Locoregional Therapies of NEN

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10.1 Introduction

Interventional Radiology, also called Interventional Oncology (IO) when applied to the field of oncology, provides several treatment options alternatives, or sometime complementary, to the traditional ones. IO can also provide unique therapies for complex clinical situations, where no or not efficient standard options, are available. Some of the techniques developed within the IO field are nowadays upgraded to standard options and included into the clinical guidelines. It is especially true for hepatic tumors where, both in primary and metastatic disease, locoregional therapies can provide outstanding clinical results with minimal invasiveness.

Also in the field of Neuroendocrine Tumors, IO plays a very important role, in the management of metastatic stages, thanks to the several locoregional treatments, available from its wide armamentarium, ranged from the percutaneous techniques to the intra-arterial ones. Several indications for locoregional therapies of metastatic liver disease, from NET, are reported from the literature, whereas radical tumor ablation, tumor debulking, and hormone release control are the most common, also because of the increasing response to the medical therapy [1].

30–50% of patients with PNETs syndromes and 98–100% of patients with carcinoid syndrome due to a malignant GI-NET (carcinoids) have liver metastases at presentation [2–7]. These patients are rarely cured surgically and thus are candidates for various forms of liver-directed therapies, particularly when the primary tumor is resected [8–14]. In those clinical settings, liver-directed therapies allow for tumor debulking and/or hormone release control. However, treatment strategy is usually based on a multifactorial evaluation, mainly related to the general clinical conditions, the therapeutic options available, and, most importantly, on the histopathological tumor characteristics. According to its complexity, treatment strategy in NET setting requires a dedicated *multidisciplinary* team and very often an individualized approach [15]. The range of effective treatment options for NET liver metastases includes surgery (only limited to a small percentage of patients), medical therapies, interventional radiology, and nuclear medicine treatments [16, 17]; however, there is still a lack of evidence-based recommendations, regarding the ideal sequence of those treatments in these patients.

Liver surgery is reported as the treatment of choice for liver metastatic disease, with 5-year survival rates >70% in patients amenable to resection [18–20], but resection is often impossible due to the extent of the disease.

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Rationale for intra-arterial liver-directed therapies, such as arterial embolization (TAE), arterial chemoembolization (TACE), or arterial radioembolization (TARE), is based on the evidence that NET liver metastases are usually hypervascular and primarily supplied by branches of the hepatic artery, whereas normal liver parenchyma is fed by the portal vein. For that reason, the arterial route to the tumor is widely accepted for affecting liver metastatic deposits, by shutting down the blood flow to the tumor, alone (TAE) or with the coadministration of chemotherapeutic agents (TACE), or with radio-emitted beads (TARE) [9–12, 21, 22].

Mechanism of action for thermal ablation (TA) techniques is based on the sensitivity of any biological tissue to the high temperature. Cell death during exposure to heat is exponential and dependent on the temperature and length of exposure [23].

Different techniques are available for providing thermal damage to the cancer tissues, but Radiofrequency (RF) and Microwaves (MW) are the most common in clinical practice, for treating liver nodules, both primary and metastatic tumors.

Indications, results, and main technical aspects of IO liver-directed therapies, in liver metastatic NET, will be described within this chapter.

10.2 Intra-Arterial Therapies

More than 95% of liver metastases from NET are hyper-enhancing during the arterial phase on contrast-enhanced ultrasonography (CEUS), meanwhile on CT or MR, they could be hypointense or hypoattenuating during the same vascular phase, mostly because of a lower temporal resolution compared to CEUS [24]. However, the basic concept behind intra-arterial treatment strategy is that liver metastases from NET are mostly fed by the arterial system as any other liver tumor, whereas normal adjacent liver is mainly supplied by the portal venous system [25].

Embolization (TAE), chemoembolization (TACE), and radioembolization (TARE) have been shown to achieve objectives responses, tumor markers decrease, and control of tumor-related symptoms, in those patients with unresectable liver metastases and/or specific carcinoid symptoms, such as diarrhea, hypertension, abdominal pain, and flushing [26]. However, there is still no clear evidence, in terms of imaging response, symptomatic response, or impact on survival, about the superiority of one out of these three approaches [13, 17]. Liver-predominant disease and/or major uncontrolled symptoms in nonsurgical candidate patients are the two most common indications for hepatic intra-arterial therapies, meanwhile extrahepatic stable metastatic tumor and/or the presence of stable primary tumor are not considered absolute contraindications [4, 9].

10.2.1 Embolization/ Chemoembolization

Transarterial Embolization (TAE), also called "bland embolization," refers to the selective distal arterial embolization, with the aim of occluding small arteries, feeding the liver metastases and consequently tumor ischemia and necrosis [27]. During the last few years, more efficient embolic material has been developed, in order to achieve a better and more distal arterial embolization, with the specific goal to improve local results, meanwhile reducing the toxicity of surrounding healthy liver tissue. Small and round-shaped beads, with size ranged between 100 and 40 microns in diameter, could better reach a deeper level of tumor embolization, if compared with bigger and with irregular shaped embolics [28, 29]. The adoption of super-selective techniques, thanks to the more and more performing micro-catheters and the improved integrated imaging for guiding the intra-arterial procedures, may allow for really efficient selective embolization of liver tumors, mainly if hypervascular, such as HCC and metastatic NET (Fig. 10.1).

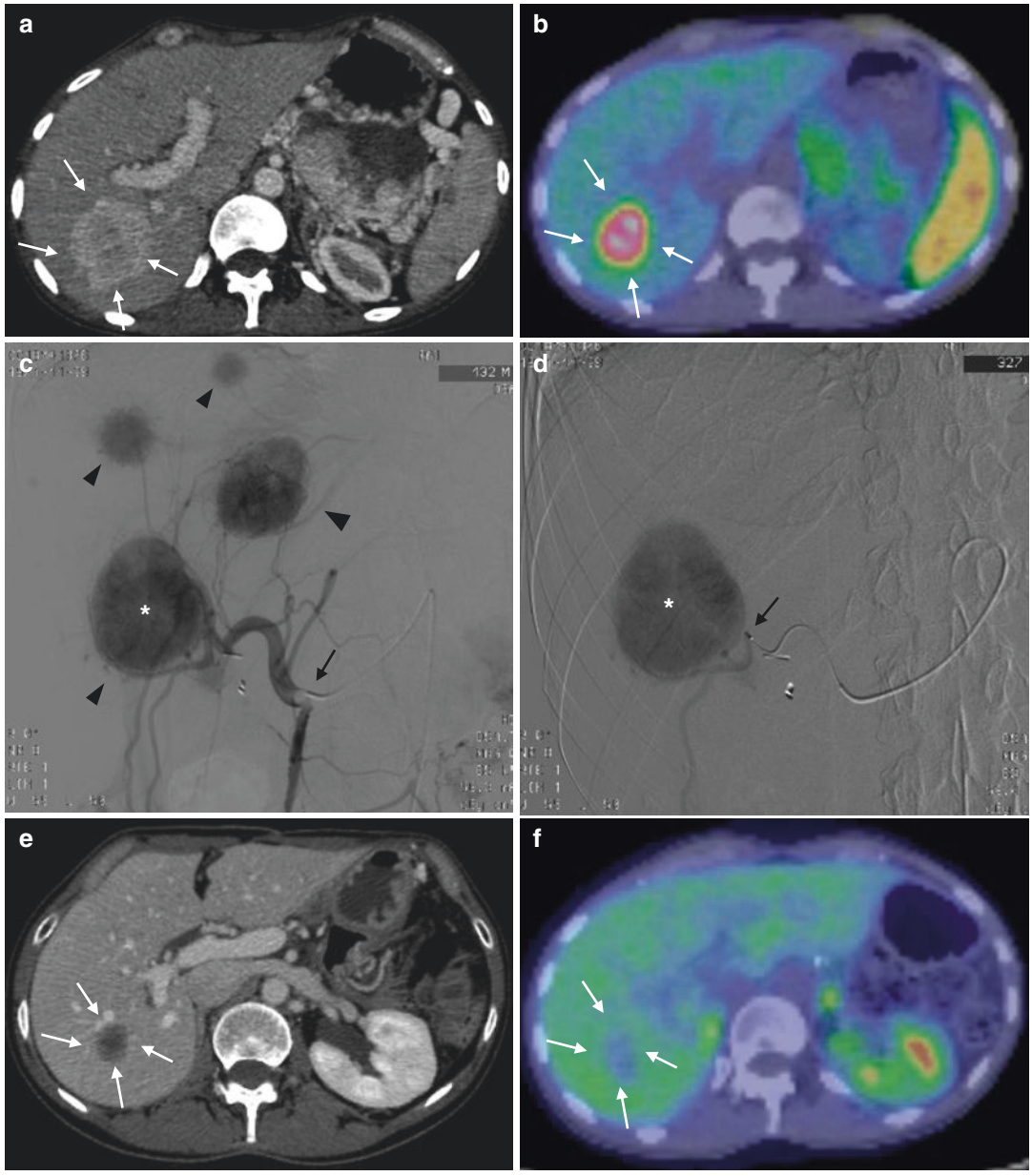

Fig. 10.1 NET G2 (Ki67 10%) of the pancreatic tail, with synchronous metastases on the right liver lobe; (**a**) CT shows the largest nodule, sited in S6 (arrows), and confirmed on Ga^{68}PET/CT (**b**). On NET-MDTB (IEO) was defined the indication to TAE, for control liver disease, followed by surgical resection of primary pancreatic tumor. Multiple sequential TAE sessions were super-selectively performed; (**c**) common hepatic artery (arrow) angiogram clearly shows how the liver lesions (arrowheads) are hyper-vascular; (**d**) super-selective angiography, performed with the micro-catheter tip (arrow) into the feeder of the lesion sited in S6 (*), confirms the right position for delivering the microbeads. After multiple sessions of TAE, patient underwent resection of the pancreatic tail. 24 months after last session of TAE, CT (**e**) shows sustained objective response at the level of S6, where the treated lesion is no more enhancing (arrows); (**f**) Ga^{68}PET/CT shows a photopenic area (arrows) at the same level

Transarterial chemoembolization (TACE) is based on the association of intra-arterial chemotherapy administration together with embolics. The rationale behind TACE is to increase the intra-tumor concentration of cytotoxic drugs, such as doxorubicin or epirubicin, with no or very few systemic side effects, if compared to the standard systemic chemotherapy, meanwhile concurrent or following embolization will reduce drug washout from the tumor, compared to drug infusion alone [30]. During conventional TACE (cTACE), the drug is emulsified with Lipiodol® (Guerbet) and selectively delivered into the tumor. In DEB-TACE, the drug is concentrated within small beads (DEB = Drug Eluting Beads), which will shut down the blood flow within the tumor and will elute the chemotherapeutic agent into the tumor microvasculature. The advantage of using eluting beads is mainly based on pharmacokinetic studies in HCC patients, which revealed that DEB-TACE resulted in a higher intra-tumor drug concentrations and a lower systemic exposure than TACE [31, 32].

Both TAE and TACE are usually performed for palliative treatment of liver-predominant disease, which is not surgically resectable, in order to reduce the hepatic tumor mass, and 25–85% of patients have an objective tumor response, with a mean response duration of 6–45 months. This approach has been particularly considered in patients with hepatic symptoms or refractory malignant F-NET syndromes [9–12, 21, 22]. In general, TACE/TAE result in a symptomatic response in 50–100% of patients, and numerous series as well as case reports have documented their control of symptoms in patients with both carcinoid syndrome and F-pNET syndromes [9–12, 21, 22, 33–39].

To date, no randomized study has sought to compare the efficacy of either embolization or chemoembolization in NET G3. CNCCN, NANETS, and ENETS guidelines include both TAE and TACE, within the list of local therapies for symptomatic and/or progressive NET liver metastases, on the basis of level IIB-3 evidence, but they offer no recommendation regarding the different techniques [13, 40–43]. No statistical difference in clinical efficacy of TAE versus TACE in the treatment of liver metastases from well-differentiated non-pNET in a prospective study has been reported [44]. According to this report, there are no data supporting the hypothesis of an additive clinical advantage of intra-arterial administration of chemotherapeutic agent compared to the arterial embolization alone. Meanwhile, some studies reported superior survival and/or outcomes of TAE compared to TACE [22, 45, 46]; two retrospective series have reported higher biliary complication rate after DEB-TACE [47, 48] compared to TAE, but there are still no definitive data regarding the superiority between cTACE and TAE.

10.2.2 Radioembolization

Radioembolization (TARE) delivers targeted radiation therapy to unresectable hepatic malignancies, by the injection of the β-emitting isotope Yttrium-90 (90Y) through micro-catheter, which is permanently bound to biocompatible, nonbiodegradable microspheres (glass or resin), into the arterial supply of the liver, in order to reach tumor microvasculature. It results in delivering doses of ionizing radiation, above 120 Gy, into the tumor compartment, with no intolerable toxicity to the healthy liver parenchyma [49, 50]. TARE demonstrated a close correlation between delivered dose to the tumor and local response [51]. The dose of the radioactive microspheres has also to be adapted to the lung shunting fraction, when present, and assessed before TARE by scintigraphy, obtained after intra-arterial infusion of ^{99}Tc-macroaggregated albumin (highest tolerable dose of the lung <30Gy).

Several authors reported data on the efficacy of TARE in the biological control of the disease and in the reduction of symptoms [52–55]. Interesting results about its feasibility and impact on survival compared to other locoregional therapies showed its possible application in particular series of patients [56–61]. One of the critical approaches in this kind of treatment is the calculation of the optimal dose that on the contrary is a

well known and investigated topic in HCC patients [62].

The most common side effects of TARE are abdominal pain, nausea, fever, and fatigue that last from 1 week to 1 month. Various complications have been described after or during the procedure of TARE. They are mainly caused by the delivery of radioactive beads to the normal liver parenchyma or to extrahepatic sites, such as the gastrointestinal system (e.g., gastroduodenal ulceration, radiation gastritis, cholecystitis, or pancreatitis), the abdominal wall (i.e., radiation dermatitis), and the lungs (i.e., radiation pneumonitis) [63]. Treatment toxicity is significantly related to the radiation activity delivered to the healthy liver, which is the main limiting factor making TARE less repeatable than TAE/TACE, because of the risk of irreversible damage of liver parenchyma. In 2008, Sangro et al. [64] described toxicity using the term "RadioEmbolization-Induced Liver Disease" (REILD), which is considered a form of sinusoidal obstructive syndrome (SOS) and includes ascites, weight gain, liver function impairment, and elevation of bilirubin levels. Furthermore, late changes in liver size and appearance, following TARE, have been described, with radiation injury potentially developing into sinusoidal congestion and portal hypertension [65, 66]. In a recent study, Yu-Kai et al. [67] evaluated the long-term (>2 years after treatment) hepatotoxicity of radioembolization in patients with mNETs, by reviewing imaging and laboratory findings and determining their correlation with clinical symptoms. They concluded that whole-liver 90Y TARE for patients with neuroendocrine tumors results in long-term imaging findings of cirrhosis-like morphology and portal hypertension in >50% of treated patients, with signs of hepatic decompensation that are more pronounced than those in patients treated with unilobar 90Y radioembolization. However, a majority of these patients will remain clinically asymptomatic. This evidence is crucial, as patients with mNETs have longer life expectancies than patients with other unresectable hepatic metastases [68]. Although this practice may result in an improved tumor response rate and overall survival, there may conceivably be manifestations of long-term hepatotoxicity from ^{90}Y. In the setting of a slowly progressive disease that remains localized into the liver for a long period of time, TARE should be considered in a very well selected patients and should be carried out with super-selective technique only (Fig. 10.2), in order to reduce the risks of early and late complications (i.e., REILD and late hepatotoxicity). TAE/TACE and TARE should not be considered competing therapies, but complementary tools. Many patients, according to their individual tumor and healthy liver characteristics, could be candidates for either TAE/TACE or TARE.

10.3 Percutaneous Liver Ablation

Radical resection is considered as the only curative treatment for liver metastases from NET, allowing for survival improvement [19, 69] and also recommended for tumor debulking in hormone-active metastases, for palliative purposes [70–72]. The overall survival after hepatic resection is 46–86% at 5 years and 35–79% at 10 years [19, 73, 74], but complete resection is achieved in only 20–57% with a local recurrence rate of 94% at 5 years [75]. Due to that high metastatic recurrence rate, repeated local treatments during patient's life might be required. Therefore, minimally invasive treatment, such as TA for liver metastatic disease, may play an important clinical role as an interesting tissue-sparing treatment, alternative to the conventional surgery, mainly for small tumor deposits. Repeatability and low invasiveness, together with a very high success rate, are the most relevant features of TA techniques for liver tumors.

TA refers to the application of high temperature to a tissue with the aim to effect tumor cell death. There are different methods and different energies for delivering the heat into the tumor, where percutaneous radiofrequency ablation (RFA) and microwaves ablation (MWA) are the most common and used in clinical practice.

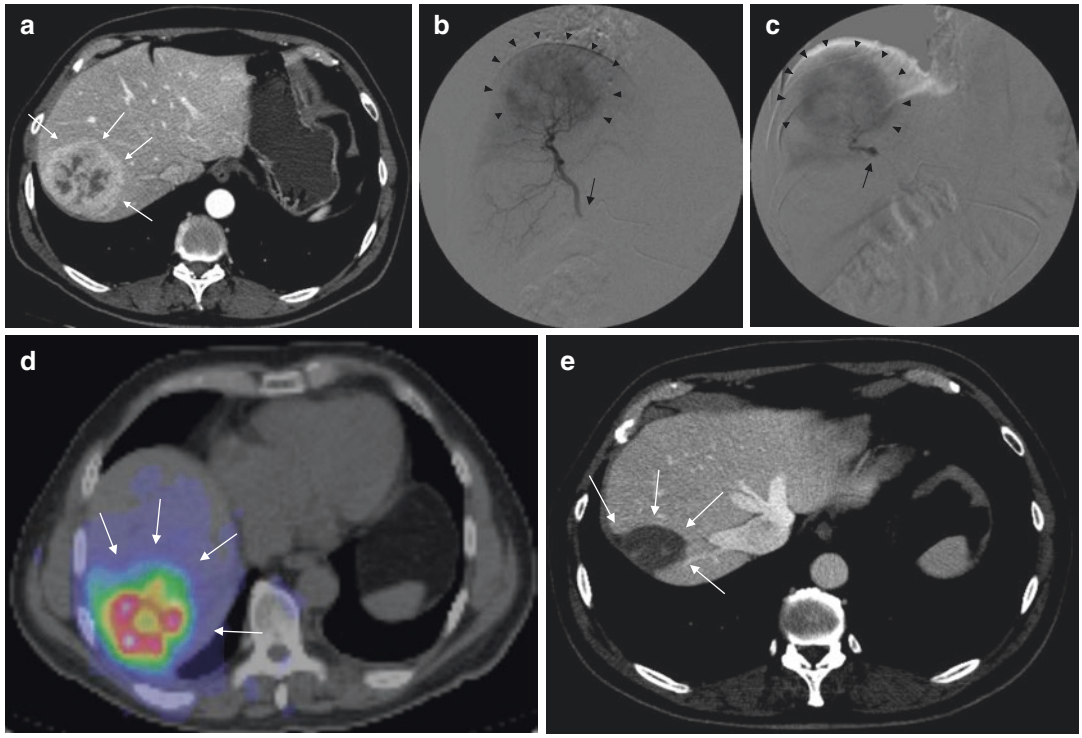

Fig. 10.2 Unknown primary site NET G1 (Ki67 1%), with single liver metastasis of right lobe. As the liver lesion was growing, the NET MDTB (IEO) put indication for local treatment. (**a**) CT scan in arterial phase shows the highly enhancing liver metastasis in S7 (arrows) (**a**), and according to its histology, super-selective TARE was indicated. (**b**) Angiography, obtained with the micro-catheter (arrow) in the right hepatic artery shows the hyper-enhancing tumor (arrowheads). (**c**) Super-selective angiogram from the tumor (arrowheads) feeder: the micro-catheter tip (arrow) is sited close to the tumor, distally to some lateral branches, in order reduce the healthy liver involvement during Y90-micro-particles injection. According to the low percentage of β + positron emission of the ^{90}Y, an abdominal PET/CT (**d**) was performed the day after TARE, in order to evaluate ^{90}Y-micro-particles distribution (arrows). The exam also shows no healthy liver was involved during the treatment. (**e**) CT scans, the last one (**d**) performed 4 years later showed a "scar" (arrows) in the site of the lesion, with no evidence of active pathologic tissue

The area affected by the heat is called "ablation zone," and its size and shape are dependent by many factors, some of them closely related to the tissue characteristics and some others to specific features of the different TA technologies. However, the size of the ablation zone should cover the whole tumor volume, including a peripheral safety margin (0.5–1 cm) of healthy liver [65]. For large lesions or for irregular shapes, multiple overlapping ablation zones might be necessary in order to achieve a complete tumor eradication [76–78].

TA can be performed percutaneously, laparoscopically, and during open surgery, where the imaging-guided percutaneous approach is the most common technique. Ultrasound and CT are the more common imaging modalities used, in clinical practice, for guiding percutaneous liver TA. The first modality has the unique feature to provide real-time imaging, which is essential for a safe needle penetration, from the skin surface to the target. The advantage of using CT is, first of all, the panoramic view and the higher spatial resolution. It is more and more emerging the need of both the two guidance modalities, during the same session, also integrated within the newer navigational tools [79], for a safer and more precise procedure. Contrast enhancement CT is also

essential for providing data regarding the outcome of the ablation, when it is performed at the end of the procedure. Clinical indications for liver ablation in liver metastases from NET are still not well defined, and patients have to be always discussed within a dedicated MDTB, meanwhile technical indications are well established and are mainly related to the tumor size, shape, and site. Generally speaking, acceptable size criteria for ablation may differ, according to the different techniques and devices used, ranging from 3 to 5 cm of largest diameter. However, it is well known that local recurrence and treatment failure are higher with larger lesions due to incomplete ablation at the periphery [80]. Ablation margin is actually reported as an independent factor affecting the local recurrence after laparoscopic RFA of liver NET metastases [81]. Hence, the precise placement of the RFA needle, which is deeply affected by the imaging modality used for guidance and ablation monitoring, has to be considered critical for achieving as large margins as possible, in order to obtain local tumor control.

10.3.1 Radiofrequency Ablation

In RFA, an alternating current is flowing between the uninsulated probe tip and a dispersive skin electrode-pad (unipolar) or between the different electrodes within one or multiple probes (multipolar). The current is converted into tissue heating by friction of the ions adjacent to the uninsulated tip of the RFA electrode [76, 82, 83]. RFA is the most frequently used ablation technique performed in this clinical setting, often in combination with surgery, especially to remove isolated metastases too deeply located for a safe resection. Several criteria regarding the possible indication for liver RFA in NET have been proposed and are mainly based on the number of lesions, size, and proximity to vital structures. Besides the use of RFA as an antitumor treatment, a number of studies have reported enhanced symptomatic control of functional NETs after its use [4, 9–11, 13, 21, 84–88]. In a series of 129 patients undergoing 177 sessions of laparoscopic RFA, for a total number of 770 liver metastases from NET, authors reported a 5- and 10-year overall survivals of 76% and 59%, respectively, and a median OS of 125 months, at a median follow-up of 73 months. Limitations of the technique include the poor efficacy of ablation in large tumors, where tumor size remains an independent predictor of poor overall survival [89].

10.3.2 Microwave Ablation

MWA is based on an oscillating electromagnetic field (0.9–2.450 GHz), generated by an antenna/needle, which induces water dipoles to continuously realign with the magnetic field. This kinetic energy induces heat in the tissue adjacent to the antenna, exposed at the magnetic field [90].

Compared to RFA, MW ablation is usually faster and less sensitive to the heat-sink effect, but its use is less common because it is more recently introduced in the clinical practice than RFA. Percutaneous application of MWA is more common in clinical practice, than during laparoscopy or open surgery, but due to the faster efficacy than RFA in destroying the tumor tissue, its use during open surgery is increasing, allowing liver tumors eradication, whereas resection only is not feasible or too invasive (Fig. 10.3).

A recent retrospective study comparing MWA, resection, and resection plus MWA, in patients affected by liver metastases from NET, reported a mean overall recurrence-free survival of 21.2 months (0 to 189 months), with no statistically significant difference when comparing patients treated with MWA only versus those who underwent surgical resection with or without MWA [91]. Moreover, patients treated with MWA only had a similar overall survival of 57 months, as patients undergoing resection with or without MWA. After MWA, the length of hospital stay is also reported to be significantly shorter than after surgery, with number of complications and their severity significantly reduced if compared with resection.

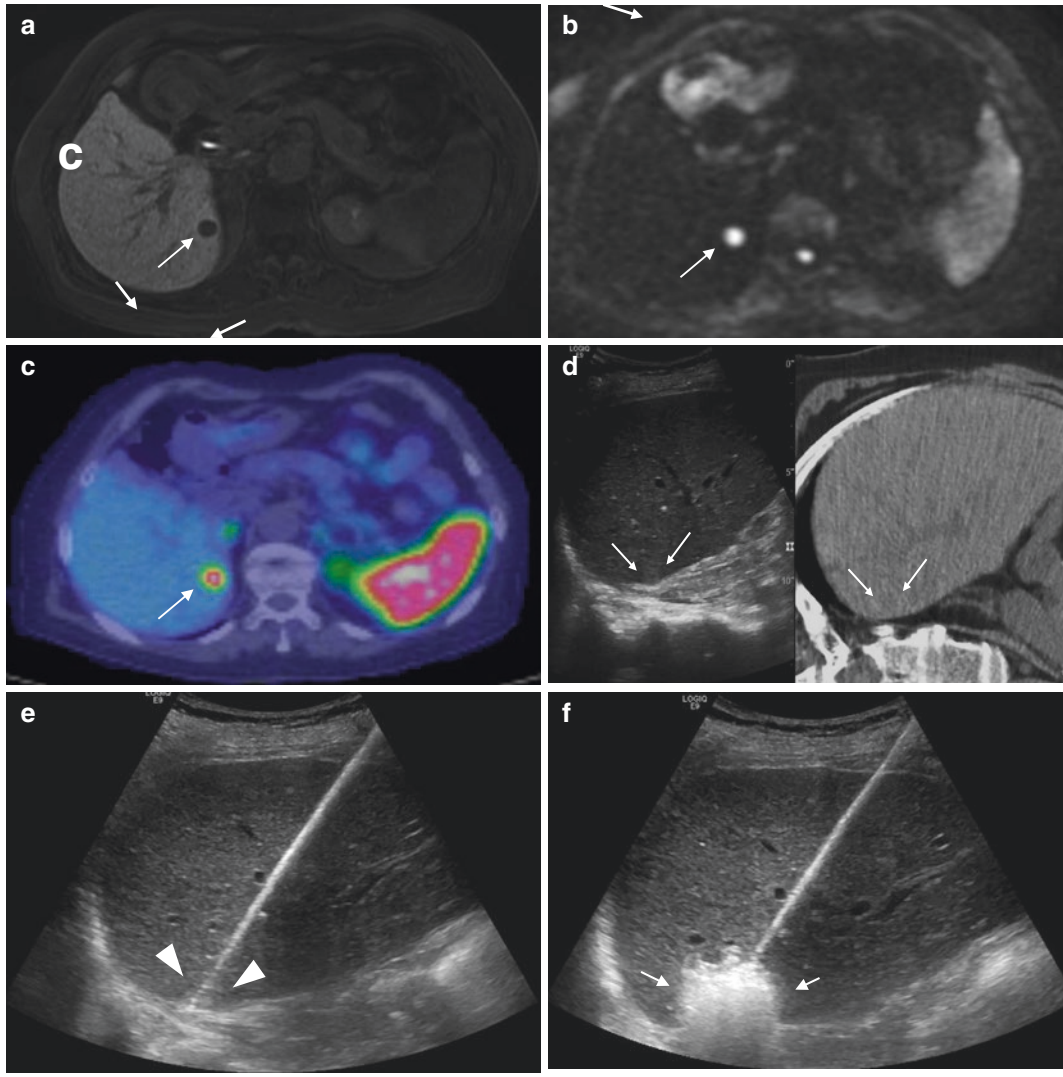

Fig. 10.3 Ileal NET G1 (Ki-67 1%) with two synchronous small liver metastases in S5 and S6. Patient previously received right emicolectomy, including the last ileal loop, and was subsequently treated with somatostatin analogues (SSAs). After 6 months, patient reported intolerance to SSAs. NET MDTB (IEO) puts indication for liver local treatment by percutaneous thermal ablation. Pretreatment-enhanced MRI clearly shows the lesion in S6 (arrow) both in T1w excretory phase (**a**) and in DWI (**b**); the lesion is also well defined on ^{68}GaPET/CT (**c**). Percutaneous MWA was performed to both the two lesions (S5 and S6) by using fusion-imaging technique (**d**) for a better precision; the lesion in S6 (arrows) is visible both on US and CT scan. (**e**) On US imaging, the tip of MWA-antenna located into the lesion (arrowheads); (**f**) as the result of the heat, tissue "vaporization" is visible at US as a white cloud (arrows). (**g**) CT performed 18 months after ablation clearly shows the hypodense scar of both the two treated liver metastases in S5 (arrowhead) and S6 (arrow)

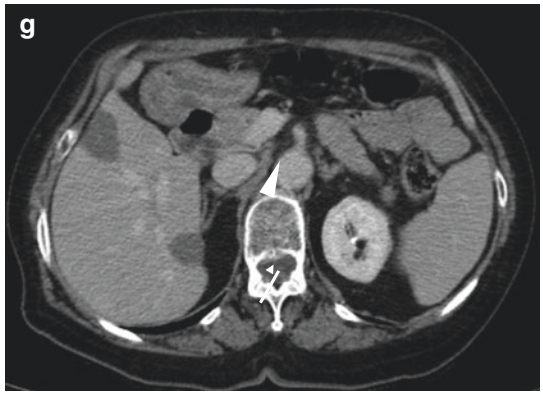

Fig. 10.3 (continued)

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