GEP-NETS UPDATE

Interventional radiology: role in the treatment of liver metastases from GEP-NETs

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Abstract

Neuroendocrine tumors from gastro-pancreatic origin (GEP-NET) can be responsible for liver metastases. Such metastases can be the dominant part of the disease as well due to the tumor burden itself or the symptoms related to such liver metastases. Intra-arterial therapies are commonly used in liver only or liver-dominant disease and encompass trans-arterial chemoembolization (TACE), trans-arterial embolization (TAE), and radioembolization (RE). TACE performed with drug emulsified in Lipiodol has been used for the past 20 years with reported overall survival in the range of 3–4 years, with objective response up to 75%. Response to TACE is higher when treatment is used as a first-line therapy and degree of liver involvement is lower. Benefit of TACE over TAE is unproven in randomized study, but reported in retrospective studies namely in pancreatic NETs. RE provides early interesting results that need to be further evaluated in terms of benefit and toxicity. Radiofrequency ablation allows control of small size and numbered liver metastases, with low invasiveness. Ideal metastases to target are one metastasis <5 cm, or three metastases <3 cm, or a sum of diameter of all metastases below 8 cm. Ablation therapies can be applied in the lung or in the bones when needed, and more invasive surgery should be probably saved for large-size metastases. Even if the indication of image-guided therapy in the treatment of GEP-NET liver metastases needs to be refined, such therapies allow for manageable invasive set of treatments able to address oligometastatic patients in liver, lung, and bones. These treatments applied locally will save the benefit and the toxicity of systemic therapy for more advanced stage of the disease.

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Introduction

The neuroendocrine tumors (NETs) are various cancers arising from the neuroendocrine system and can theoretically develop from any organ in the body. NETs from gastro-entero pancreatic (GEP) origin are most often originating from the small intestine and more rarely from the pancreas. WHO classifies tumors in three groups, which are grade 1 (G1) tumor, grade 2 (G2) tumor, and grade 3 (G3) carcinoma. These G1, G2, and G3 groups were formerly called carcinoid, well-differentiated, and poorly differentiated tumors respectively. In addition to their

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morphological features, G1 tumors represent <2 mitoses per ten microscopic large fields and a Ki-67 below 2%, while G2 tumors present 2–20 mitoses and Ki-67 from 3 to 20%, and G3 carcinoma has more than 20 mitoses and Ki-67 >20% (1). GEP-NET are metastatic at the time of initial diagnosis in 21, 30, and 50% for G1, G2, and G3/G4 tumors respectively, and metastatic status represents the most important prognostic factor after tumor grading (2, 3). Liver metastases constitute the most frequent metastatic site that can be isolated or dominant. According to ENETS recommendations (4), only G1 and G2 tumors are potential candidate for liver-directed (locoregional) therapies where G3 carcinoma is candidate for systemic treatment due to the rapid progression of the disease and usually widespread metastases. Locoregional treatments of liver metastases from GEP-NET include surgery and image-guided therapies (ablative therapy and hepatic intra-arterial therapies).

This article will discuss the benefits and risks of image-guided therapies for treatment of G1 and G2 GEP-NET liver metastases. Image-guided therapies can be recommended in two different indications: control of tumor growth and control of secretory syndrome. For secretory syndrome, liver-directed therapies are second-line treatment after failure or insufficiency of somatostatin analogs. For control of tumor growth, liver-directed therapies are used after tumor progression is demonstrated or in case of large tumor burden.

Hepatic intra-arterial therapies

Rationale

The rationale for treatment via intra-arterial hepatic delivery is that the normal liver has a dual vascular supply including 30% inflow from the hepatic artery and 70% inflow from the portal vein, while liver metastases are fed exclusively by the hepatic artery. Moreover, liver metastases from GEP-NET usually present a higher degree of arterialization when compared with other metastases such as colorectal cancer, thus they are ideal targets for preferential delivery of drug, or embolic treatment through injection into the hepatic artery.

Intra-arterial therapies of GEP-NET liver metastases combine occlusion of the arterial tumor feeders, with or without chemotherapy or radiation therapy. Dearterialization of the liver was initially achieved through surgical ligation, but is currently attained percutaneously with particle embolization with equivalent results (5). I.v. chemotherapy, which was added to surgical ligation, is nowadays directly injected into the hepatic artery (6). Hepatic intra-arterial therapies encompasses several different treatments, which required angiographic image guidance to reach the hepatic artery. The most common treatment of GEP-NET liver metastases is trans-arterial chemoembolization (TACE), trans-arterial embolization (TAE), and radioembolization (RE).

Indications

Non-surgical candidates with liver predominant disease or major uncontrolled symptoms are best candidates for hepatic intra-arterial therapies. The presence of low volume lung, lymph node, or bone metastases is not an absolute contraindication. GEP-NET liver metastases treated with intra-arterial therapy are usually bilobar and commonly two treatment sessions will be delivered sequentially 4–8 weeks apart to treat each lobe because treatment of the entire liver volume in a single session has been described to increase complications (7). If the tumors are in small number, selective catheterization of arterial tumor feeder(s) will be performed to increase local efficacy and reduce the toxicity of treatment on non-bearing liver tumor.

Contraindications

Contraindications to intra-arterial therapies include liver insufficiency, obstructive jaundice, bilioenteric anastomoses, portal vein thrombosis, renal insufficiency, and <50% fraction ejection volume for the use of doxorubicin. Massive liver invasion responsible for impaired liver function (bilirubin >1.5 times normal value or prothrombin time <75%) is a contraindication because intra-arterial therapies will probably induce liver failure by ischemic damage after TACE or TAE, or radiation-induced liver disease (RILD) for RE. Patients with more than 75% of liver involvement must be treated with great caution, treating a few segments of the liver at once, and will require several sessions of treatment. Pre-existing obstructive jaundice could be exposed to post-treatment infectious complications (cholangitis, bile duct necrosis, and liver abscess). Biliary anastomosis has been reported for a long time as a major risk factor for severe infectious complications after TAE and TACE (8). In these patients, RE could be an interesting alternative with early results reporting low risk of post-treatment abscess (9). TACE and TAE are contraindicated in case of major portal vein thrombosis. However, segmental thrombosis is not a contraindication to TACE or TAE. Renal insufficiency with creatinine levels above 1.5 times the normal value is a

relative contraindication due to induced renal toxicity after intra-arterial therapies through the use of contrast medium, tumor necrosis, and toxicity of cisplatinum when used. Patients must be World Health Organization (WHO) 0 or 1 for receiving therapy. When general condition is significantly altered, it is recommended to deliver treatment in several subsequent courses targeting limited liver volume, in the same way to what is recommended in case of major liver extension.

Treatment schedule is different from systemic therapy, which is most often delivered at a regular time interval until discontinued upon tumor progression or toxicity. Frequently, two to three courses of TACE or TAE are performed at 6–8 week intervals with patient evaluation for tolerance and response after each course. Subsequent treatments are delivered according to treatment tolerance, time required for liver function to return to baseline, and signs of efficacy in the treated territories (measured by Lipiodol uptake and devascularization). The treatment is suspended when complete tumor volume has been treated and response has been obtained, and may be reintroduced upon further disease progression at any point in time with cumulative treatments up to eight or ten times over several years (10). A sustained response rate to TACE upon reintroduction has been demonstrated, with lower complication incidence after repeated TACE than after first TACE (11).

Imaging follow-up of intra-arterial therapies of GEP-NET metastases

First follow-up imaging is usually obtained 2–4 weeks after intra-arterial therapy and is used to evaluate the anatomical location of treated tumors and help plan for subsequent treatment sessions, if any. At this early time point, morphological response according to Response Evaluation Criteria in Solid Tumors (RECIST) cannot be fully assessed, but Lipiodol uptake or devascularization of the targeted segments (Figs 1 and 2), which represent tumor necrosis (12), can be evaluated according to modified RECIST (mRECIST) using either computed tomography (CT) or magnetic resonance imaging (MRI) with arterial phase acquisition (13). Briefly, mRECIST is based on monitoring of the change in the sum of the longest diameters of the contrast-enhancing tumor components. Lipiodol uptake is a biomarker of response with CT; however, its strong radio-opacity may render difficult the evaluation of small foci of enhancement. MRI is the most sensitive cross-sectional imaging technique for depiction of endocrine tumor liver metastases (14, 15) and can predict early tumor response to TACE with the help of volumetric imaging, where a 25% or greater decrease in arterial enhancement or 50% or greater decrease in venous enhancement correlate with better prognosis (16). The best imaging technique to monitor response after RE is still debated, with morphological response occurring often several months later than with other techniques (17, 18).

Chemoembolization and embolization

Principle and techniques ▸ TACE includes both injection of chemotherapy drug and then embolization of the arterial tumor feeders with particles. The drug is injected as an emulsion after mixing it with Lipiodol (ethiodized oil, Guerbet, Aulnay, France). The radio-opacity of ethiodized oil allows for fluoroscopic monitoring at the time of injection. Ethiodized oil has a propensity for tumor and vectorizes the drug toward the tumor with a ratio of 4.3 to 10, due to the propensity of Lipiodol droplet to follow larger caliber arteries, which are usually tumor feeders (19). The property of vectorization allows for a pharmacokinetic benefit in terms of lower systemic exposure, higher liver concentration, and a tumor vs non-tumor liver ratio in the magnitude of fivefold (20). Ethiodized oil allows dual (arterial and portal) transient embolization and passes through the peribiliary plexus and within a few seconds first droplets of oil appear in the portal venules (21) (Figs 1 and 2). More recently, drug eluting bead (DEB) 100 to 700 microns in diameter preloaded with doxorubicin has been used as a drug delivery device with a pharmakokinetc benefit in a novel TACE technique, usually defined as DEB-TACE (22).

The chemotherapy drugs used in TACE have demonstrated low effectiveness to decrease the tumor burden when used intravenously, but intra-arterial injection associated with vascular occlusion allows for concentrations up to 100 times higher than those obtained by i.v. injection (23, 24). The vast majority of interventional radiology teams are using doxorubicin at adjusted body weight doses in the range of 1 mg/kg. Some North American studies have used a combination of cisplatin, doxorubicin, and mitomycin C. Streptozotocin demonstrates a better tumor response than doxorubicin in multivariate analysis, while it was not demonstrated on univariate analysis, with no difference in TTP (25), while requiring general anesthesia due to significant pain during hepatic intra-arterial injection induced by acid pH (26).

TAE involves selective catheterization and obstruction of the arterial vessel that supplies blood to a tumor and injection of an embolizing agent into it.

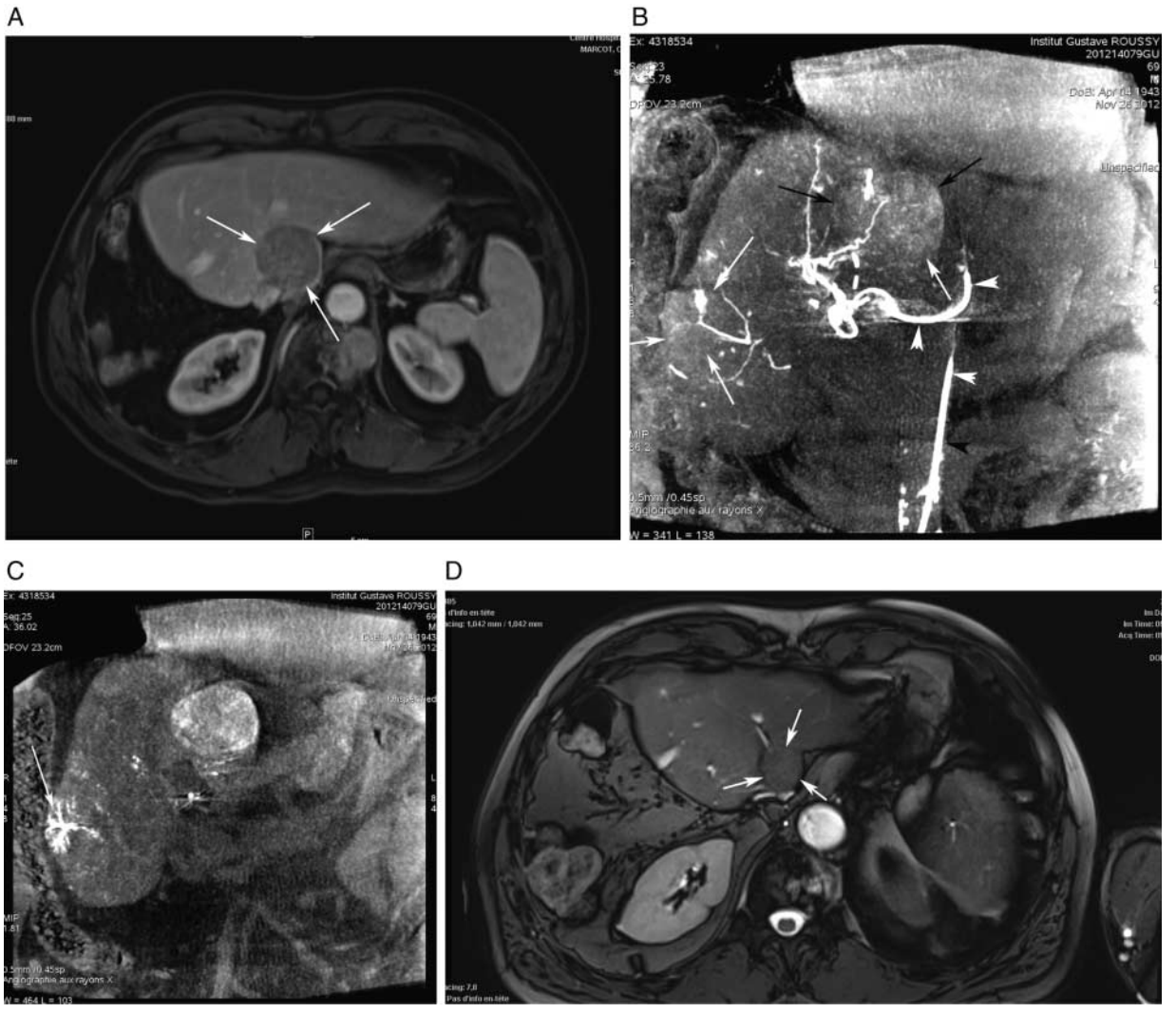

Figure 1

Ileal NET G1 tumor with previous right hepatectomy that developed six small (<1 cm) metastases associated with a 3.5 cm metastasis in segment 1 (arrows), viewed on T1 MRI at the venous phase 1 (A). On the same MRI, note that there is a metastasis to the left lateral part of the vertebral body, that was subsequently treated with cryoablation (arrowheads). Cone-beam CT image obtained during injection of contrast through the catheter (arrowheads) placed in the hepatic artery demonstrates arterial enhancement of the segment 1 large metastasis (black arrows) and other foci of metastases (white arrows) (B). Cone-beam CT image obtained during TACE procedure while the catheter has been removed shows Lipiodol uptake in both metastases (C). Note the portal shunting on the lower tumor (arrow), described as a predictive factor of local control. T2-weighted MRI obtained 14 months after TACE shows sustained objective response of the segment 1 metastasis (arrows), and decreases in size and signal intensity of the vertebral metastasis (arrowheads) (D), and the patient remains today a responder.

Results ▸ Chemoembolization is among the most effective medical treatments of liver metastases from GEP-NET, and conventional TACE using Lipiodol has been used for more than 20 years (27, 28, 29, 30, 31). Response on the secretory syndrome is obtained in 52–86% of cases with a duration of response often longer than 12 months (30, 32). The symptomatic response is even higher when treatment is used as a first-line therapy with 70% complete symptomatic response and 20% partial response (10).

Reported overall survival (OS) values are in the range of 3–4 years with a median of 38.6 months (55 months for non-pancreatic (np) NET and 27.6 months for pancreatic

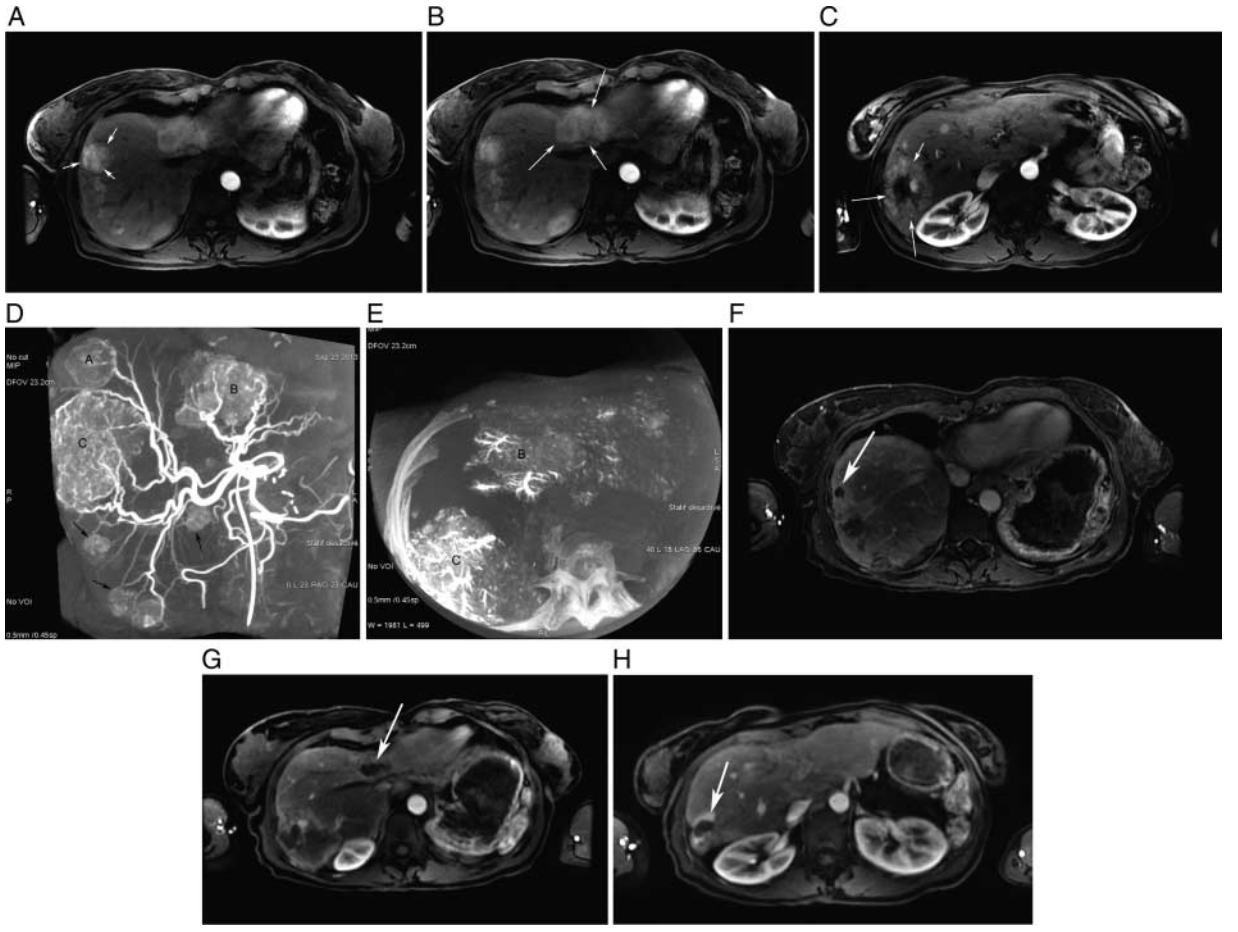

Figure 2

A 54-year-old female with 50% liver replacement by ileal NET liver metastases (arrows) viewed on axial plane MRI at the arterial phase (A, B and C). Coronal view of volumetric reconstruction of cone-beam CT angiography obtained before treatment demonstrates the hyperarterialized tumor observed in A, B and C, tagged A, B, C, and other smaller ones (arrows) (D). Axial view of volumetric reconstruction from cone-beam CT obtained without contrast immediately after the first course of TACE, which targeted metastases B and C, demonstrates Lipiodol uptake in the tumors and Lipiodol shunting in small peripheral portal veins (E). MRI at the arterial phase obtained 12 months after the first course of TACE and after four courses of TACE has been delivered demonstrates morphological response to tumors A, B and C (F, G and H).

(p) NET) for Hur *et al.* (33), 43.1 months (43.2 months for npNET and 43.1 months for pNET) for Sofocleous *et al.* (34), and 33.8 month for npNET and 23.2 months for pNET for Gupta *et al.* (35). Our recent institutional unpublished data highlight a median OS of 7 years in 103 patients treated with TACE for G1 and G2 GEP-NETs. Our results reflect the improvement of TAE/TACE outcomes throughout the last 20 years and a better selection of patients for treatment. This overall improvement in outcome of metastatic GEP-NET patients can also be explained by the increase in systemic lines of treatment available today including systemic therapies such as everolimus (36, 37) or sunitinib (38) and the widespread use of somatostatin analogs (39, 40), or even more recently radiolabeled peptide therapy (41). Other contributing factors, more directly linked with TACE, include patient selection (treatment of G1 and G2 only, TACE performed early in the disease) and TACE technique improvements (e.g. catheters). Improvements in image guidance, namely 3D vascular imaging using cone-beam CT imaging, have recently demonstrated a benefit in patient outcomes when performing TACE in a patient with hepatocellular carcinma (HCC), which can probably also be applied to TACE in NET patients (42).

In the absence of randomized trials evaluating locoregional therapies, no definitive answers to factors influencing outcomes of treatment can be provided. However, from retrospective series, tumor grade has been reported to have an impact on TTP after TAE with 54.5 months, OS for patients with low-grade tumors and 24 months for patients with high-grade tumors (34). npNETs have significant better outcomes after TACE with a response rate of 66.7% and progression free survival (PFS) of 22.7 months, vs 35.2% response rate and 16.1 months PFS for pNETs (43), higher rate of symptoms control (7), and improved median survival (80 months vs 20 months) (44). A tumor burden below 30% (7), arterial phase enhancement on abdominal CT, and high BMI are among other reported predictors of TACE efficacy including response and TTP (25). Contrarily, high hepatic tumor burden and extrahepatic metastasis are reported as significant prognostic factors for poor OS after TACE (33). Greater than 50% liver replacement by tumor, urgent treatment for control of symptoms, and extrahepatic metastasis are reported as independent predictors for a shorter OS after TAE (34). When TACE is used as an early-line therapy, as recommended by ENETS consensus guidelines (4), it is associated with better results including better control of symptoms (7), and a 5- and 10-year survival rate from diagnosis of 83 and 56% when used in first-line treatment (10). Moreover, according to our institutional unpublished data, objective response rates were 74 and 75% when treatments were delivered as first- or second-line therapy, 59% in third-line therapy, and 40% when subsequent lines of treatment were delivered.

DEB–TACE combines the theoretical advantages of an aggressive embolization, high tumor exposure to a chemotherapy drug, and low systemic passage of the drug in animal tumor models (22, 45). Early publications reporting on DEB–TACE in NET liver metastases show a high response rate of 57–80% according to mRECIST, with TTP of 14–15 months (46, 47). After these two early reports, our institution reported a series of 120 patients with GEP-NET liver metastasis treated with either DEB–TACE or Lipiodol–TACE. In this patient cohort, the occurrence of liver/biliary injury in non-tumoral territories was strongly and independently associated with DEB–TACE (odds ratio (OR)=6.63; $P<0.001$), and more serious complications such as bilomas and parenchymal infarcts were as well both significantly associated with DEB–TACE vs Lipiodol–TACE (OR=9.78; $P=0.002$) (48). Baghat *et al.* (49) reported interim analysis of DEB–TACE in 13 patients with NET hepatic metastases as part of a phase II trial. Despite an encouraging objective response rate of 78%, seven patients developed bilomas (54%), and four patients underwent percutaneous drainage (three for abscess formation and one for symptoms related to mass effect). This trial was therefore discontinued prematurely for seriousness of the adverse events. A similar efficacy was reported in a historical series for Lipiodol–TACE and DEB–TACE with TTP of 16–18 months (7, 50), and 14–15 months respectively (46, 47). In the absence of randomized clinical trials, and obviously no signal of better efficacy of DEB–TACE as illustrated above, it is advisable to use Lipiodol–TACE especially when the total liver is treated. A randomized trial is urgently needed to clarify the benefits over toxicity ratio of both procedures in patients with limited liver replacement.

The choice in between TACE and TAE remains controversial. Historical data on liver-directed therapy for NET liver metastases demonstrated that the use of i.v. therapy in combination with arterial ligation or embolization, improve objective responses rates from 56 to 75%, improve the duration of response from 6.6 to 19.8 months, and improve OS from 27 to 49 months in a retrospective study (6). In 2005, Gupta *et al.* (35) reported on 69 patients that TACE did not show any therapeutic advantage over TAE in patients with carcinoid tumors, while for pNET, TACE provided significant clinical advantage with 31.5 months OS and 50% objective response rate vs 18.2 months and 25% for TAE, even if these differences were not statistically significant. In another series of 67 patients receiving TAE ($n=23$) or TACE ($n=44$), PFS at 1, 2, and 3 years were 49, 49, and 35% after TACE and 0, 0, and 0% for TAE respectively. Duration of symptom response was 15 months for TACE and 7.5 months for TAE. OS values at 1, 3, and 5 years were 86, 67, and 50% for TACE and 68, 46, and 33% for TAE respectively (43). In the same study, toxicities of grade 3 or worse occurred after 25% of TACE and 22% of TAE. Owing to the small sample size, the differences were not significant.

One of the largest retrospective series comparing TACE and TAE included 100 patients at three different centers, and reported a median OS from the time of metastasis diagnosis of 50.1 and 39.1 months ($P=0.62$), and a median OS from the time of the first embolization of 25.5 and 25.7 months, with no significant differences in the rate of complications of 2.4 and 6.6% respectively for TACE and TAE (51). Another series with 30 patients with GEP-NET liver metastases received TAE ($n=17$) or TACE ($n=13$) and were retrospectively compared for effectiveness and safety. Significant per lesion reduction occurred with 2.2 ± 1.4 cm vs 3.3 ± 1.5 cm for TAE and 2.2 ± 1.5 cm vs 3.4 ± 1.7 cm for TACE. The median PFS for all patients was 36 months

(16.2–55.7 CI), without a significant difference between TAE and TACE. No patient death or grade 3/4 adverse events occurred, while the post-embolization syndrome occurred in 41% of TAE and 61% of TACE (52). The only prospective randomized trial comparing TACE and TAE includes only 26 patients in a 6 year period, and demonstrates no differences in the primary end point, which has PFS of 2 years, with response rates of 38 and 44% and disease control rates of 100 and 92% after two treatments, for TACE and TAE respectively (53).

Side effects and complications ▸ Owing to its potential morbidity, TACE and TAE should be performed in experienced centers. The most common side effect of TACE or TAE is the post-embolization syndrome, which associated fatigue, fever, pain, nausea, vomiting, with hyperleukocytosis, hyperthrombocytosis, and cytolysis related to a major increase in liver enzyme, and a mild increase in bilirubin level. Post-embolization syndrome is best prevented by dexamethasone and ondansetron administered 6 h before and 30 min before treatment. Omeprazole is used by most centers. Antibiotics are started at the time of TACE and continued for 2 days. Pain control relies on paracetamol and the level of medication is increased according to the degree of pain.

Systemic passage of doxorubicin after TACE is responsible for vomiting and nausea, while alopecia is very unusual. Most of the time post-embolization syndrome is self-limited, improving within 3–5 days with conservative management. The degree of post-embolization syndrome and the length of hospital stay decrease after subsequent TACE sessions when compared with initial treatment with odds ratios of 0.5 and 0.4 respectively (54).

A >60% liver invasion and treating the entire liver in a single session increase the risk of complication and specifically liver failure, and therefore two courses of TACE are usually performed with a 4–8 weeks delay. In patients with more than 75% liver involvement, Kamat *et al.* (55) reported a disease control rate of 82%, symptomatic response of 65%, a median PFS of 9.2 months, and a median OS of 17.9 months.

Acute carcinoid crisis may be triggered by these treatments and consequently prophylactic use of somatostatin analogues before chemoembolization is recommended in patients with tumors that are functionally active. In our institution, we administer s.c. sandostatin (100 μg three times a day) starting 24–48 h before the procedure. In such patients, screening and treatment for carcinoid heart disease is required before TACE. Acute kidney failure is caused by acidosis secondary to tumor necrosis, preexisting renal failure, and iodinated contrast agents; however, proper hydration before and after embolization may prevent this complication. Infection of embolized liver is exceptional, unless there is a bile retention or biliary-digestive anastomosis. The presence of gas in the embolized territory can be observed on imaging a few weeks after TACE in 13% of the patients and it is signaling the presence of an abscess in 11% of this subset of patients (56). Moreover, a large tumor diameter, DEB–TACE, super-selective approach, and a significantly higher objective response rate are independently associated with the presence of gas (56). A proximal arterial occlusion of the hepatic artery during interactive chemoembolization may require temporary interruption of TACE or TAE. Frequently, the treatment can be carried out later by a collateral circulation (57, 58). If the arterial occlusion is extensive or distal, often due to the toxic effect of embolic treatment, drug, or radiation, retreatment later is often compromised.

Radioembolization

External radiation therapy of the liver is limited by the relatively low radiation tolerance of liver tissue when compared with the doses needed to be tumoricidal. Indeed, when >70 Gy are required to achieve solid tumor destruction, the tolerance of normal liver tissue is in the range of ~30 Gy; therefore, the treatment can cause RILD (59). RE delivers targeted radiation therapy to unresectable hepatic malignancies by the injection of β-emitting isotope Yttrium-90 (^{90}Y), which is permanently bound to biocompatible, non-biodegradable microspheres (glass or resin), into the arterial supply of the liver in order to reach tumors. This results in delivering doses of ionizing radiation above 120 Gy to the tumor compartment without causing intolerable toxicity to the normal liver (60, 61). RE demonstrated a close relation between delivered dose and tumor response (62).

The dose of the radioactive microspheres is adapted to the lung shunting fraction, if present, and assessed before RE by scintigram obtained after intra-arterial infusion of ^{99}mTc-macroaggregated albumin (highest tolerable dose of the lung ≤30 Gy). RE can be performed concomitant with systemic chemotherapy including 5-fluorouracil (5-FU) (63, 64), FOLFOX (65), and irinotecan (66).

Results ▸ A retrospective review of ten institutions including 148 patients treated with 185 separate RE procedures reported the following responses: complete response (CR) for 2.7%, partial response (PR) for 60.5%, stable disease (SD) for 22.7%, and progressive disease (PD)

for 4.9% of the patients. The median OS was 70 months, and despite retreatment of the same lobe(s) in 33 patients, no RILD occurred in this cohort (67). Grade 3 or higher adverse events were fatigue (6.5%), nausea (3.2%), pain (2.7%), and ascites (0.5%). When combining RE with concomitantly 7-day systemic infusion of 5-FU (225 mg/m^2) as an early line of therapy, 34 patients with progressive NET liver metastases had 17% of CR, 32% of PR, 23% of SD, and 23% of PD, and OS was 29.4±3.4 months. Best overall hormonal response rate was 43% at 6 months (68, 69).

Side effects and complications ▸ The most common side effects of RE are abdominal pain, nausea, fever, and fatigue that last from 1 week to a month. Complications may result from non-targeted delivery of RE products including gastroduodenal, right gastric, falciform, and cystic arteries as well as pancreaticoduodenal branches. For King *et al.* (68), among 34 patients treated, two developed biopsy-proven radiation gastritis, one developed a duodenal ulcer, and there was one early death from liver dysfunction and pneumonia.

A retrospective analysis from 515 patients with various histologies of hepatic metastases receiving 680 separate RE in 16 institutions demonstrated RILD in 4%, with 75% of the events occurring in one center, which used the empiric method (70). The toxicity of treatment was significantly related to the activity delivered, the number of previous liver treatments, and a medical center with two out of 94 patients with NETs who died from RILD (67).

Which intra-arterial therapies?

There is no strong argument today to choose between available intra-arterial therapies, and further randomized studies would help rule out some of the therapies based on efficacy, safety, or pharmacoeconomic outcomes. At present, Lipiodol–TACE is the intra-arterial therapy with the largest volume of data, followed by TAE, while DEB–TACE and RE are more recent and consequently have much less data, namely on long-term toxicity. The benefit of TACE over TAE has not been demonstrated. Owing to the small size of retrospective studies, dramatic differences in TTP only results in a trend for superiority of Lipiodol–TACE over TAE, with a benefit that appears more important for pNET (43, 71). This trend for benefit in Lipiodol–TACE comes with no increase in toxicity for TACE vs TAE (Table 1).

Presently, as the terminology for TACE often confounds the use of Lipiodol or DEB during the TACE procedure, a clear comparison between these two methods is essential. In the absence of such randomized clinical trials favoring DEB–TACE, it is advisable to use Lipiodol–TACE especially when the total liver is treated, due to safety concerns discussed earlier (48, 49, 72)

RE carries the advantage of minimal side effects in the early post-treatment period, but irradiation delivered to

Table 1 Literature summary of TACE and TAE series for GEP-NET metastases with at least 20 patients.

References	No. of patients	Tumor type	Treatment	Radiological tumor response (%)					Hormone response (%)	Med. TTP (months)	Med. OS (months)	OS from first TACE (%)			
				OR	CR	PR	SD	PD				1Y	2Y	3Y	5Y
(95)	30	NET	TACE	95						24					
(96)	20	NET	TACE	95							24				
(97)	26	NET	TACE	7			54	19							50
(7)	64			74					52						83
(35)	69	npNET	TACE	75		67	16	9		23	33.8	95.3	68.6		28.6
	54	pNET		37			59	4		16	23.2	68.8	48.7		13.7
(32)	122	NET	TACE	94		82	12	6	80	19	33		18		0
(11)	27		TACE							5	28				
(25)	67	NET	TACE	73	1	36	36	27		15					
(43)	44	NET	TACE	66			22	12		12	44	86		67	50
(47)	20	NET	DEB–TACE	80			15	5		15					
(51)	100		TACE							19	25.5				43
(72)	28	NET	DEB–TACE	100						18	25				
(98)	123			86		62	24	14			38			59	36
(33)		npNET	TACE	24	50		50			17.4	55				
		pNET		22	66.7		33.3			15.3	27.6				
(34)	137	npNET	TAE	78							43.2	88		59	37
		pNET		59							43.1	72		53	33

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Table 2 Literature review of RE series for GEP-NET metastases.

References	Number of patients	Tumor	Hormone response	Radiological response (%)				OS (months)
				CR	PR	SD	PD	
(67)	148	npNET=82%		2.7	60.5	22.7	4.9	Med: 70
(68)	34	npNET=68%	55	18	33	16	33	Mean: 14.6
(99)	42 treated (29 analyzed)	npNET=67%			36 treated (51 analyzed)	29 treated (41 analyzed)	35 treated (8 analyzed)	Med: 22–28
(100)	48	npNET=71%		15	40	23	23	Med: 35

the healthy liver makes the treatment less repeatable than TACE because of the risk of RILD. In the setting of a slowly progressive disease that remains localized to the liver for a long period of time, a repeatable technique is of clinical importance. Cost–benefit studies are urgently required in order to demonstrate that the added cost of RE translates in added benefit to the patient; indeed, in a comparative study, the median cost was $25 243 for RE and $13 400 for TACE (72). For now, possible indications for RE are within contraindications or patients at risk for TACE, including major portal vein thrombosis, bilioenteric anastomoses, and low cardiac ejection fraction contraindicating TACE with doxorubicin. Overall, it seems that there is a minor advantage for Lipiodol–TACE in efficacy, especially in pNETs, while there is no added toxicity (Table 2).

Percutaneous tumor destruction in the liver

Percutaneous tumor destructions, also known as percutaneous ablation therapies, require image guidance during treatment (ultrasound, CT, or MRI) to guide the needle/probe to the targeted tumor to deliver energy (radiofrequency, microwaves, laser, cryoablation, and electroporation) to the tissue to be destructed. Radiofrequency ablation (RFA) is among the first techniques used for liver ablation and the one with the largest experience reported today in treatment of liver tumors; therefore, most of the studies reported in this publication refer to RFA.

Ablation can be performed percutaneously or intraoperatively during laparotomy or laparoscopy. During surgery, ablative therapies are most often used to destroy a small metastasis that cannot be resected often together with resection of larger tumors, allowing the most comprehensive surgery. Percutaneous RFA can be achieved if the targeted metastases are visible on ultrasound or CT scan without contrast injection, while a metastasis visible only at MRI or only at enhanced CT will be more difficult or impossible to target.

Percutaneous RFA is used in a curative intent when metastases are confined to the liver.

Principle and techniques

RFA is a thermal destruction obtained through delivery of a radiofrequency sinusoidal current with a frequency of 400–500 KHz, that induces ionic agitation, responsible for friction in between particles then inducing tissue heating up to tissue boiling temperature (73), with a temperature above 60 °C responsible for immediate irreversible cell denaturation.

Microwave ablation is another tool that relies on excitation of the water molecules' electric dipole, providing a temperature higher than RFA of up to 160 °C, and consequently less sensitive to convective tissue cooling and to this regards probably more efficient to destroy tumors close to large vessels (74).

Limitations of thermal ablation are hilar location of tumors, with proximity of large vessels (>4 mm) responsible for increased rate of incomplete local control due to convective cooling effect by the vessels, and proximity of major bile ducts with an increased risk of complication (75, 76). However, incomplete local control due to vessel cooling can be overcome by percutaneous endovascular manipulations (77) or intraoperative clamping of the hepatic pedicle (78). Subcapsular tumors in contact with hollow digestive structures that pose the problem of possible heat-induced damage to these organs during percutaneous use (79, 80) can nowadays be treated with the use of artificial ascites or carbon dioxide pneumoperitoneum obtained in order to shield neighboring organs.

Imaging follow-up of ablation of GEP-NET metastases

The goal of RFA is to ablate not only the tumor tissue, but also a crown of healthy liver tissue to obtain the so-called 'safety margins'. These ablated tissues necessarily remain in place and form a larger area of abnormality at imaging surrounding the ablated tumor, at least at early follow-up called the ablation zone (Fig. 3), that with time will decrease in size. Consequently, it is therefore impossible to

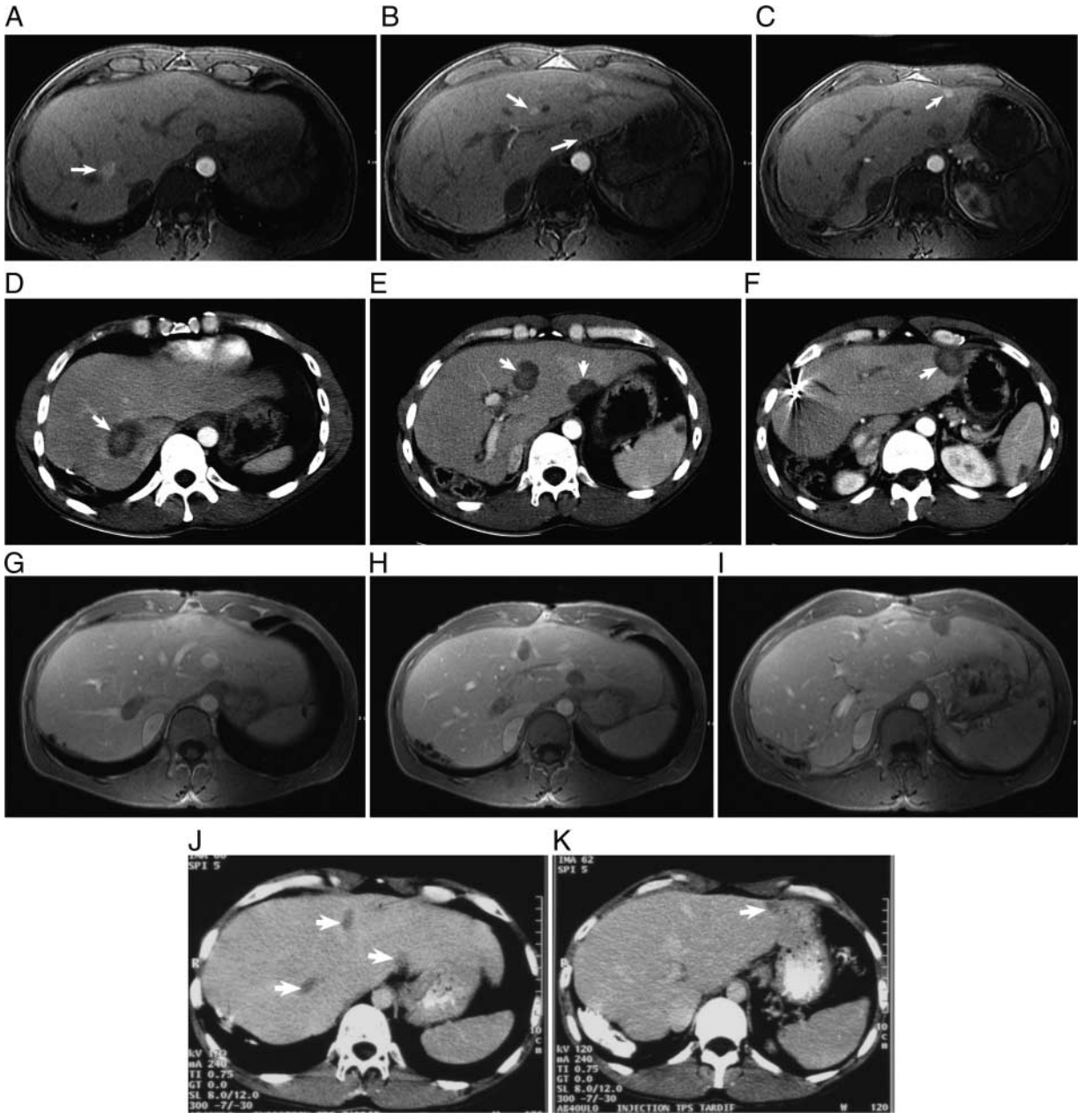

Figure 3

Ileal NET G1 tumor with four small liver metastases highly enhanced at the arterial phase of the axial plane MRI (arrows; A, B and C). Percutaneous RFA has been performed to the four liver metastases, and 1 month axial plane follow-up CT at the arterial phase demonstrated a hypovascular zone of ablation larger than the initial tumor location due to ablation margins (arrows; D, E and F). Contrast enhanced axial plane MRI at 1 year demonstrates a decrease in the size of the ablation area (G, H and I). This complete local control is furthermore assessed at 2 years on the contrast-enhanced axial plane CT that shows a further decrease in the size of ablation zone (arrows; J and K).

use RECIST based only on the usual decrease in tumor size on the early follow-up imaging.

The intensity of the inflammatory response during the first weeks after RFA significantly hampers the MRI and CT interpretation. Therefore, it is recommended that the first follow-up MRI or CT is made at least 1 month after the procedure (81) in order to evaluate devascularization of the treated tumor and safety

ablation margin beyond the tumor (Fig. 3) (82). A recent study has reported a sensitivity of 100% and a specificity of 100% of (11)C-5-hydroxytryptophan positron emission tomography for detection of incomplete ablation after RFA, when using radiological follow-up as the gold standard, with earlier detection in five out of eight incomplete ablation cases (83).

Results

There are very few reports of ablation therapies in GEP-NET liver metastases and most of them include a small number of patients. The size of the tumor is the factor that most influences the effectiveness of the treatment with 91% of metastases from various origins with a diameter from 5 to 42 mm (mean=21) fully ablated (84), when only 61% of metastases with a diameter from 9 to 96 mm (mean=32) are fully ablated (85). Concerning NET metastases, in a study carried out in 34 patients with 234 metastases, the mean diameter of incompletely ablated tumors was 4.2 cm vs 2.3 cm for the all studied groups (86). Patients with an overall ablated tumor volume below 30 cc, 31–75 cc, and over 76 cc had a median survival period of 130, 125, and 33.5 months respectively. After a median duration of 21 months, 25 patients with 189 GEP-NET liver metastases demonstrated a 74% control rate with 24% CR, 29% PR, 4% SD, and relief of hormone-related symptoms in 69% of the patients (87). After a median follow-up of 30 months, 89 patients (carcinoid=55, pancreatic islet cell=23, and medullary thyroid cancer=11) with metastases measuring 3.6 ± 0.2 cm and in a number of 6 ± 1, treated with laparoscopic RFA, achieved 97% symptom relief with 22% local liver recurrence, 63% new liver metastases, and 59% extra-hepatic disease. Median disease free survival (DFS) and OS were 1.3 and 6 years with liver tumor volume, symptoms, and extra-hepatic disease as independent predictive factors of survival (88).

Consequently, only patients with a low tumor volume are amenable to RFA, with best indication for ablative therapies being metastases in small numbers, usually <5 and with a diameter below 3–3.5 cm, due to a maximum volume of destruction around 5 cm for currently available RFA systems, and the need to ensure the safety margins of 1–2 cm of ablation around the tumor. The fact that metastases of tumors that are 2, 3, 4, and 5 cm in diameter are approximately 4 cc, 15 cc, 33 cc, and 65 cc, respectively, must be taken into consideration. In order to select the best candidate, an easy rule could be a single metastasis <5 cm, or in case of multiple tumors a sum of the diameters <8 cm.

The benefit of ablation or surgery alone for survival remains difficult to demonstrate, because patients will receive several subsequent lines of treatment. A retrospective study compared 103 patients after liver RFA/resection vs 273 patients with non-surgical treatment. Patients were matched on Charlson co-morbidity index, age, symptoms, carcinoid heart disease, extent of metastases, and proliferation index. At 5 years, there was no difference in OS and disease-specific survival, while urinary 5-hydroxyindoleacetic acid levels were lower and the proportion of patients with progressive disease within the liver was smaller in the resection/RFA group after 5 years (89). In such patients, the need for aggressive surgery can be obviate, especially when large resections are necessary to resect small metastases.

Complications

Reported post-RFA death rates and major complication rates (portal vein thrombosis, hemoperitoneum, colonic perforation, liver abscess, and tumor seeding) are in the range of 0.5–1.5 and 3–5% respectively. Liver abscess is very rare as long as the patient has no biliary-digestive anastomoses or a biliary stent crossing the ampulla. Minor complications involve skin burns, segmental biliary dilatation, pleural effusions, and subcapsular hematoma of low abundance.

Percutaneous tumor destruction outside the liver

Percutaneous tumor destruction has been applied outside of the liver to treat metastases, namely in the lung and bones. Even if there is no specific series dealing with metastases of GEP-NET in such organs, possible indications and results of such treatments will be briefly reviewed.

For lung metastases, the rate of complete ablation is 93% per tumor in data collected for 60 patients with 100 lung metastases of various origins, measuring <40 mm in diameter (mean$\pm$S.D.$=17\pm10$), with a trend toward better efficacy for tumors smaller than 2 cm in diameter ($P=0.066$) (90). Pneumothorax occurred in 54% of procedures, but a chest tube was required in only 9% of the procedures. No modification of respiratory function was found when spirometry measurements were obtained before and within 2 months after RFA, making lung RFA a highly repeatable technique in case of new occurrence of the disease. Similar to the liver, tumors close to the hilum are at a higher risk of complication with a lower chance of success.

In bone metastases, percutaneous thermal destruction can fully ablate a small bone metastasis or provide pain

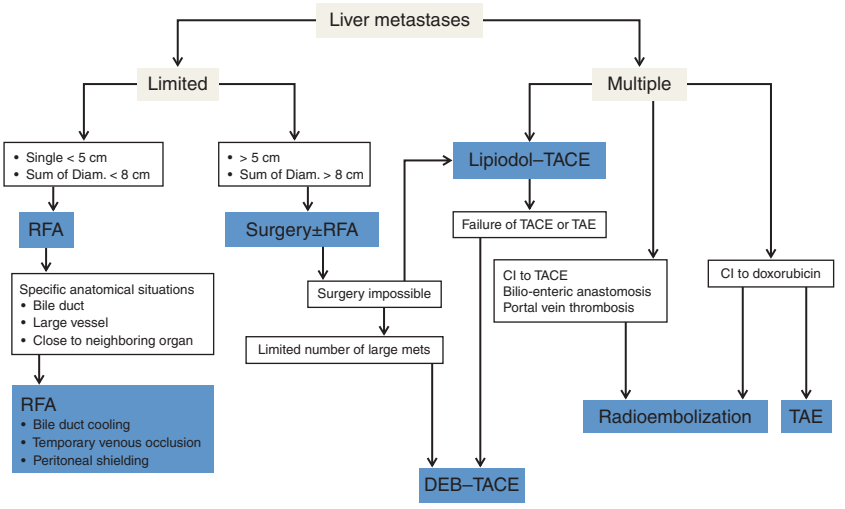

Figure 4 Gustave Roussy algorithm for liver-directed therapy making strategy. TACE, trans-arterial chemoembolization; TAE, trans-arterial embolization; DEBs, drug-eluting beads; RFA, radiofrequency ablation; Diam., diameters of all metastases; CI, contraindication.

palliation. Curative intent thermal ablation of 122 bone metastases resulted in 89 (67%) complete ablation cases in 1 year. The favorable prognostic factors for complete ablation were oligometastatic status ($P=0.02$), metachronous ($P=0.004$), and small-sized bone metastases ($P=0.001$), without cortical bone erosion ($P=0.01$) or neurological structures in the vicinity ($P=0.002$) (91). For bone-related pain treatment, only a part of the tumor will be ablated, usually the lytic margin in between the metastasis and the bone, with the goal to destroy the highly heat-sensitive distal nerves, which are responsible for pain. A prospective multicenter study of 43 patients with painful osteolytic metastases (visual analogic score (VAS) >4) treated with image-guided RFA showed a clinically significant decrease in pain in 95% of patients (41/43). The mean score for worst pain was 7.9 before treatment and significantly decreased to 4.5, 3.0, and 1.4 at 4, 12, and 24 weeks following treatment respectively. Opioid usage significantly decreased at weeks 8 and 12 (92). When pain is due to osteolytic bone metastases, the patient can benefit from percutaneous cementoplasty or percutaneous osteosynthesis, which aims to consolidate a fragile bone, and as a consequence reduces pain and may prevent possible future fractures. Cementoplasty is the injection of radio-opaque acrylic cement through a percutaneously inserted needle often with the use of CT guidance (93). Percutaneous osteosynthesis is the deployment of orthopedic hardware after insertion is guided with CT or cone-beam CT imaging (94).

Conclusion

Owing to its complexity, NET metastatic disease requires expert medical centers able to perform a work up according to common standards of evaluation, in order to help to define a treatment strategy including the short- and long-term disease planning. Very few patients diagnosed with metastatic NETs will be cured and most will probably require treatment for many years. The strategy for treatment needs to take into account the complexity of the disease with differences in primary origins, in metastatic organs, and in natural history. Expert centers must be able to provide high-quality care and the most recent type of imaging includes functional imaging with several tracers. These expert centers must be able to deliver optimal systemic, and local therapies either combined or sequentially delivered with a long-term strategy. It is important to avoid much aggressive treatment in the early stage of the metastatic disease.

Within the therapeutic armamentarium needed in GEP-NET patients, interventional radiology provides the physician with a manageable invasive set of treatments able to address locally oligometastatic patients in either liver, lung, and bones through ablation, or complete liver through intra-arterial therapies, as summarized in Fig. 4. These treatments applied locally will save the benefit and the toxicity of systemic therapy for more advanced stage of the disease. Local therapy can be used sequentially with systemic therapies in order to help control an aggressive location such as bone tumor, or to debulk a large tumor load in the liver.

Future randomized studies evaluating relative benefit in terms of efficacy and toxicity among available intra-arterial therapies are essential for better disease control. It is also critical to evaluate treatment strategy in between different intra-arterial therapies to establish any benefit of the subsequent use of one after the other,

and the role of combination between systemic and local therapies given sequentially or concomitantly.

Declaration of interest

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