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Review

Liver metastases of neuroendocrine carcinomas: Interventional treatment via transarterial embolization, chemoembolization and thermal ablation

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ABSTRACT

The aim of this review article is to provide a practical clinical guideline for indication, technical aspects, protocol guideline and strategies for the interventional treatment of liver metastases from neuroendocrine tumors and focusing on the results of various protocols of management. The response to therapy, in the published articles, is calculated on the basis of the following clinical parameters; including symptomatic response (SR), biologic response (BR), morphological response (MR), progress free survival (PFS), and survival periods (SP). Transarterial chemoembolization (TACE) has been associated with SR rates of 60–95%, BR of 50–90%, MR of 33–80%, SR of 20–80 months, and a 5-year survival of between 50% and 65%. PFS was also between 18 and 24 months. In the transarterial embolization (TAE) group, SR was similar to the TACE group, MR was 32% and 82%, survival was between 18 and 88 months with a survival rate of 40–67%, and BR was between 50% and 69%. Radiofrequency ablation (RFA), either percutaneous or during surgery, has been associated with SR of 71–95% for a mean duration of 8–10 months, BR of 65%, and mean SP of 1.6 years after ablation. The mean survival following surgical resection for operable cases is 4.26 years ± S.D.: 1.1.

Conclusion: The interventional protocols for the management of liver metastases from neuroendocrine tumors: for oligonodular liver metastatic deposits, local resection or RFA and/or LITT is recommended, while in multinodular diseases with higher tumor load, TACE or TAE is recommended.

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Contents

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1. Introduction

Neuroendocrine tumors are slowly growing tumors with an indolent course. These tumors arise from the amine precursor uptake and decarboxylation (APUD) system, found in the gastrointestinal tract (entrochromaffin cells), the lung (Kulchitsky's cells, bronchus), and the pancreas (islet cells) [1,2,3]. These tumors involve carcinoid tumors of the stomach, small intestine, rectum, bronchus, islet cells of the pancreas, and primary hepatic carcinoids. The gastrointestinal carcinoids go undetected for a long time before they are diagnosed and are generally asymptomatic because the liver deactivates the released hormones, with the products released by these tumors as they drain into the liver via the portal vein [1,4,5]. These tumors generally become symptomatic when they are associated with liver metastases, and 80–90% of these tumors are inoperable at the time of presentation [6,7]. This is because the liver has to produce sufficiently large quantities of hormones in order for symptoms to appear, which may occur when there is extensive or diffuse liver disease. The liver lesions develop in about 46–93% of the neuroendocrine tumors [7–10] (Fig. 1).

Liver metastases can be divided into an active and an inactive group. The active tumors produce symptoms of diarrhea, flushing, cardiac arrhythmia, and abdominal pain; these manifestations are referred as carcinoid syndrome depending upon their severity, and are generally related to their production of serotonin [7]. Carcinoid syndrome is only associated with 4–10% of the primary carcinoid tumors, however, in the presence of hepatic metastases, the frequency of occurrence goes up to 60% [7,11]. The main reason for the treatment of these metastatic liver lesions is to: firstly, control the symptoms in patients with active tumors and, secondly, to control tumor growth and tumor size related symptoms. It has been shown in literature that the control of liver lesions significantly improves the 5-year survival rate as well as quality of life [1,6–9]. The treatment of liver lesions also reduces the symptoms that are associated with carcinoid syndrome [1–8].

1.1. Review of literature

Different approaches for the treatment of hepatic metastases have previously been described; at present, liver resection is the best radically curative treatment available, however, only 10–20% of all patients with hepatic metastases are eligible or fit the criteria for surgical resection [6,7]. Recent medical treatment with octreotide or lanreotide somatostatin analogs and interferon have been reported to be effective regarding control of the clinical symptoms, and many reports state that they have a tumor static activity in around 35.6–75% of the treated patients, lasting for a period of 3–12 months. These treatments, however, tend to become refractory with time and, on a long term, their efficacy drops [7,12–15]. Radiofrequency ablation, laser interstitial thermotherapy (LITT) of tumors and cryo-ablation of tumors have also been proposed. Intra-arterial regional therapy has been described with many retrospective studies as well as a few phase II trials and prospective studies using newer drugs, radioactive substances, or drug delivery systems [1–3,6,8,13,14,16–19] (Fig. 2).

2. Non-interventional radiology related approaches

2.1. Hepatic resection and liver transplantation

Liver resection still remains the gold standard for the treatment of liver metastases, however, only 10–20% of patients actually have a resectable disease [6,7] and unless more than 90% of the tumor load can be debulked during surgery, it is not useful as a palliative tool [7,20]. Hence, despite being a good approach for the treatment of these tumors, along with its ability to be used with curative intent, resection is done in limited cases due to large diffuse lesions. The presence of tumor involving the central veins and the portal vein also adversely affects the chance of resection. Ideal cases for hepatic resection are those with single lobe involvement or those with less than 3–5 metastases in both lobes of less than 3 cm in cross sectional diameter.

Two-stage hepatic resection has also been proposed for diffuse metastases. Here, the less affected lobe is operated at the same as time as the ligation of the contralateral portal vein in order to allow hypertrophy of the less affected lobe. Six weeks later, the more affected lobe is operated upon. Hepatic resection may be possible after cytoreduction of the tumor following transarterial chemoembolization or other ablative therapies [6].

Hepatic transplantation has been performed on patients suffering from severe carcinoid syndrome with life threatening disease, and when all the other therapies have been ineffective. It has been shown to have positive results, but the prognosis changes readily when the age of the patient is more than 50 years old or when more than 50% of the liver is infiltrated [7]. It is also used as a last line treatment. The indications for liver transplantation are well defined by the Milan criteria [21]. Transplanted livers are not, however, exempt from recurrent metastases in the organ [22]. Blonski et al. have stated the occurrence of; (a) a shortage of donor organs, (b) the presence of high recurrence rates, and (c) declared that hepatic transplantation should be undertaken when other therapeutic options have failed [7]. Florman et al. have reported a high rate of mortality and morbidity in patients who underwent extensive surgery such as the Whipple operation or abdominal exenterations and hepatic transplantation [23].

Hepatic resection and transplantation have been associated with higher complication rates than other therapies, though advances in techniques and equipment have brought the figures down drastically. Touzios et al. have shown in their study; 30 days mortality of 5.3% and morbidity of 42%. Mortality is higher with liver transplantation as well as in patients with larger tumor loads. Morbidity includes biloma, anastomotic leaks, biliary leaks, pancreatic fistulas, biliary fistulas, rarely portal vein thrombosis, bleeding, and hepatic abscesses, etc. [8,24].

2.2. Somatostatin analogs and interferon therapy

Somatostatin analogs like octreotide and lanreotide have been effectively used subcutaneously in patients with carcinoid syndrome, improving the symptoms significantly with a remarkable improvement in the quality of life. Some reports have also shown the therapy to have anti-tumor activity, further delaying the spread
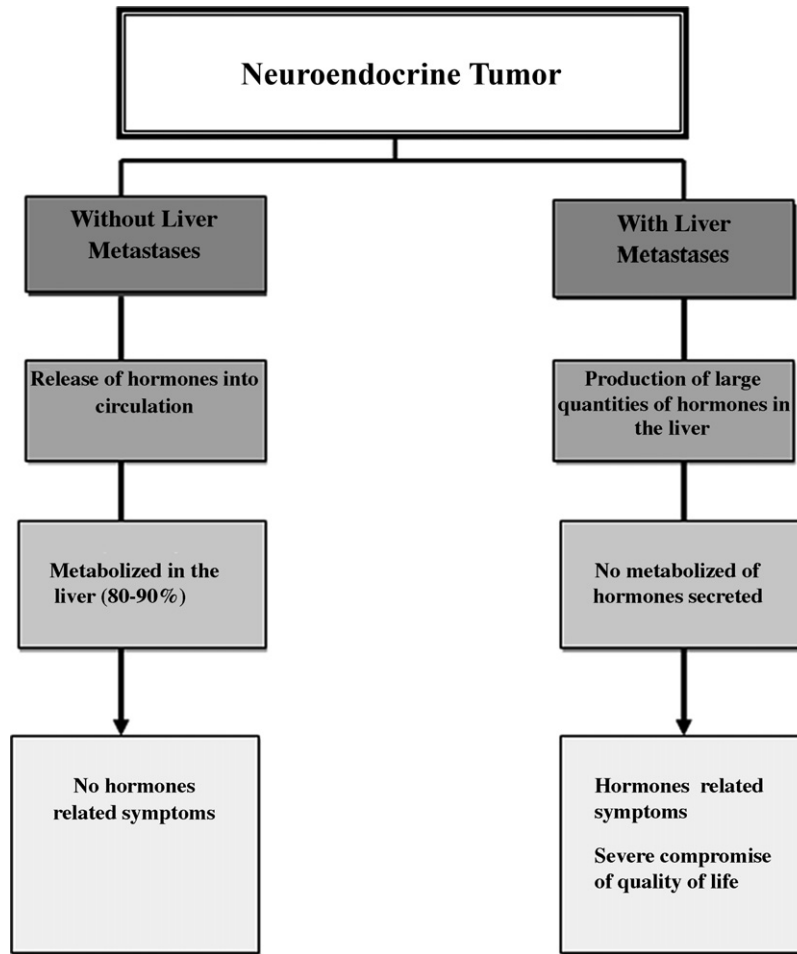
Fig. 1. Schematic diagram of relation of functionally active tumors and symptomatology due to liver metastases.

of disease [14]. Alpha interferon at doses of 3–9 million units three to seven times per week subcutaneously, has given biochemical response rates of 50% and significant tumor reduction in about 15% of patients with long duration, up to 3 years. Somatostatin analogues have been used in the treatment of neuroendocrine gut and pancreatic tumors. Octreotide is registered in many centers for the treatment of patients with carcinoid syndrome and also VIP (vasoactive intestinal peptide) and glucagon producing tumors. Regular octreotide at standard doses of 100–300 μg/day gives symptomatic responses in a medium of 60% of patients and biochemical responses in up to 70% of patients. However, significant tumor responses are less than 5% [25,26]. It has been seen that with time, however, the tumors become refractory to the medications and hence, alternative treatment is necessary. These medications are more effective in the presence of carcinoid syndrome. Interferon therapy has also been tried and found effective in controlling the symptoms. Interferon is associated with many reported systemic side effects such as elevated liver enzymes, diarrhea, nausea, fever, steatorrhea, alopecia, hyper/hypoglycemia, thyroiditis and thrombocytopenia [27].

2.3. Systemic chemotherapy

Chemotherapy has been used in patients with high proliferating neuroendocrine tumors such as endocrine pancreatic tumors and lung carcinoids. Streptozotocin-based combinations including 5-flourouracil and doxorubicin have generated only partial remis-

sions in 40% of the patients giving a median survival of about 2 years. Cisplatin plus Etoposide have demonstrated significant antitumor effects in anaplastic endocrine pancreatic tumors and lung carcinoids. However, in low proliferating tumors such as classical midgut carcinoids the response rates with the same combinations of cytotoxic agents have only generated short lasting responses in less than 10% of patients [28]. Other chemotherapeutic agents used are 5-FU, Cisplatin, and Adriamycin.

3. Interventional radiology related approaches

3.1. Transarterial therapy

3.1.1. Principle

Loco-regional transarterial therapy can be further sub-divided into transarterial embolization (TAE) and transarterial chemoembolization (TACE). Both of these techniques have been effectively used in the palliative management of hepatic metastases from neuroendocrine tumors. Because the neuroendocrine tumors are prone to produce highly vascular metastases in the liver, and these metastases receive their blood supply predominantly (>90%) from the hepatic artery [2,6], whereas the normal liver parenchyma receives 75–80% of its supply form the portal vein with only 20–25% of the supply derived from the hepatic artery. The hepatic metastases are known to compress the adjacent portal sinusoids [6]. Tumor ischemia has been proven as a method for the control of primary hepatocellular carcinoma, and now in cases of neuroendocrine liver
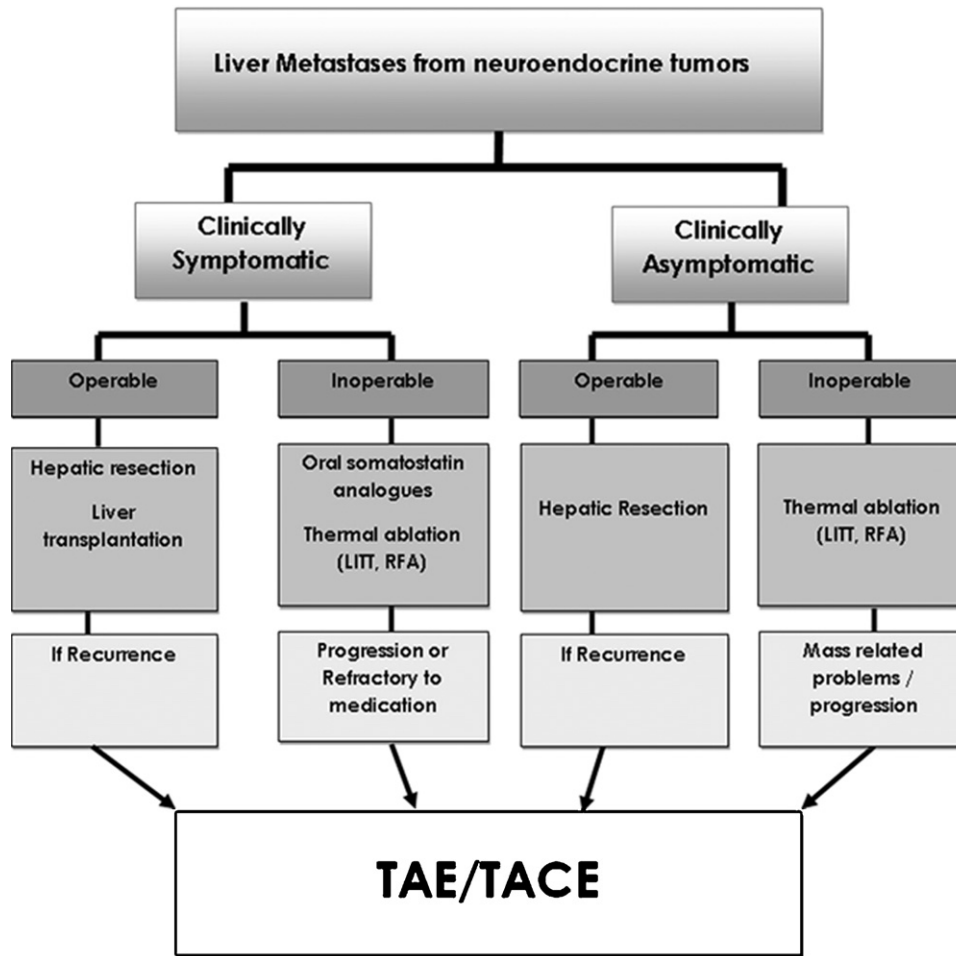
Fig. 2. schematic diagram of available treatment options for liver metastases from neuroendocrine tumors which reveals that TAE/TACE are at the heart of the treatment program for liver metastases from neuroendocrine tumors.

metastases as well, which are very vascular. This therapy is slowly and steadily paving its way to become the standard protocol in the treatment of metastatic liver lesions from neuroendocrine tumors particularly in high liver tumor load (Fig. 3).

3.1.2. Materials and protocols of therapy

In case of hepatic arterial embolization (TAE), there have been different protocols used with the intent to create tumor ischemia by embolizing the hepatic arterial branches supplying the tumor. Permanent embolic agents such as cyanoacrylate (histoacryl) have been effectively used by Loewe et al. in conjunction with lipiodol to create complete embolization of the tumor feeding artery [1]. In other studies, embolization has been performed using gel foam particles, with or without lipiodol [13,29]. Moertel et al. performed hepatic artery embolization followed by systemic chemotherapy, which they found to be useful [26]. Permanent embolic particles like PVA (Polyvinyl alcohol) foam and microspheres have been used by Gupta et al. [30]. Surgical ligation of the hepatic artery has been performed, however it is not as effective as distal embolization achieved by transarterial method; in the latter, there is complete embolization of the vessels adjacent to the tumor. Moreover, due to distal embolization, effective devascularization is achieved with a lower possibility of collateral supply. The other advantage is that in case of recurrence or revascularization, a repeat procedure can be done which is not possible with surgical ligation of the hepatic artery. When proximal embolization of tumor-feeding arteries in hepatic metastases is performed using large particles or coils, the

peripheral hepatic circulation reconstitutes immediately through collateral vessels. The earlier the revascularization of the tumor, the more incomplete the necrosis is, necessitating repeated embolization. In case of transarterial chemoembolization, the basic principle is the same as that of hepatic arterial embolization, however in this case, a chemotherapeutic agent is added to the intra-arterial therapy. It has been proven that the intra-tumoral concentration of a chemotherapeutic agent is 10–20 times higher with an intra-arterial loco-regional injection when compared to that of systemic chemotherapy [2,6]. Synergistic effect is achieved by using both the chemotherapeutic agents and the tumor ischemia, created by the use of embolic agents such as lipiodol, gel foam particles, PVA particles, or microspheres. There are many different protocols used in different centers; Roche et al. [15] and Kress et al. [3] have used doxorubicin as the chemotherapeutic agent with lipiodol, gel foam, and iodinated contrast, whereas Dominguez et al. used streptozocin in an emulsion with lipiodol and a gelatin sponge [16]. Drougas et al. [18] preferred to give the patients 5 days of 5 FU (5 Fluorouracil) followed by TACE with a combination of drugs including Adriamycin, Cisplatin, Mitomycin C, and PVA particles. In a phase II study conducted by Diamandidou et al., microencapsulated cisplatin was used, prepared by emulsifying PVA and cisplatin. It was then mixed with contrast to cause chemoembolization [19].

TACE and TAE have been used in an adjuvant setting to reduce the tumor load before a patient goes in for hepatic resection, hepatic transplantation, or for tumor ablation techniques.
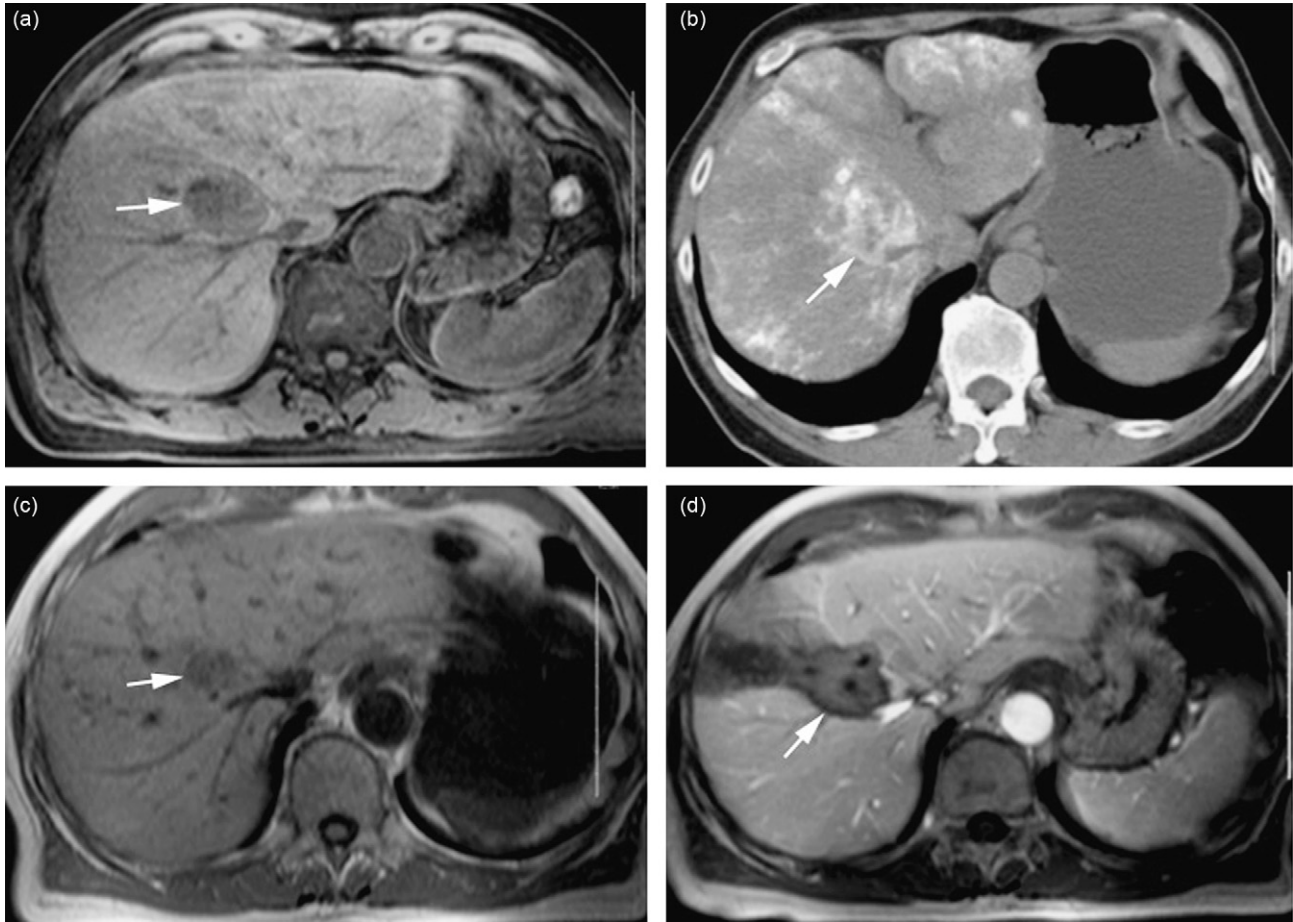
Fig. 3. Example of TACE in the treatment of hepatic metastases from neuroendocrine tumors that was followed by LITT ablation after downsizing of the lesions by TACE therapy. A 60-year-old female with multiple liver metastases of neuroendocrine origin. (a) Reveals one of the multiple metastases in the liver (arrow) on axial MRI (TR 77, TE 2) imaging. (b) Axial CT scanning showing the lipiodol uptake by the active metastasis (arrow). (c) Axial MRI scanning of the same lesion demonstrating more than 50% reduction of the size of the lesion (arrow) after 4 months of treatment. (d) Corresponds to the last axial MRI post-contrast injection (TR 104, TE 5) after LITT ablation, with wide ablation zone at the metastatic bed, with absence of any enhancing tumor residue.

3.1.3. Selective intra-arterial radiotherapy (SIRT)

McStay et al. performed intra-arterial radiotherapy (SIRT) using ^{90}Y-DOTA-Lanreotide particles to give loco-regional radiation therapy. The presence of metal chelator tetrazacyclodecane tetraacetic acid (DOTA) considerably improves the stability of somatostatin radio-conjugates and makes it possible to use various radionuclides such as yttrium 90 (^{90}Y), which delivers high radiation for receptor targeted radionuclide therapy. DOTA chelated lanreotide can be attached to beta emitting therapeutic radionuclide ^{90}Y, at which point the ^{90}Y DOTA lanreotide then binds to the somatostatin 2–5 receptors with high affinity and to the somatostatin 1 receptors with low affinity. 30% of the ^{90}Y DOTA lanreotide is lost through renal excretion in the first hour when injected intravenously [31]. Hence, McStay et al. proposed direct hepatic transarterial injection to achieve greater intra-tumor concentration of the ^{90}Y-DOTA lanreotide. They administered a standardized dose of 1 GBq with or without the addition of PVA microparticles. This procedure was repeated over a period of 2 months, depending on tumor response [31].

3.1.4. Complications of TAE and TACE

Complications seen with TACE and TAE vary in literature. With Touzios et al., a high 30 day mortality of 5.6% and a morbidity of 28% have been reported, while other authors have zero percent in early

post-procedure mortality. Morbidity includes liver abscess, transient hepatorenal failure (which, if not corrected urgently, can be fatal), pleural effusion, sepsis, bowel ischemia requiring surgery, septicemia requiring antibiotic therapy and prolonging hospital stay, and hepatic infarction. Other less morbid adverse reaction includes post-embolization syndrome, which is seen in most of the patients, some reports putting the figure at 80–90%. It also includes a fever that subsides in a couple of days, leukocytosis, abdominal pain sometimes requiring morphine, and a transient increase in liver enzymes predominantly transaminases and LDH which generally comes down within a few days to 2–3 weeks. Increased bilirubin levels have also been noted. Ischemia of the biliary tree has also been rarely reported when over enthusiastic embolization has been performed.

In addition, moderate elevation of alkaline phosphatase have also been noticed. The best possible way to reduce post-embolization syndrome is to keep the patient well hydrated and in supportive care [8].

3.2. Thermal ablations

3.2.1. Radiofrequency ablation

Radiofrequency ablation (RFA) has been used extensively in hepatic metastases form colorectal carcinomas, and few studies

exist using radiofrequency ablation for treatment of hepatic metastases form neuroendocrine tumors [32]. RFA has previously been performed either percutaneously or with laparoscopic surgery. The procedure has been used with a cooled tip electrode or a non-cooled tip, though the prior system is normally preferred in cases of larger lesions as it gives a larger area of ablation due to reduced charring at the tip [36]. RFA has been used for lesions larger than 3 cm with multiple applicators in the same sitting [32]. Henn et al. have treated up to 12 lesions in a single sitting under mild diazepam with CT guidance; the maximum tumor size they ablated was 7.1 cm [33]. Elvin et al. have successfully treated tumors up to 7 cm in size [34], while Gillams et al. have treated tumors up to the maximum size of 9 cm [35]. The technique varies with different authors; Elvin et al. followed a protocol where they were able to achieve an average final temperature in the tumor of 65 ± 8.2 degrees C which was delivered at 72 ± 19 W [34]. Gillams et al., on the other hand, have used the saline perfused electrodes predominantly with a single or cluster of three internally cooled electrodes [35]. Con-

trast enhanced Ultrasound, CT and MRI are used to monitor the efficiency of the ablation therapy and monitor the complications associated [35].

Complications associated with radiofrequency ablation have been generally related to the electrode application, such as pneumothorax and neuritis at the site of skin entry. Liver abscess have also been reported, as well as infrequent sub-diaphragmatic hematomas. Major complications are rare and have been reported in 5% or less cases; death is extremely rare. Skin burn at site of skin pads in the case of a unipolar electrode system has also been reported. Post-ablation transient elevation of liver enzymes AST and ALT has been documented by most authors, but seem to return back to normal within a few days.

3.2.2. LITT (laser interstitial thermotherapy)

Laser induced interstitial thermotherapy has been used extensively by Vogl et al. for the treatment of liver metastases with very encouraging results [36]. This technique, using laser (ND.YAG) with
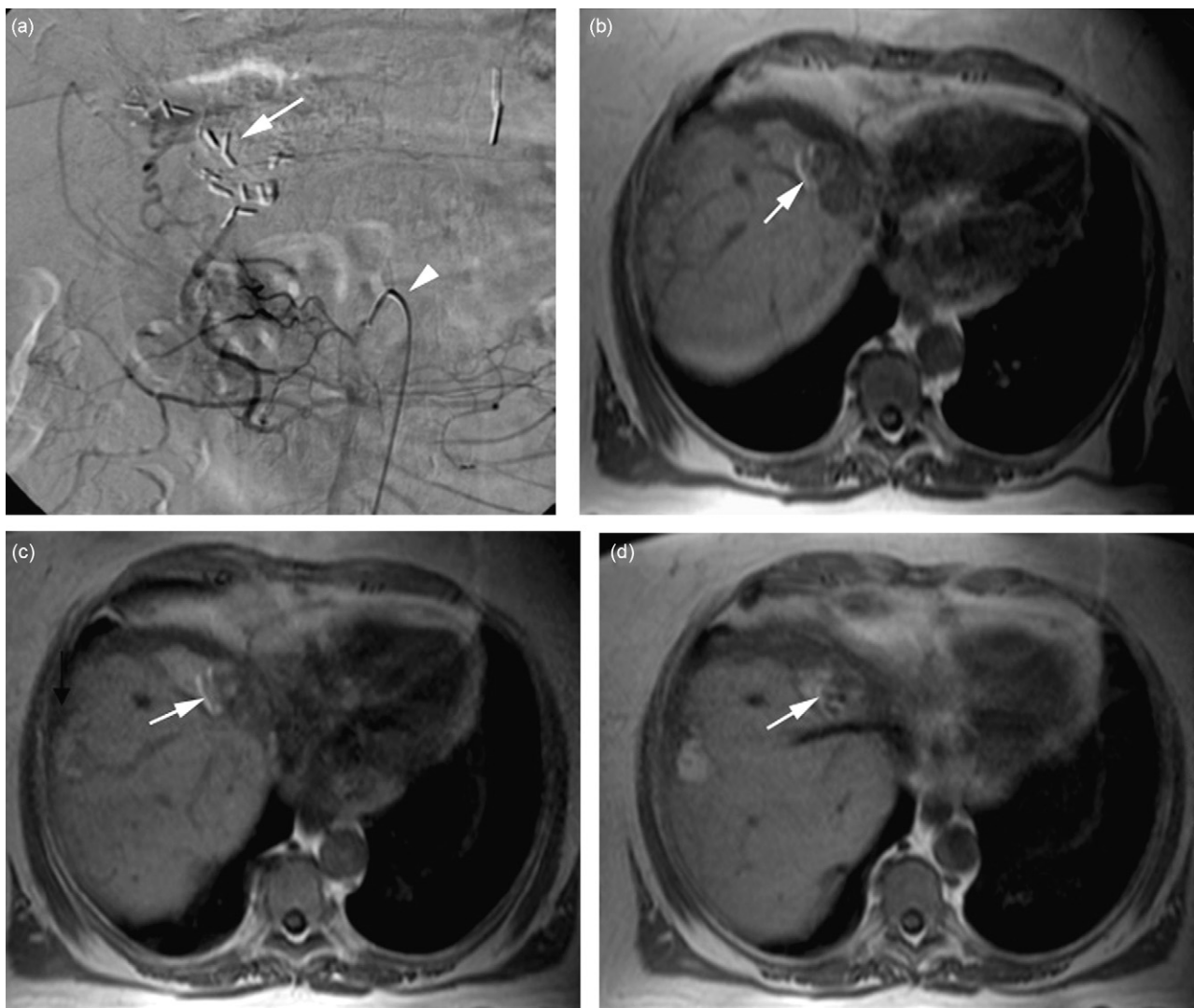
Fig. 4. Example of use of TACE in post-resection recurrence in a neoadjuvant setting to achieve cytoreduction before laser therapy. MRI and angiographic images of a 68-year-old female with liver metastases from neuroendocrine tumors. (a) Right hepatic arteriogram. Note the presence of surgical staples (arrow) and 5F cobra catheter in the right hepatic artery that arises from the superior mesenteric artery. (b) An axial MRI (TR 116, TE 5) revealing a recurrence in post-hepatic resection patient (arrows). (c) An axial MRI scan (TR 110, TE 5) reveals post-trans hepatic arterial chemoembolization partial response (>50% reduction in tumor size)(arrow). (d) Reveals immediate post-laser therapy MRI (TR 119, TE 5) (arrow) note complete tumor ablation with no evidence of residue.

a bare 400 μm laser fiber, creates coagulative necrosis, secondary degeneration, and atrophy via light of the wavelength 1046 nm emitted through the tip of the laser fiber into the tumor tissue, which is converted into heat. The laser fiber is introduced via a laser application kit consisting of a cannulation needle, guide wire, a sheath system with mandrin (10F, 20 cm in length), and a special protective catheter (9F, 43 cm in length) that is closed at the end. This protective catheter, which is heat resistant, prevents direct contact of the laser fiber with the tissue and enables safe and easy removal of the fiber post-therapy. The laser system is cooled with saline and so prevents the carbonization of the laser fiber. The advantage of the laser application system is that it can be done under MR guidance; this is of great value as the efficacy of the therapy can be evaluated simultaneously under MRI. The temperature changes can be evaluated in the tissue by performing a thermo-sensitive T1WI sequence. The zone of necrosis can be immediately evaluated, post-therapy. The other advantage of MRI guidance is lack of radiation exposure to the patient [36]. Gillams used a solid-state (805 nm wave length) laser for performing laser therapy on liver metastases from neuroendocrine tumors [37]. They operated with multiple [2–8] 19 gauge needles through which they inserted laser fibers (400–600 μm), using a beam splitter to employ multiple fibers. A 1 cm zone of necrosis was acquired, after which the fiber was repositioned. Complication associated with LITT include post-therapy pain, pleural effusion, and, although seldom, subcapsular hematoma. One death due to sepsis within 30 days of therapy has been reported by Vogl et al. putting the major complication at 1.2% [36] (Fig. 4).

4. Response evaluation

Response evaluation has been performed on the following different parameters (Fig. 5).

4.1. Symptomatic response

The secretion of different biologically active amine (endocrine secretions) form tumors generally arrive into the systemic circulation in the presence of extensive liver involvement, bypassing the liver metabolism into the systemic circulation. However, in the absence of liver metastases, symptoms have not been noted as often as in cases with the presence of liver metastases [38–40]. 90% of symptoms are noted after the development of metastases [38–40]. Symptoms seen are cutaneous flushes, diarrhea, bronchospasms, and right sided heart failure [38]; these all also come under the umbrella of carcinoid syndrome which can be noted in 7.7% of patients with these tumors [38,39]. Carcinoid heart disease is associated with a worse prognosis and is caused due to endocardial damage due to serotonin secretion and is noted in 17.4–33% of patients [38,41,42]. The response to therapy and the duration of response has been used as a parameter. TAE is generally associated with 64–93% of patients to have symptomatic improvement for a period varying between 1 and 18 months. TACE is associated with symptomatic response between 53% and 95% of patients for a period of 10–55 months. Surgery is associated with a symptomatic response of 90–95% of patients for a mean of 19.5 months in one report. A combination therapy of octreotide, intra-arterial chemotherapy, and TACE seem to have a
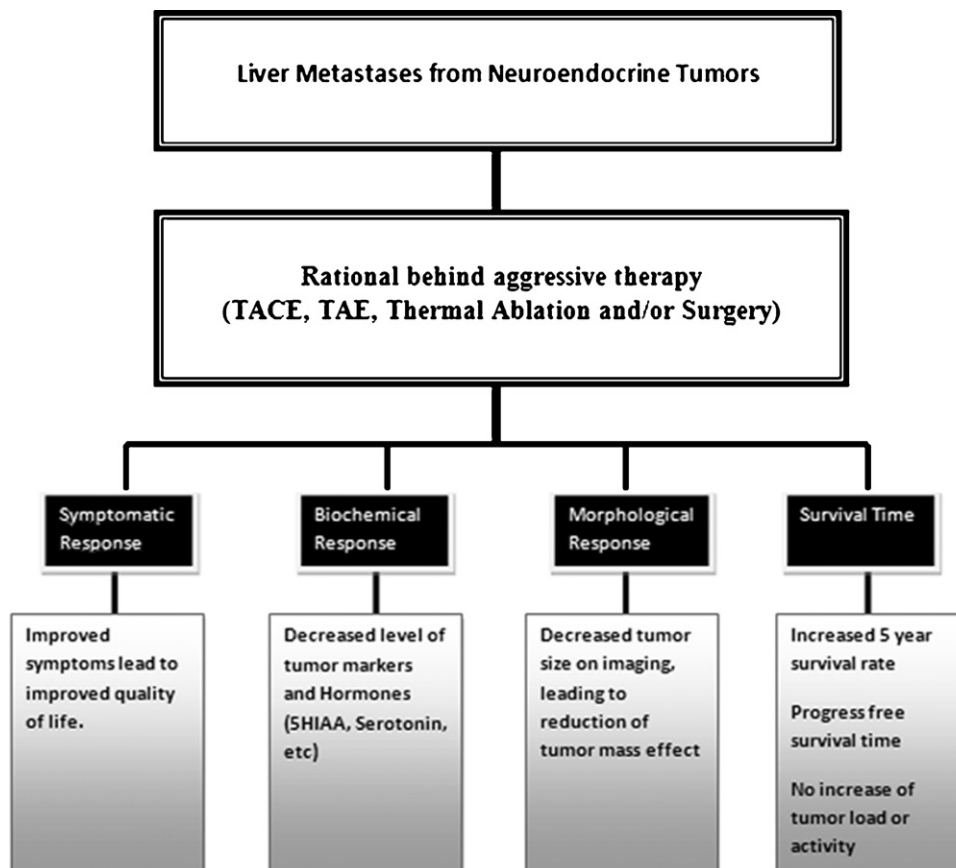

Fig. 5. Schematic demonstration of treatment of liver metastases of neuroendocrine tumors and rational of therapy.

Table 1
Charting of symptomatic response seen in different studies in literature with relation to type of treatment, number of months/percentage with reference to liver metastases from neuroendocrine tumors

Name	No. of patients	Type of T/T	Response	Time (months)	Percentage	Reference no.
Nobin et al.	19	Surgical dearterilazation	11	Minimum 12		[43]
Carrasco et al.	25	PVA Part, gel foam, coils	14 (70%) PR, 6 MR, 1 (4%) No RES	11mean (1–50), 4 recur 14 mean (9–230)	70 PR, 30 MR, 4 NR	[44]
Touzios et al.	23	Non aggressive medical			42%	
	18	TACE with 11 ablation			88%	[8]
	19	Surg + ablation			95%	
Que et al.	36/38	Surgery		19.3	90%	[45]
Perry et al.	30	Doxorubicin, lipiodol, gel foam	27		90%	[46]
Dominguez et al.	15.5 symptomatic	Streptozocin, lipiodol, gel foam	3/5	10–17	60%	[16]
Diaco et al.	10	Octreotide, IA 5 FU + TACE	10/10	51.5	100%	[47]
Ruszniewski et al.	24.11 symt	Doxorubicin, lipodol, gel foam	8/11	14 (3–24)	72.7	[48]
Therasse et al.	24.18 cs	TACE		29	70CR, 30PR	[17]
Stokes et al.	20.16 symptomatic	Doxo, lipodol, iopamadol, gel foam	16/16		100	[49]
Desai et al.	34	Adriamycin, mitomycin, lipodol, particles, helibrix	31		78%	[50]
Roche et al.	64	TACE		15	93	[51]
Roche et al.	15	TACE	10cr, 3pr	17 (6–53)	70cr, 20pr	[15]
Diamandidou et al.	20, 18 symptomatic	Microencapsulated cisplatin	12/18 > 50%	14 (3–24)	66.66%	[52]
Kress et al.	26.9 symptomatic	Doxoru, lipodol, PVA, microspheres, ethanol, contrast	No response in any patients			[3]
Ruszniewski et al.	15	Adriamycin or streptozocin, lipodol, gel foam	Object response 8/15	10.5	53%	[53]

Please note. PR: partial response, OR: objective response, SD: stable disease, PD: progressive disease, CR: complete response, MR: minor response and no RES: no response.

complete symptomatic response with a mean 51.5 months in some studies (Table 1).

4.2. Biological response

There are multiple biological tumor markers depending upon the site of the primary tumor and the tumor secretions. Urinary 5 HIAA is an important metabolic product of serotonin synthesis. Other tumor markers include Chromgranin A, serum serotonin, serum, gastrin, insulin, dopamine, and neuro specific enolase. Reduced survival rates were noted with urinary 5 HIAA levels

of above 300–500 μmol/day [34,35]. Many authors evaluated the effective clinical response to therapy by assessing the amount of reduction of the tumor markers (Table 2).

4.3. Morphological response

The morphological response includes the tumor size regression response to the treatment. It is evaluated by measuring tumor dimensions in different imaging modalities. This morphological response has been classified into: (a) complete response (CR) when the tumor is no longer seen post-therapy, (b) partial response (PR)

Table 2
List of response rates seen in post-treatment in the levels of tumor markers in different published articles in literature with reference to the type of treatment and the percentage of reduction

Name	No. of patients	Treatment	Response	Time	Percentage	Reference no.
Carrasco et al.	23	TAE	18		41% mean 8–67	[44]
Eriksson et al.	29 carcinoid	TAE	11 PR, 9 SD			[54]
	12 PAN	TAE	5			
Loewe et al.	15	TAE	8 PR, 2MR, 2 Mi=		>50%	[1]
Perry et al.	30	TACE	79%PR, 92%PR + MR		PR > 50%	[46]
Dominguez et al.	20	TACE	CR 4	7 months		[16]
Ruszniewski et al.	24	TACE	57%	14 months	>50%	[53]
Therasse et al.	23	TACE	73% CR, 18% PR, 9%MR	21 months		[17]
Drougas et al.	15	TACE			60% hi, 75% chA, 50% nse	[18]
Kim et al.	30	TACE	12/17 (75%CHa) 9/10 (90%isl)			[55]
Stokes et al.	20	TACE	16		90%	[49]
Fiorentini et al.	10	TACE			75% red 5 HIAA	[56]
Desai et al.	34	TACE	Pancreastatin 31pts (78%), serotonin 24 (60%)			[50]
Roche et al.	64	TACE	52%PTS	15mts		[51]
Clouse et al.	20	TACE	14 PTS 95%	8.5mts	90%-69–90%	[57]
Roche et al.	14	TACE	6/8 (78%)	16mts 12–24	>50%	[15]
Kress et al.			6/9 < 25%sero, 2 > 25%hiaa, chromo a >100% 10,>50% 3, >25% 2			[3]
Ruszniewski et al.	15	TACE	4 CR	7 months		[53]
Hanssen et al.	36	Alpha interferon	24% PR	1 yr	>50%	[58]

Please note. PR: partial response, OR: objective response, SD: stable disease, PD: progressive disease and CR: complete response.

Table 3
List of response rates, seen in post-treatment, of the tumor size in different published articles in literature with reference to the type of treatment and the percentage of reduction and time

Name	No. of patients	Treatment	Response	Time	Percentage	Reference no.
Nobin et al.	19	Surgical dearterialization	12 stable disease	4–12		[43]
Eriksson et al.	29	TAE	PR 11, SD 9, PD 4	8–12		[54]
	12	TAE	2 CR, 6 PR, 1 SD, 2 PR	10	17%, 50%, 8%, 16%	
Loewe et al.	24	TAE	CR4, PR12, SD5, PD1	53–88	18%, 55%, 22.7%	[1]
Dominguez et al.	15	TACE	Objective response 8	10.5	53%	[16]
Diaco et al.	10	TACE	6 PR, 3 SD	Mean 42	60% PR, 30% SD	[47]
Ruszniewski et al.	18	TACE	6 PR, 2CR, 3SD	6–40 mean 14	33% SD	[48]
Therasse et al.	23	TACE			11% CR, 24% PR, 24% MR	[17]
Drougas et al.	15	TACE	10/13			[18]
Kim et al.	30	TACE	11/30	6–63 med 24	37%	[55]
Stokes et al.	20	TACE	PR 84% Decrease			[49]
Fiorentini et al.	10	TACE	CR 2, 5 PR	12–34		[56]
Desai et al.	34	TACE	18		45%	[50]
Roche et al.	64	TACE		Mean 15	74%	[51]
Roche et al.	14	TACE	PR 6, MR 4, SD2	25, 14, 4–11	PR 43%, MR 29%, SD 14%	[15]
Diamandidou et al.			6PR, 8MR, 4 SD		PR 33%, MR 44%, SD 22%	[52]
Kress et al.	26	TACE	14 SD, 2 PR, 5 PD			[3]
Ruszniewski et al.			8 pr, 2 SD, 5 pd	7/36. 10/12		[48]
Skinazi et al.	10	5 FU, Streptozocin	OR2, MR10		OR 20%, MR 10%	[59]
Skinazi et al.	10	TACE	OR 3/7, MR 2/7		43%, 29%	
Skinazi et al.	10	Octreotide	OR 0, MR 2		MR 20%	
Hanssen et al.	36	Alpha interferon Plus embolization		1 yr	SD 43%, 19% PD 20%SD, 20% PD	[58]
Hellman et al.	21pts with 43 lesion	RFA	41 CR, 2 Recurrence	2.1 yrs mean		[32]
Gupta et al.	69 caricinods	TAE/TACE	PR 46, MR 6, SD 11, PD 6		PR 67%, MR 8.7%, SD 16%, PD 8.7%	[30]
	54 islet cell tumor	TAE/TACE	PR 19, MR 1, SD 32, PD 2		PR 35%, MR 2%, SD 59%, PD 4%	

Please note. PR: partial response, OR: objective response, SD: stable disease, PD: progressive disease and CR: complete response.

when there is a >30% reduction in tumor size, (c) stable disease (SD) when there is 25% reduction or 25% increase in size, and finally, (d) progressive disease (PD) in which there is more than a 25% increase in the size of the tumor, post-therapy. Morphological response has been calculated by measuring the size of the lesions before and after 4–6 weeks of completion of therapy, with some authors doing a comparison on long term follow up. Objective response, meaning partial and complete response in the case of TAE has been around 37–74%, going as high as 95% when stable disease is added to the figure. The time periods vary between 3 and 88 months. With respect to TACE, the objective response was between 35% and 74% of patients, going up to 98% when stable disease was also added. Time periods have been between 6 and 63 months (Table 3).

4.4. Survival rate

The survival rate has generally been calculated from the first onset of metastases and the first time of interventional therapy to the date of death. The second aspect is the percentage of persons living at the end of 1, 2, and 5 years after the onset of metastases and the first time interventional therapy was applied; this is the final and most important factor. All of the above factors have been evaluated by different authors and their influence on the over all survival quota and whether their response to therapy rates were statistically significant to the survival rate. Surgery has the longest 5-year survival rater of 70–76%, TACE with rates between 48% and 83%, and TAE is associated with rated between 40 and 54%. Non-interventional medical therapy has the poorest survival rates between 0% and 25% (Table 4).

5. Discussion

Neuroendocrine tumors are infrequent tumors in routine clinical practice with most of the cases found in tertiary oncology referral centers. Liver metastases from these tumors are generally detected in a late stage when curative surgical options can normally not be offered to the patients. These tumors, due to their indolent course and prolonged survival, have attracted the attention of many scientific studies. The interest in these tumors for scientific studies extends yet further, considering their production of debilitating symptoms which, when tackled through treatment of liver metastases, lead to significantly improved quality of life with a longer survival period. In summary, one can extend good quality of life and prolonged survival through controlling the liver metastases (Fig. 1).

Evidence in literature demands that liver metastases from neuroendocrine tumors should be treated aggressively. Non-aggressive treatment is primarily associated with only 40 months survival and a poor 5-year survival, however, a 5 year survival with aggressive therapy can be between 48% and 83%. Symptomatic response is also significantly better in patients when treated aggressively. The aggressive treatment of these patients is based on a multifaceted approach; firstly, to achieve relief from symptoms associated with carcinoid syndrome or hormone release. Secondly, reduction of serum levels of different hormones which are tumor specific, such as serotonin and other tumor metabolites responsible for systemic manifestations. Thirdly, reduction of the over all tumor burden in the liver, interpreted as morphological response on different imaging modalities. The final and probably most important factor is to increase survival of the patient, which, in these cases, is either survival without progress of the tumor in terms of symptoms of tumor load (activity), or over all survival in months or per 5 years.

Table 4
Survival rates of patients in terms of 5-year survival or months post-therapy noted in literature

Name	No. of patients	Treatment	Number	Time	Percentage	Reference no.
Carrasco et al.	25	TAE	15L/8D	16 months, 1–50 (Death)5 d to 22 months		[47]
Brown et al.	35	TAE		5 yrs	54%	[60]
Eriksson et al.	29	TAE		5 yrs	40%	[54]
	12 pancreas	TAE		20 months, 5 yrs	0	
Loewe et al.	23	TAE		5 yrs, 68 months	65.4%	[1]
Perry et al.	30	TACE		median 24 months		[46]
Diaco et al.	10	TACE		40 months 12–65		[47]
Therasse et al.	24	TACE		median 24 months		[17]
Drougas et al.	15	TACE		16 median 1–77		[18]
Kim et al.	30	TACE		15 median 2–67		[55]
Stokes et al.	20	TACE	17	6–2 months		[49]
Fiorentini et al.	10	TACE		mean 22 months		[56]
Clouse et al.	20	TACE		24 months		[57]
Roche et al.	14	TACE		10 yrs, 5 yrs	56%, 83%	[15]
Kress et al.	26	TACE		5 yrs	48%	[3]
Que et al.	74	Surgery		4 yrs	73%	[45]
Hanssen et al.	36	Alpha interferon		5 yrs	40%	[58]
		With HAE		5 yrs	75%	
Chamberlain et al.	85	Non aggressive medical therapy		1/3/5 yrs	76/39/na	
	33	Surgery		1/3/5 yrs	94%, 83%, 76%	[61]
	34	TAE		1/3/5 yrs	94%, 83%, 50%	
Touzios et al.	23	Non agressive		20 months, 5 yrs	25%	
	19	Sx ± RFA		96 months, 5 yr	72%	[8]
	18	TACE ± abl, sx		50 months, 5 yrs	50%	
Gupta et al.	69 carcinoid tumors	TAE/TACE		Median 33.8 months	95.3%, 68.6%, 28.6%	[30]
	54 islet cell tumor	TAE/TACE		Median 23.2 months	68.8%, 48.7%, 13.7%	

Evidence from literature shows that the surgical resection of hepatic metastases with curative intent is still the best treatment option for hepatic metastases from the neuroendocrine primary with a 5 year survival rate up to 76%. However, considering the fact that 10% to an optimistic figure of 20% of patients with liver lesions can be treated with the surgical scalpel, a large 80–90% of patients are left whose lesions need to be addressed. We have tried here to address this exact population. The evidence in literature signals that intravenous chemotherapy currently has no practical role to play in the treatment of these lesions, as it is associated with poor symptomatic response and survival rates. Kulke et al. reported various systemic complications on systemic therapy including neuropathy, thrombocytopenia, neutropenia, rash, and infection, leading to therapy discontinuation in 55% of their study group [62].

As for Interferon and oral somatostatin analogues, which initially were considered a very promising option, literature shows that although symptomatic response is good, it only lasts for a short period and that these tumors become refractory to these treatments. One can also not ignore that the morphological response with them is less than satisfactory. Interferon alone has show 5-year survival up to 40%, but when embolization is added to interferon therapy, the percentage mounts to 75% for 5 years.

Evidence in medical publications of the overwhelming role played by TACE or TAE in the treatment of these lesions in terms of any of the above mentioned approaches via symptomatic response (53–100% patients for 10–55 months), biochemical response, and morphological response (35–74% for 6–63 months), as well as rate of survival (40–83% 5 years survival). TACE and/or TAE appear to be the best possible available treatment approach for inoperable liver metastases from neuroendocrine tumors. Some authors recommend it as the first line of treatment in the case of inoperable disease. Most of the authors advocated multiple sessions, some recommend intervals in relation to patients symptoms, and some recommend a 4–6 weeks interval between two successive sessions. There are multiple different chemoembolization and embolization

protocols used, providing good symptomatic responses and morphological responses, as well as good survival rates. TACE and/or TAE can also be used for cytoreduction prior to surgery or thermal ablation. It is also the treatment of choice in cases where there is recurrent post-resection or thermal ablation. Thermal ablations such as RFA or laser ablation are currently used for treatment in some centers with promising results.

Ho et al. showed in their study, which 46 patients with carcinoid ($n = 31$) and islet cell ($n = 15$) tumors and underwent hepatic artery chemoembolization or HAE using chemotherapy mixture of 50 mg cisplatin, 20 mg doxorubicin, and 10 mg mitomycin-C mixed with 10 ml of ethiodized oil followed by particle embolization with 300–500-μm polyvinyl alcohol particles or gelfoam powder, that the mean overall survival time for the entire group was 1273 ± 185 days, with insignificant difference detected for both tumor subgroups, and the progression-free survival times for the carcinoid and islet cell tumor subgroups also were similar ($p = 0.72$). The survival time of patients without known extrahepatic metastasis trended toward significance compared with that of patients with known extrahepatic disease. Resection of the primary tumor in 19 of 46 patients did not affect survival (resection survival, 1558 ± 400 days; nonresection survival, 1000 ± 179 days; $p = 0.44$). They also concluded that the presence of extrahepatic metastasis or an unresected primary tumor should not limit the use of hepatic artery chemoembolization or HAE [63].

Some authors also recommend a multimodality approach, including a combination of surgery and TACE/TAE with somatostatin analogues. Most authors recommend interventional radiology as a highly effective treatment of liver metastases from neuroendocrine tumors, particularly in inoperable cases; thus, a multimodality approach seems to be the best way to go.

6. Conclusion

In oligonodular liver metastases with size less than 5 cm and number less than 5, one should consider surgical resection,

however non-surgical interventional therapeutic approach is the ablation therapy using radiofrequency or Laser ablation with tendency towards LITT due to lower recurrence rate. But for higher metastatic load TACE or TAE is the preferable approach for management for symptomatic and local tumor control and for survival rate improvement. In this field selective intra-arterial radiotherapy (SIRT) could also be considered as an alternative therapy.

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