complication reported varied widely and included pancreatic fistulae, portal vein thrombosis, gastrointestinal bleeding, acute pancreatitis, pneumonia, peritoneal cavity abscess, acute renal failure, transient ascites, hepatic insufficiency, pseudo-membrane colitis, haemoperitoneum, abdominal fluid collection, gastric bypass fistula, gastric ulcer, choledocholithiasis and sepsis [33]. These complications were reported after the treatment of all types of pancreatic tumours and not specifically NETs.

High Intensity Focused Ultrasound (HIFU) is another innovative ablation technique that has been recently introduced for the treatment of non-resectable tumours. HIFU achieves ablation by way of focused US energy from an external source that is targeted within the body, resulting in thermally induced necrosis. Acoustic energy is absorbed and delivering high-acoustic intensity to the tissue generates heat. Because it is focused, the acoustic intensity is high only within the focal region; however, outside the focal region, the intensity is substantially lower, thus minimizing the risk of unintended injury to the surrounding structures. Orgera et al. reported the treatment of two cases of pancreatic insulinomas treated with HIFU in two inoperable young female patients [9]. Both suffered from episodes of severe nightly hypoglycaemia that was not efficiently controlled by medical treatment. After HIFU ablation, local disease control and symptom relief were achieved without complications. Chen et al. described the treatment of an unresectable giant pancreatic neuroendocrine tumour successfully treated with HIFU with no significant complication detected [34].

Irreversible electroporation (IRE or non-thermal irreversible electroporation) is yet another novel technique of tissue ablation that uses short pulses of high voltage and leads to cellular death. IRE demonstrated to be a feasible technique for the treatment of pancreatic lesions in the swine model; recent studies demonstrated the feasibility of this novel approach on pancreatic masses, mainly an intraoperative setting [35]. However, IRE is technically demanding and may lead to significant complication and the best results are offered for the treatment of metastatic liver disease whereas there is no experience yet with primary GEP-NETs [36].

Metastatic Lesions

Liver is the predominant site for GEP-NET metastases. Dissemination from a primary GEP-NET to the liver parenchyma may occur in 25–90 %, and it is the major factor altering both quality of life and prognosis regardless the primary site considering that patients with metastatic GEP-NETs appear to show worst prognosis compared to patients with only primary tumour localization [37–42].

Imaging Characteristics

Hepatic metastases and the degree of liver involvement are considered the major prognostic factors for survival in patients with neuroendocrine tumours. GEP-NET-derived liver metastases are in their majority hypervascular,

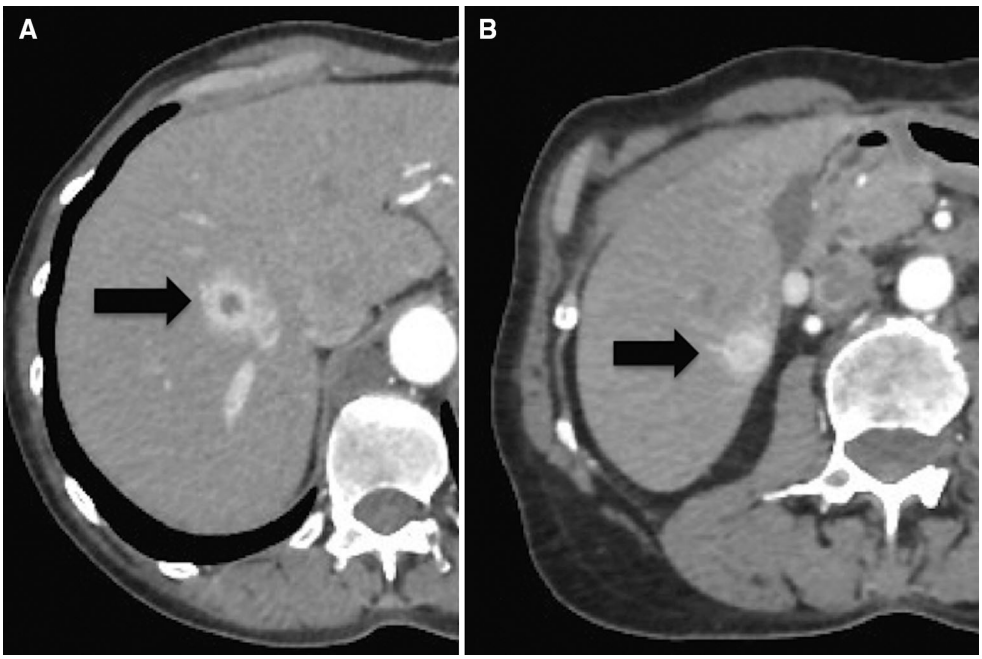

Fig. 1 CT scan in arterial phase of a 61-year-old female with carcinoid located in the small bowel. The primary was removed surgically, however, the patient remained symptomatic due to the presence of two metastatic lesions in the segments VII (**A**) and V (**B**) of the liver (*arrows*)

demonstrating avid contrast uptake during arterial phase imaging regardless of the used imaging technique (CT or MRI). However, liver metastases may also present with atypical hypovascular or delayed enhancement, in a reported 16 %, and a peripheral enhancement with progressive fill-in, mimicking haemangiomas, in 11 %, respectively [43]. It is also important to keep in mind that chemotherapy may alter liver metastases vascularity, lowering the performance of hepatic arterial phase imaging.

The combination of arterial phase and fat-suppressed fast spin-echo T2-weighted images depicts at least 80 % of hepatic metastases derived from neuroendocrine tumours, rendering these cardinal sequences for their detection.

Image-Guided Treatment

The choice of the type of treatment depends on the local expertise, the disease location and extension (number and size of lesions). Minimal invasive treatment may be applied to both functional and non-functional tumours. Loco-regional therapies may also be used in combination with somatostatin analogues (SSA), particularly in functional GEP-NETs. If bulky disease is present, loco-regional therapy is indicated as an early measure even in the case of non-functional tumours, and may be useful for down-staging. In patients with functioning tumours, loco-regional therapies may be considered in the presence of extrahepatic disease if liver is the major site of the disease. If extrahepatic tumour load is higher than hepatic tumour burden, and if pancreas is the primary tumour site, systemic medical therapies or peptide receptor radionuclide therapy (PRRT) may be combined to the loco-regional approach [13]. Patients with G2 disease and diffuse liver involvement may be treated with SSA/Interferon-alfa, or chemotherapy, molecular-targeted therapy (sunitinib or everolimus), PRRT or TACE/TAE depending on primary tumour site and the individual conditions. In highly selected candidates with diffuse metastases, liver transplantation may be also an option [13].

Embolization

Embolization techniques may be used to treat liver metastases in patients where surgery is not feasible regardless of the origin of the primary tumour. These techniques appear to be effective in the control of symptoms and tumour growth and result in significant decrease in biochemical tumour activity [13].

Embolization is based on the principle that the lesions are hypervascular and therefore may be visible in the angiographic pictures (Fig. 1). Trans-arterial Embolization (TAE) may be performed with a large variety of embolizing materials like polyvinyl alcohol particles, gelfoam and microspheres aiming for tumour ischaemia [44, 45]. Embolization therapies can be subdivided in various sessions, according to the extension of the lesion and the tumour response, and may be repeated when there is progression of disease. In general, when there is an

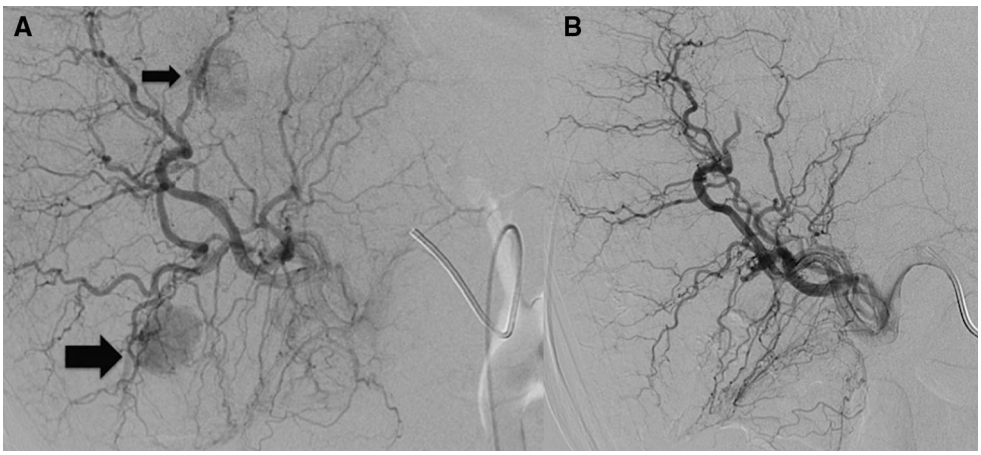

Fig. 2 Selective angiogram from the right hepatic artery confirmed the presence of two hypervascular lesions (**A**, *arrows*). Embolization of the lesions with microparticles (75 micron) was performed; no contrast blush is further detected in the post-embolization angiogram (**B**)

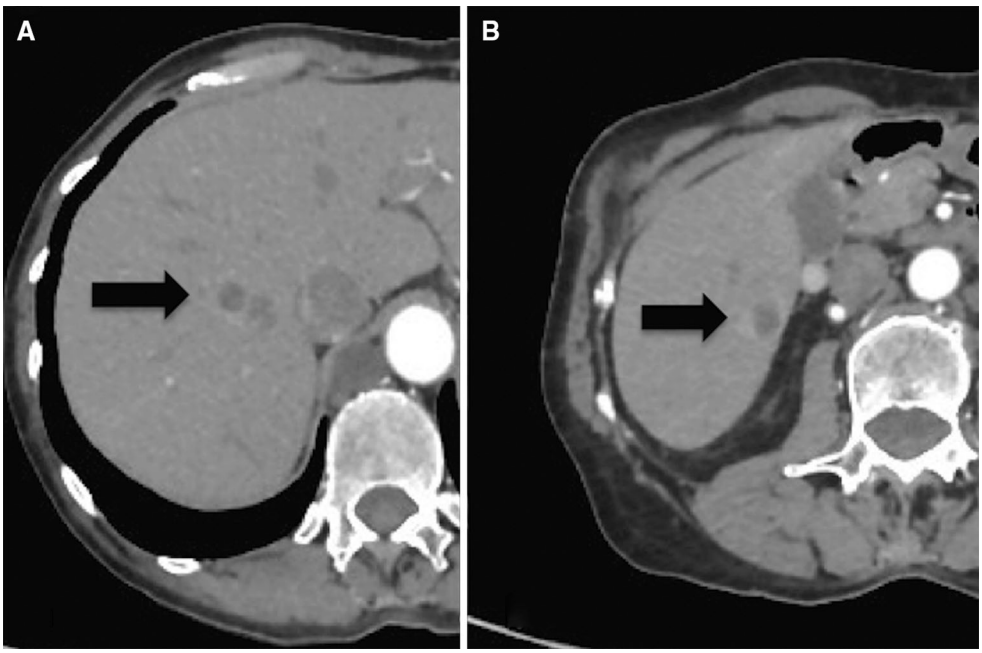

Fig. 3 CT scan in arterial phase at 3 weeks post-embolization confirmed lack of enhancement of the previously treated lesions. The patient's symptoms were controlled at this stage

involvement of more than 50 % of the liver parenchyma, embolization needs to be performed as a staged procedure to reduce cytotoxic effects [46, 47]. Other factors, like the requirement for urgent treatment or the presence of additional extra hepatic metastases are predictors of shorter survival after embolization of hepatic neuroendocrine metastases [46]. In addition, octreotide may be injected subcutaneously before TAE as prophylaxis against a potential exacerbation of a hormonal crisis [44]. An increase of angiogenetic factors was demonstrated after TAE in GEP-NET liver metastasis [48]. It is supposed that these factors affect the success of TAE; in fact, after TAE, lesions do not show a complete necrosis, and the development of new peripheral neo-vessels was demonstrated [49]. The association of TAE with new anti-angiogenetic drugs (as sunitinib) showed promising results in liver metastasis treatment [50] (Figs. 2, 3, 4).

Embolization may also be combined with drug delivery in the case of Trans-arterial Chemoembolization (TACE), most commonly with doxorubicin, streptozotocin, cisplatin, mitomycin C or gemcitabine that may be injected in the arterial tree and then embolization with conventional material may follow or that can be delivered in the form of drug-eluting beads. The advantage over systemic delivery is the higher drug concentration in hepatic circulation with lower systemic side effects.

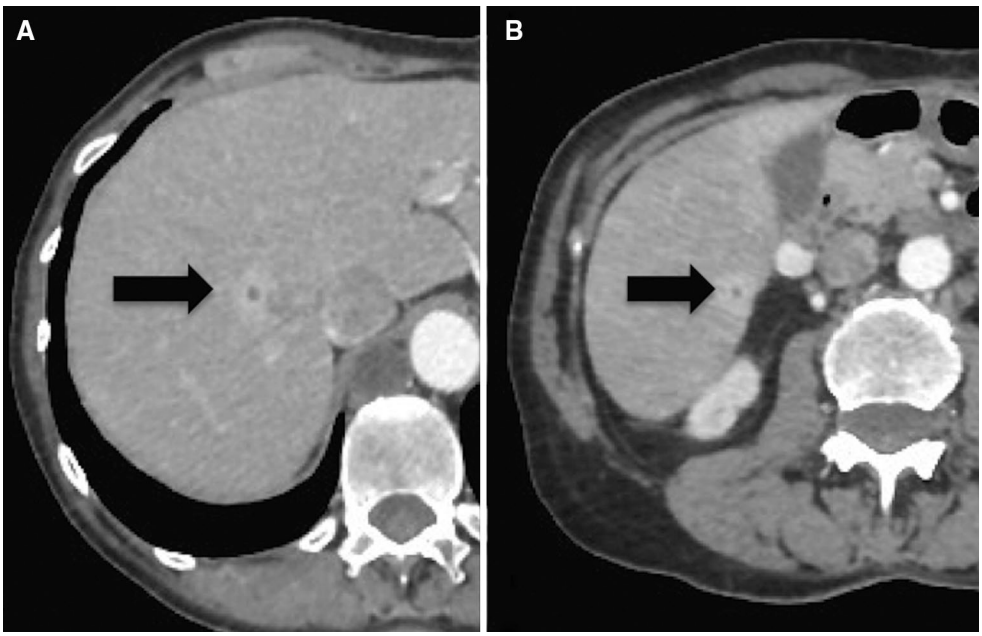

Fig. 4 CT scan in arterial phase at 6 months post-embolization shows minor rim enhancement of the lesions that, however, appear significantly smaller. The patient's symptoms were still controlled at this follow-up scan

The effectiveness of TACE over TAE is still debatable for hepatic neuroendocrine metastases. The retrospective study of Ruutiainen et al. which included 67 patients who received either TAE ($n = 23$) with polyvinyl alcohol particles or TACE ($n = 44$) with cisplatin, doxorubicin or mitomycin C, reported a small advantage of TACE regarding rates of freedom from progression at 1, 2 and 3 years, symptom relief and survival rates at 1, 3 and 5 years, however, without statistical significance [51].

The results were not confirmed in the study of Pitt et al. that performed also a retrospective review of 100 patients with hepatic neuroendocrine metastases who underwent either TAE ($n = 51$) or TACE ($n = 49$) and reported that morbidity, mortality, symptom improvement and overall survival are similar between the two groups [52]. The authors used polyvinyl alcohol particles, gelfoam or embospheres for the embolization, and the drugs administered for the TACE were cisplatin, adriamycin and mitomycin C. In addition, the authors performed a significant higher number of procedures in the TACE group (123 TACE vs. 106 TAE; $p < 0.02$).

Maire et al. in a smaller prospective randomized study of 26 patients who underwent TAE ($n = 14$) or TACE ($n = 12$) also reported that progression-free survival and overall survival were similar in the two groups without statistically significant difference [53].

Fiore et al. in another retrospective study of 30 patients with a histologically confirmed NET and liver metastases who underwent either TAE ($n = 17$) or TACE ($n = 13$) reported similar results, with no significant difference in the progression-free survival between the two groups [54]. In addition, patients treated with TAE in this study developed post-embolization syndrome in 41 versus 61 % of the patients who were treated with TACE, suggesting that TAE offers not only similar results to TACE but also a slightly better toxicity profile.

With the use of drug-eluting beads (DEB), the drugs—usually doxorubicin—are released slowly within a time frame of 7–14 days after the embolization. De Baere et al. in a small study of 20 patients used TACE with DEBs (500–700 mum) loaded with doxorubicin and reported a partial response of 80 % at 3 months and 45 % disease control at 15 months with no liver toxicity [55]. Gaur et al. in a similar study of 18 patients used 100–300 and 300–500 μm doxorubicin-eluting beads and reported 65 % of response at intermediate-term follow-up (mean, 445 days; range, 163–1247) [56].

Bhagat et al. [57] in a phase II trial of 13 patients with hepatic metastases from neuroendocrine tumours who underwent DEB-TACE with 100–300 μm beads loaded with ≤100 mg doxorubicin reported a mean of 12 % decrease in tumour size ($p < 0.0003$) and a 56 % decrease in tumour enhancement ($p < 0.0001$) at 1 month post-procedure. However, 54 % of the patients developed bilomas, and 30 % underwent a drainage procedure which was unexpected by the authors and led to forced interruption of the trial. The explanation was mainly based on the potential deposition of chemotherapeutic agents into the peribiliary arterial plexus. The authors observed also that the presence of large (>4 cm) multiple lesions was

protective against the formation of bilomas, which occurred in patients with small (<4 cm) multiple lesions. In addition to the small tumour burden, the smaller bead size may be another predisposing factor for biloma formation due to more profound ischaemic changes, which ultimately affect the peribiliary plexus. Guiu et al. compared DEBs-TACE with TACE both in Hepatocellular Carcinoma (HCC) and GEP-NET liver metastases; DEBs-TACE demonstrated an higher risk (OR: 6.6) of liver or biliary injury than TACE; moreover, biloma and liver infarct were independently correlated with both DEBs-TACE (OR: 9.78) and NET (OR: 8.13), so they suggest to carefully consider this procedure in a non-cirrhotic liver, as well as in NET metastases [58].

Trans-arterial Radio-embolization (TARE) is another embolization technique that allows to apply high radiation doses in a selective area of the liver using microspheres of glass (diameter 20–30 μm) or resin (diameter 20–60 μm) loaded with a radioisotope, conventionally Yttrium-90. There are various studies that analysed the effects of TARE in NET hepatic metastases. Kennedy et al. in a retrospective review of 148 cases, treated with a median radiation dose delivery of 1.14 GBq per session, reported that imaging response to the treatment was stable in 22.7 %, partial in 60.5 %, complete in 2.7 and 4.9 % of patients presented progressive disease [59]. The median survival was 70 months. The range of treatment as described by other authors varies between studies 39 and 66 % [60–63]. Paprottka et al. reported a partial response of only 22.5 %, however, in 97.5 % of patients, the liver lesions appeared either hypovascular or partially necrotic [64]. Rhee et al. reported no significant difference in terms of tumour response and median survival between patients treated with glass or resin microspheres [65]. Saxena et al. have identified three factors associated with a complete/partial response: female gender ($p = 0.040$), well-differentiated tumour ($p < 0.001$) and low hepatic tumour burden ($p = 0.041$) [62]. The control of symptoms varies from 50 to 100 % of cases [60, 66]. The most common complications after Yttrium-90 radio-embolization are fatigue, abdominal pain, nausea and fever [59]. Radiation-induced gastritis, liver dysfunction and pneumonia may also occur. King et al. reported 2 cases of gastritis, 1 of duodenal ulcer and 1 case of liver dysfunction and pneumonia among 34 treated patients [60]. An advantage of TARE over TAE and TACE is that it generally needs no more than one session of treatment and that the majority of patients may be treated on an outpatient basis [59, 67].

Infusion of In-111-DTPA-Phe^1-octreotide after selective catheterization of hepatic arteries allows delivering the labelled octreotide directly to the lesions avoiding drug spread in other organs and especially in the kidneys. Repeated infusions are usually performed achieving stabilization or regression of the disease in up to the 70 % of patients [68]. Also Y-90 and Lu-177 are available to label DOTA and to be used in selective arterial catheterization. The number and the dimension of the lesions to embolize limit the performance and feasibility of this technique.

Thermal Ablative Techniques

Radiofrequency ablation (RFA) for NET hepatic metastases may be performed either percutaneously under Computed Tomography (CT) or Ultrasound (US) guidance or intraoperatively with or without concomitant liver resection. RFA conventionally is adopted for liver lesions smaller than 5 cm in size [69] (moreover other ablative techniques are not considered a suitable single therapy for lesions larger than 5 cm) [13].

The intent of the ablation is not only tumour debulking but also control of hormonal symptoms, and sometimes treatment of several lesions may be required in the same session, particularly in an intraoperative setting.

In a study from Akyildiz et al. 89 patients with metastatic lesions mainly from carcinoid and pancreatic islet cell underwent RFA under laparoscopic guidance; no liver resection was performed [70]. The mean number of treated lesions was 6 ± 1, and the mean tumour size was 3.6 ± 0.2 cm. Symptom control was successful in 97 % of patients 1 week after the procedure, however, perioperative morbidity was 5.6 % due to post-operative haemorrhage, and the 30-day mortality was 1 % due to intra-abdominal sepsis. Median follow-up was 30 ± 3 months with 15 months of disease-free survival. Local liver recurrence occurred in 22 %, new liver lesions occurred in 63 % and extra hepatic metastatic disease occurred in 59 % of the cases. In case of single lesions, repeated RFA was performed in 27 % of the cases, whereas if the recurrence was multifocal, chemoembolization (7 %) was performed. Median disease-free survival was 1.3 years, and the overall survival was 6 years. The effect of RFA in such patients is mainly local control and symptom relief, which is achievable, however, the multifocal lesions may be difficult to be treated with RFA and extensive ablation may lead to generalized sepsis. Mazzaglia et al. in a study of 63 patients reported similar results in terms of local control and symptomatic improvement and also noted a correlation between lesion size and median survival that was less than 3 years for lesions bigger than 3 cm. RFA complications as liver abscess, pain, bile leakage and haemorrhage were not correlated with the histology of the tumour treated [71]. Microwave ablation (MWA) is performed with electromagnetic devices usually with a frequency higher than 900 MHz. The basic principle of this technique is not different from RFA but there are some differences that

theoretically result in a better control of the disease: in fact, in MWA, we do not observe "heat sink" effect (it should be particularly indicated to treat lesions close to vessels), and MWA permits a higher temperature within the lesion treated with a corresponding higher cytotoxic effect. Some studies on MWA in liver lesions include metastases from NET. Martin et al. treated 11 patients with a mean number of 4 lesions per case, the majority of the procedures were performed intraoperatively in combination with hepatic resection or with extra hepatic tumour resection [72]. Complete ablation of 90 % was reported. Complications occurred in three patients and there was no recurrence at the ablation site. Groeschl et al. [73] treated in a large multicentre analysis of 450 patients treated with MWA included 61 patients with neuroendocrine liver metastasis. Complete ablation was confirmed for 97.0 % of the subgroup patients. They noted that patients with 3 cm or more tumours showed a propensity for early recurrence, regardless of histology. No significant differences in complication rates or survival based on the surgical approach were reported; however, local recurrence rates were highest for percutaneously treated lesions.

Cryotherapy is another thermal ablation method that is based on the concept that low temperature (<−50 °C degrees) causes cell death and may reduce the tumour burden and lead to symptomatic relief. Some authors in the treatment of NET liver metastases used cryotherapy. Shapiro et al. [74] in 1998 reported that in 5 patients with symptomatic liver metastases from carcinoid tumour underwent intraoperative, ultrasound-guided cryotherapy. Immediate symptomatic relief occurred in all patients and in 4 out of 5 lasted more than 3 months. However, survival was limited in this small series, therefore immediate symptomatic relief was the only benefit. In another study from the same year, Seifert et al. [75] treated 13 patients with cryotherapy. At the follow-up of 13.5 months, 12 of them were alive with satisfactory control of the disease. Bilchik et al. [76] in a study published 1 year earlier of 19 patients with metastatic lesions from NETs who underwent intraoperative US-guided cryotherapy with resection of the primary tumour also reported relief from symptoms with reduction in tumour markers. However, in both studies cryotherapy led to post-procedural coagulopathy that required transfusions [75, 76]. Jansen et al. have shown in a rat liver model that cryoablation induces greater inflammatory and coagulative response compared to radiofrequency ablation and that coagulation anomalies are related with the volume of the tissue treated and not with the number of performed sessions [66]. Seifert et al. suggested also that cryotherapy in metastatic NETs could cause release of substances that may influence the coagulation system [77].

Sheffer et al. in a recent systematic review of IRE safety and efficacy reported a low incidence of complication in the treatment of liver metastasis, where only minor complication were reported; otherwise in the primitive pancreas tumour ablation they reported major complications (bile leak and portal vein thrombosis).

Conclusion

Neuroendocrine lesions and the metastatic disease that derives from them are a very vast and heterogeneous group of diseases that are not all approached with the same strategy. The role of Interventional Radiology in the management of these tumours is to provide symptom control and local control in the cases that are considered inoperable. Embolization appears to be the most diffuse method in the management of both primary and metastatic lesions. Ablation techniques have also shown promising results. IR is an effective treatment option even if there is the necessity of assessing the impact on the patient's quality of life.

Conflict of interest Gianluigi Orgera, Miltiadis Krokidis, Matteo Cappucci, Sofia Gourtsoyianni, Marcello Andrea Tipaldi, Adam Hatzidakis, Alberto Rebonato and Michele Rossi have no conflicts of interest.

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