11 Neuroendocrine Liver Metastases

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- *Neuroendocrine liver metastases (NELMs) occur in 50-95% of endocrine tumors and represent the main cause of death. Management of NELMs is challenging and should take into account factors such as the tumor biological behavior, the presence of symptoms, and the age and performance status of the patient.*
- *Different therapeutic options (such as partial hepatectomy, liver transplantation, non-surgical liver directed therapies, and systemic treatments) can be used alone or in combination.*
- *Surgical resection remains the gold standard and the only potentially curative treatment for NELMs. Despite high recurrence rates, partial hepatectomy is performed with curative intent (in a minority of patients due to the high frequency of multiple and bilateral metastases) or for control of symptoms. Partial hepatectomy is usually indicated in patients with no extrahepatic disease when at least 90% of tumor burden can be resected.*
- *The role of liver transplantation (LT) for NELMs remains unclear and established selection criteria are lacking. Reasons to support LT are the usual indolent tumor behavior, tendency to metastatize to the liver, reduced possibilities for curative intention partial hepatectomy, and high recurrence rates after partial hepatectomy. Liver transplant should be considered in carefully selected patients with unresectable NELMs confined to the liver.*

INTRODUCTION

Neuroendocrine tumors (NETs) are a heterogeneous group of cancers that can arise from neuroendocrine cells and their precursors located throughout the body. They most commonly arise in the lungs and bronchi, small intestine, appendix, rectum, and pancreas. The natural history of NETs is quite variable, most often presenting an indolent biologic behavior. The ability to secrete peptides is a characteristic of NETs and can result in typical hormonal syndromes. Also, a small group of patients with NETs are affected by Multiple Endocrine Neoplasia type 1 (MEN1), which includes carcinoid tumors, pancreatic islet cell tumors, paragangliomas, pheochromocytomas and medullary thyroid carcinoma.

NETs are usually classified according to histologic features in well-differentiated (usually originated from the gastro-intestinal tract, lung, kidneys, and ovaries) and poorly-differentiated tumors. The first group usually presents with slow progression and better prognosis, in contrast with the second group, which is more aggressive and has a behavior similar to pulmonary small cell carcinoma. Well-differentiated gastroenteropancreatic NETs are classified by the World Health Organization (WHO) as low-grade (G1) or intermediate-grade (G2), based on proliferative rate as assessed by mitotic count and/or Ki67 proliferation index (≤2% for G1 and 3-20% for G2 tumors). Poorly-differentiated NETs (also called neuroendocrine carcinoma) are classified as high-grade (G3, Ki67 index >20%), with rare exceptions (**Table 1**).[1] Prognosis in low- or intermediate-

grade histology depends on diverse factors, such as the location of the primary tumor, and results of different therapies are difficult to compare.

Despite the characteristic indolent course of NETs, about 40% of patients develop metastases during the course of their disease. Indeed, most NETs (40-80%) present metastases when diagnosed, the liver being the most common site of metastases.[2] Small bowel NETs develop hepatic metastases in 50-75% of cases.[3–5]

Neuroendocrine liver metastases (NELMs) are present at the time of diagnosis in 40-93% of cases and represent one of the most important factors in poor prognosis.[6–9] Indeed, the 5-year survival of patients with NELMs receiving supportive care alone is 0-40%.[7,10–14] Surgical resection of NELMs has provided the best long-term outcomes; however, complete tumor resection is possible in only a minority of patients (approximately 10% of cases), due to the presence of multiple bilateral liver metastases. Less common sites of metastases from NETs are bones (12-20%) and lungs (8-10%).[9,11,15–17]

Patients with metastatic disease may present symptoms due to tumor hypersecretion of hormones rather than due to tumor bulk. Hormonal syndromes occur in approximately 10-30% of metastatic NETs, and hormonal secretions originate either from the primary tumor or from the metastasis; for example, carcinoid syndrome can develop from vasoactive substances produced by liver metastases in a neuroendocrine tumor of the midgut. The standard treatment for NETs is the surgical resection of the primary tumor, irrespective of the presence of liver metastases or clinical symptoms (**Figure 1**).[9] Resection of primary midgut NETs prevents eventual bowel obstruction or ischemia.[18] Some authors advocate tumor resection if 90% of tumor burden is resected.[19] The therapeutic approach for metastatic disease from NETs is more controversial than the management of the primary site.

SURGICAL TREATMENT

Liver metastases are the main cause of death in patients with NETs. The best management of neuroendocrine liver metastases (NELMs) is a challenging task, and should take into account factors such as the biological behavior of the tumor, the presence of symptoms, and the age and performance status of the patient. The heterogeneity of primaries and the usual indolent tumor growth make it difficult to evaluate the exact role of treatment options for NELMs. Treatment of NELMs can be palliative, aiming for reduction of symptoms, or focus on increasing patient survival.

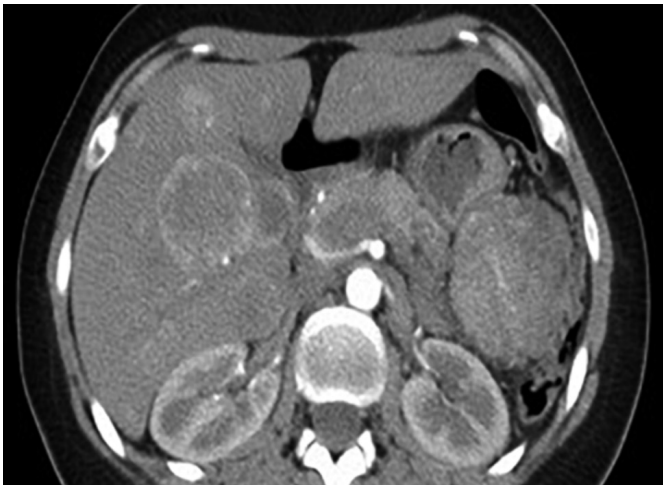

Figure 1. Computed tomography of a patient with pancreatic neuroendocrine tumor and liver metatases.

The different available therapeutic options for NELMs can be divided as follows: i) surgical resection (partial hepatectomy, total hepatectomy followed by liver transplantation); ii) non-surgical liver directed therapies (local ablation, arterial embolization); and iii) systemic therapies (systemic chemotherapy, somatostatin analogues, peptide receptor radionuclide therapy). These therapies can be used alone or in combination.

SURGICAL RESECTION

Results

Surgical resection, whenever possible, remains the best approach for patients with NELMs, despite the high recurrence rate after resection.[7–9,20–27] Studies comparing surgical resection of NELMs with conservative treatments showed increased long-term survival and symptom control with hepatic resection. Thus, hepatectomy is the only potentially curative therapy and remains the gold standard

Table 1. World Health Organization (WHO) grading system for neuroendocrine tumors.

	Grade 1 (G1)	Grade 2 (G2)	Grade 3 (G3)
Ki-67 index	< 3%	3-20%	> 20%
Mitotic count	< 2/10 HPF	2-20/10 HPF	> 20/10 HPF
Differentiation	Well-differentiated	Well-differentiated	Poorly-differentiated

HPF: high power field

of care for NELMs, despite the lack of prospective studies (**Figure 2**).

Surgical resection of NELMs comprises i) resection with curative intent (achieved in 10-54% of patients), and ii) cytoreductive surgery to control local and systemic effects or to increase overall survival. Surgery is usually only feasible when the removal of 90-100% of tumor burden is amenable.[11,28] However, selection of patients for aggressive surgical resection is still ill-defined.

Overall, liver resection can achieve symptom relief in most patients, with 5-year overall survival at 47-92% and 10-year overall survival at nearly 50%.[9,25,27,29–32] However, hepatic recurrence is common after hepatectomy. Even after complete resection with curative intent, the 5-year disease-free survival rate is only 16-45%.[9,14,33] The 5-year overall survival rate after palliative resection is 26-63%.[7,25]

Some studies have attempted to identify prognostic factors for NELMs and select patients that will benefit from liver resection. Recently, Watzka et al.[34], in a retrospective analysis of 204 patients with NELMs, found that surgical resection of NELMs could reduce or control endocrine-related symptoms and improve survival in selected patients with a Ki-67 index less than 20%. The 10-year survival after R0, R1, and R2 resection was 90%, 53%, and 51%, respectively. However, most patients (54%) in this series could not undergo resection and had a poorer 10-year survival (19%).

Another study examined outcomes associated with the morphological characteristics of liver metastases.[33] Hepatic lesions were classified as i) type I (single metastasis, any size), ii) type II (isolated metastatic bulk with accompanying smaller deposits, both lobes involved), and iii) type III (disseminated spread, both lobes involved, little normal liver parenchyma). All patients with type I lesions underwent curative resections with better long-term survival. Type I metastases would be more suitable for curative hepatectomy, type II would benefit from cytoreductive resection in addition to adjunctive therapies, and type III might benefit from liver transplantation.[33]

The presence of extrahepatic disease at the moment of liver resection, nonfunctional hormonal status, and synchronous disease were independent significant factors contributing to worse survival rates in a large multi-institutional study by Mayo et al.[26] The most common sites of extrahepatic disease in this study were the lung and peritoneum. The benefit of surgical resection in nonfunctional NELMs is somewhat controversial, although some authors have reported improved survival with cytoreductive surgery in this situation.[9,16,35] Another report from the cited multi-institutional cohort included an analysis of a matched subset of patients with high-volume liver burden (>25% liver involvement), and found that symptomatic patients benefited the most from surgical resection while asymptomatic patients did not derive a comparative benefit from surgery versus intra-arterial therapy.[11] Thus, surgical resection in patients with asymptomatic nonfunctional NELMs seems to be reasonable in cases of low-volume disease (**Figure 2**); however, in cases of high-volume disease and high surgical risk, other therapeutic options could be considered, as discussed later in this chapter.[27]

The high rate of intrahepatic recurrence may be related to an underestimation of the extent of the disease with preoperative cross-sectional imaging. A study with pathologic examination (including thin serial slices) of the surgical specimen found that less than half of hepatic metastases were detected preoperatively. Most lesions found only with pathologic study were less than 2 mm, and the accuracy of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging was 24%, 38%, and 49%, respectively.[36]

Despite high recurrence rates, overall survival is quite favorable after liver resection, probably due to the low proliferative rate of NETs. Treatment approach for recurrence should be similar to that for initial liver metastases. Whenever possible, repeat hepatectomy (second, third, or fourth hepatectomies) for recurrence results in an overall 5-year survival rate of more than 60%.[26,31]

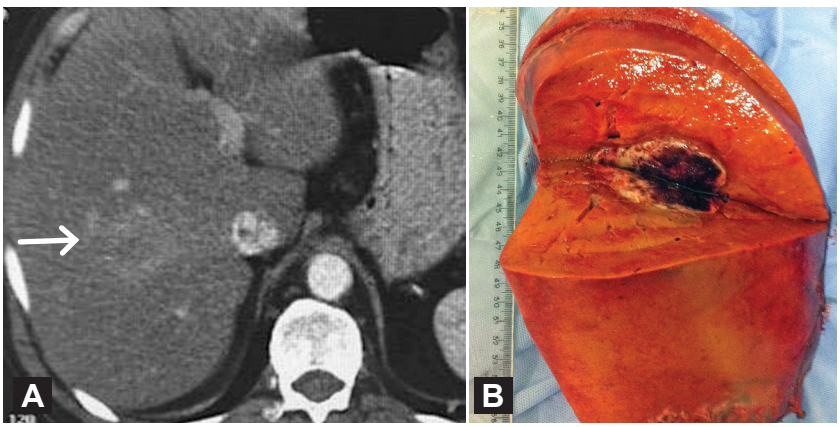

Figure 2. Metachronous hepatic metastasis from small bowel neuroendocrine tumor. **A**) Computed tomography shows a lesion centrally located in the right hemi-liver. **B**) Surgical specimen of a right hepatectomy showing the tumor macroscopic aspect.

Associated procedures

Hepatic embolization (intra-arterial embolization or chemoembolization) has been used together with surgery and without. However, surgical resection should be preferred whenever possible, since studies comparing these modalities of treatment have shown 5-year overall survival rates after ablation of only 35-40%, compared to 70-78% after surgery.[24,37]

Further, local ablation (mainly by radiofrequency or microwave ablation) associated with hepatic resection can increase the number of candidates for cytoreductive surgery, since the majority of patients with NELMs have bilobar disease. Radiofrequency ablation has been reported in the treatment of unresectable NELMs with a 5-year survival rate of 48%.[38,39] The combination of local ablation and surgical resection can lead to more complete cytoreduction and more conservative surgery in cases of lesions deep in the parenchyma. A large study evaluating adjunctive ablation found overall 5-year and 10-year survival rates of 80% and 59%, respectively.[40]

Technical aspects

Since the majority of patients with NELMs present with bilateral disease, surgical resection frequently involves nonanatomic resections, with most patients undergoing multiple wedge resections.[26,31] Other surgical approaches to accomplish adequate cytoreductive surgery include the use of preoperative portal vein embolization, staged procedures, and adjunctive local ablation. Most NELMs occur in non-cirrhotic livers, and a functional remnant liver volume of 20% from total liver volume is usually acceptable. Patients with chronic underlying liver disease (cirrhosis, hepatitis, non-alcoholic steatohepatitis) require higher hepatic remnant liver volume. Portal vein embolization (generally right portal vein embolization) leads to hypertrophy of the non-embolized hepatic segments. Staged hepatectomy consists mostly of a first procedure including tumor clearance of the left lobe plus right portal vein ligation, followed by a right lobectomy after left lobe hypertrophy. Adjunctive local ablation is most commonly by radiofrequency ablation lesions deeply located in the hepatic parenchyma, in addition to multiple wedge resections or to a major contra-lateral hepatectomy. Adjunctive local thermal ablation includes radiofrequency ablation and microwave ablation and can be performed preoperatively (percutaneously or by laparoscopy) or intraoperatively.

Conclusions

In summary, cytoreductive surgical resection of symptomatic NELM, in combination or not with adjunctive embolization or ablation, is indicated when at least 90% of the tumor burden is resected or destructed. This approach results in excellent symptom control and overall survival, despite hepatic recurrence being the rule. In asymptomatic patients with nonfunctional high-volume NELMs, surgical resection is more controversial. Practical clinical guidelines may result from ongoing studies on effectiveness of liver resection versus non-surgical treatment of NELMs. Future studies should provide additional directions on usefulness of neoadjuvant and adjuvant therapies, role of liver transplantation, and importance of primary tumor resection in the presence of unresectable NELMs.[41,42]

LIVER TRANSPLANTATION

The precise role of total hepatectomy and orthotopic liver transplantation (OLT) in the treatment of patients with NELMs remains unclear. The lack of established criteria for OLT for NELMs reflects the scarcity of large series of OLT for the treatment of NELMs, the variety of available therapeutic options, and the heterogeneity of patients (with potentially different tumor biological behavior). Usually, OLT is considered for unresectable NELMs.

The relatively indolent course of NETs and the propensity to metastasize exclusively to the liver, associated with the feasibility of hepatectomy in a minority of cases and the very high hepatic recurrence rate, are theoretical reasons to support liver transplantation for NELMs. However, overall 5-year survival after OLT for NELMs is quite variable (from 33% to 90%), and tumor recurrence occurs in most patients within a 5-year follow-up, contesting the curative role of liver transplantation.[43–56]

Specific inclusion criteria for OLT were proposed by Mazzaferro et al.[57] in a study including patients with low-grade NETs leading to excellent survival with low recurrence rates. The overall and disease-free 5-year survival in this series was 90% and 77%, respectively. The proposed criteria comprises: i) age less than 55 years, ii) low-grade tumor on histology, iii) primary tumor drained by the portal system (pancreas and midgut) and removed with a curative resection before transplantation, iv) no other extrahepatic spread, v) metastatic liver involvement of no more than 50%, and vi) stable disease for at least six months. This criterion was based on a limited number of patients. Another report on OLT for NELMs, which included patients with higher proliferation tumors, larger liver tumor involvement, and older patients, found a similar overall 5-year survival rate of 90%.[51]

However, a review of the European Liver Transplant Registry (ELTR), which included 213 patients who underwent OLT for NELMs, found overall and disease-free survival rates at five years after transplant of only 52% and 31%, respectively.[52] The 90-day postoperative mortality rate was 10%, and predictors of poor long-term outcomes were concomitant major procedures (in addition to OLT), poor tumor differentiation, and large hepatic involvement. Similar results were reported in a United Network of Organ Sharing (UNOS) database study, where overall and disease-free 5-year

survival rates after OLT for NELMs were 49% and 32%, respectively.[55] In this series, patients with longer wait-times for OLT had better long-term outcomes, suggesting that disease stability should be confirmed before considering OLT. Patients who waited more than two months had a 5-year survival rate of 63%, versus 36% for those who waited for a shorter period of time.

The site of the primary tumor was also implicated in outcomes after OLT, with NELMs from pancreatic primaries having poorer outcomes than those from gastrointestinal NETs.[47,48,52,54,58,59]

The worldwide scarcity of liver donors calls for an appropriate selection of patients, in order to allocate grafts for patients who would benefit the most from OLT. Thus, the European Neuroendocrine Tumor Society (ENETS), using the established guidelines for the management of patients with NELMs, have proposed the following minimal requirements for consideration of OLT: less than 10% operative mortality, exclusion of extrahepatic metastasis (accomplished by an extensive work-up), primary tumor removed prior to transplantation (at least six months prior), favorable histology (well-differentiated G1 or G2 tumors, Ki67 proliferation rate preferably less than 10%), stable disease for at least six months before liver transplantation, and liver involvement of less than 50% of the organ (and less than 75% for patients with refractory hormonal symptoms). This consensus considers liver transplantation a palliative treatment for patients with life-threatening hormonal disturbances refractory to medical therapy, or patients with nonfunctional diffuse unresectable liver metastasis. Liver transplantation with intent to cure is considered an exception.[43]

In view of the scarcity of cadaveric liver donors, some authors have advocated for the use of living donors in highly selected cases and in emergency situations. This approach is not a well-established indication for OLT, and there have been few cases reported.[60]

In summary, OLT should be considered in carefully selected patients with unresectable neuroendocrine liver metastases restricted to the liver (**Figure 3**). However, prospective studies are needed for appropriate patient selection.

NON-SURGICAL LIVER-DIRECTED THERAPIES

ABLATIVE TECHNIQUES

Ablative methods mainly comprise radiofrequency ablation (RFA), microwave ablation (MWA), and cryotherapy.[61,62] There is no available data comparing these methods for NELMs. Local ablation has been used in different settings of NELMs, as primary therapy or as an adjunctive procedure, and by different access (percutaneously, by laparoscopy, or during laparotomy). Globally, local ablation usually has lower morbidity rates than surgical resection or even intra-arterial embolization. However, destruction of lesions greater than 3 cm is less efficacious, and generally local ablation is limited to lesions up to 5 cm.[63]

Ablation as primary therapy for NELMs should follow the same selection criteria for surgical cytoreduction, i.e. a reduction of at least 90% of tumor burden should be achieved. The best scenario would be small liver metastases in patients who do not qualify for surgery. One study reported a 5-year survival rate of 48% after RFA of unresectable NELMs.[39] The use of ablation instead of surgical resection in patients suitable for surgery is controversial, and surgery probably leads to better long-term outcomes. Comparative studies including ablation and surgical resection were favorable to surgery.[24,64]

Ablation can also be used as primary therapy for recurrence of NELMs after surgical resection.[65] However, studies comparing ablation and re-hepatectomy or other non-surgical therapies are lacking.

Local ablation as an adjunctive procedure to complement surgical resection is very promising. Since most NELMs are bilateral, proper cytoreductive surgery (reduction of at least 90% of tumor burden) is frequently unattainable due to a future remnant liver that is too small. The association of surgical resection (usually a major hepatectomy) with ablation of contra-lateral lesions allows for proper cytoreduction in a subset of patients initially deemed unresectable, increasing the number of prospective candidates for cytoreductive surgery.[40] Local ablation can also allow for a more complete

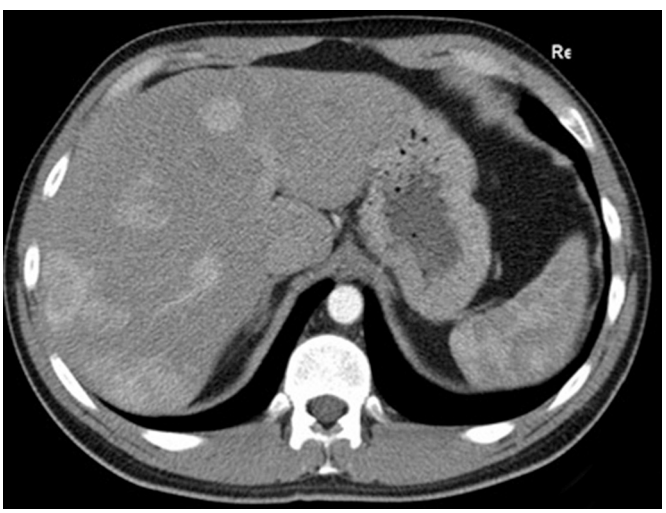

Figure 3. Computed tomography showing multiple hepatic hypervascular neuroendocrine metastases. No extrahepatic disease was detected and the treatment choice was liver transplantation.

cytoreduction in surgical patients. Taner et al.[40] reported 5-year and 10-year overall survival rates of 80% and 59%, respectively, in a series of 90 patients that underwent hepatic resection and adjunctive intraoperative RFA. These results are similar to those from some large series of surgical resection alone for NELMs.[9,26] Although the disease-free 5-year survival rate was only 16%, results of combined surgical and RFA procedures are better than those from other non-surgical therapies. This approach has been used for the treatment of other tumors, such as colorectal liver metastases.

Complications with local ablation are uncommon and include thermal injury to bile ducts (with subsequent stricturing) or adjacent organs, and local abscesses. Local recurrence after NELM ablation (4-11%) is probably due to incomplete tumor obliteration.

INTRA-ARTERIAL LIVER-DIRECTED THERAPIES

NELMs are highly vascular and mostly dependent on arterial blood for their oxygenation (80-90% of blood supply from the hepatic artery). Thus, occlusion of the arterial supply can lead to ischemia and necrosis. Selective arterial occlusion is performed alone or in combination with chemotherapeutic agents (chemoembolization), with drug eluting beads, or with radiotherapeutic agents (**Figure 4**).

All of these methods are options for symptom and locoregional tumor control in unresectable disseminated NELMs. They are used alone or in combination with systemic therapies, and they can allow for symptom control and decreases in somatostatin analog use, and can even prolong survival. Results using the different modalities of intra-arterial therapies for NELMs are similar, thus all of them have been considered reasonable options for palliative treatment in patients who are not candidates for surgical resection.[37,66,67]

Transarterial embolization (TAE) and Transarterial chemoembolization (TACE)

Hepatic artery embolization involves administering an embolic agent into the hepatic artery that is supplying the tumors, with the goal of inducing tumor ischemia. TACE combines temporary intra-arterial embolization (obtained through the use of a variety of embolic agents, such as ethiodized oil or lipiodol) with loading of chemotherapeutic agents (such as doxorubicin, cisplatin, gemcitabine, streptozocin, mitomycin C, or 5-fluorouracil). In addition to the ischemia, the reduction of blood flow by the embolic agents leads to a reduced washout of the chemotherapeutic agents, prolonging their local action.[68] TACE is usually performed sequentially, with a variable number of cycles. In a retrospective series with 123 patients with multifocal NELMs treated with TACE, the overall 5-year and 10-year survival rates were 36% and 20%, respectively.[69] There is no consensus regarding technique, embolizing agents, or chemotherapeutic agents in TACE. Furthermore, studies (including a small randomized trial) have shown similar results with TAE and TACE for NELMs, suggesting supremacy of the embolic effect over the chemotherapeutic one.[66,70–73]

Drug eluting bead transarterial chemoembolization (DEB-TACE) consists of intra-aterially loading large beads with cytotoxic drugs that are gradually released over a period of time, allowing for a longer intratumoral exposure with less systemic exposure and toxicity than conventional TACE.

Adverse effects after arterial embolization include pain, nausea, fatigue, fever, and liver enzyme elevation. Relative contraindications for arterial embolization include occlusion of the portal vein (due to the risk of parenchymal hepatic necrosis), severe liver dysfunction, and presence of bileodigestive anastomosis (due to the risk of cholangitis).[74] Intra-arterial embolization for NELMs is not contraindicated in the presence of extrahepatic disease, especially if the goal is symptom control.[75] Prophylaxis of carcinoid crisis (such as with octreotide) should be implanted before TAE in patients with carcinoid syndrome.[76]

Transarterial radioembolization (TARE)

Liver tumor radioembolization involves delivery of yttrium-90 (Y90) labeled microspheres through the hepatic artery. These microspheres are preferentially implanted within liver tumors (due to particularities of tumor arterial supply) with selective

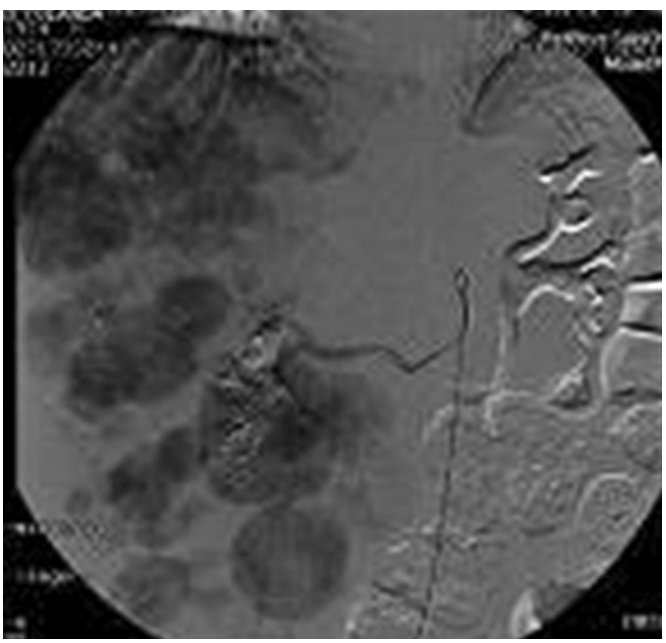

Figure 4. Hepatic arteriography. Multiple neuroendocrine liver metastases are shown. The patient underwent chemoembolization with irinotecan.

radiation of tumors, while limiting the dose to normal liver parenchyma.[77,78]

Radioembolization, alone or in combination with systemic therapies, has been used for symptom and locoregional tumor control in unresectable disseminated NELMs. Its use can allow for symptom control and decreases in somatostatin analog use, and can even prolong survival. Effectiveness of TARE is comparable to that of TACE, with the advantage of typically requiring a single treatment, while TACE is usually applied multiple times.[79,80] Also, adverse effects after TARE typically have low severity.[81,82]

More recently, intra-arterial delivery of somatostatin analogs labeled with therapeutic radioactive agents (yttrium-90, indium-111, and lutetium-177) has been used for NELM. Tumor response was observed in 16-53% of cases.[83,84]

SYSTEMIC THERAPY

Systemic therapies for NELMs include cytotoxic systemic drugs, somatostatin analogues, and other agents.

CYTOTOXIC CHEMOTHERAPY

Cytotoxic systemic therapy is ineffective for low-grade and intermediate-grade NETs. However, for poorly differentiated tumors with a high proliferative index (Ki67 >20%), cytotoxic chemotherapy can induce an initial response, although it is not durable and progression is common. The overall response rate to chemotherapy varies from 25% to 78%, and overall survival can be improved in 12-24 months compared to patients without treatment.[85–94] Various drugs have been used in the treatment of NETs, including streptozocin, dacarbazine, 5-Fluorouracil (5-FU), doxorubicin, paclitaxel, gemcitabine, temozolomide, and topotecan, with similar results when used as monotherapy.[85,88,89,92–94]

Numerous agents has been tested for low-grade and intermediate-grade tumors, albeit with low response rates. Temozolomide is an orally bioavailable drug that has been used, alone or in combination with other agents, due to its low toxicity. Streptozocin-based therapy, alone or in combination with other drugs, is one of the most used for aggressive high-grade tumors. The combination of two drugs has shown a higher response rate and improved overall survival when compared to a single agent.[91,95,96]

SOMATOSTATIN ANALOGUES

Somatostatin receptors are expressed in approximately 70% of NETs. Somatostatin analogues bind to the somatostatin receptors and consequently limit hormonal release, being used for symptom relief. Patients treated with octreotide show a clinical improvement of 85% and a biochemical recovery of 70% during the first weeks of treatment.[97] Additionally, an anti-proliferative effect was demonstrated in patients with metastatic NETs and somatostatin analogues could be an option for inoperable metastatic carcinoid tumors, even without symptomatic disease.[98–100] Octreotide is also useful to prevent carcinoid crisis after certain therapies, such as intra-arterial therapies. Somatostatin analogues can be used safely in patients that have undergone liver resection.[101] Somatostatin analogues are useful agents for the treatment of metastatic NETs that produce symptoms.[98]

Somatostatin analogues have also been used with a radioligand (such as beta-emitting Yttrium-90 or Lutetium-177) to treat NET-expressing somatostatin receptors (peptide receptor radionuclide therapy). The combination is administered in the systemic circulation and internalized into the target cells, and the radiotoxicity affects the deoxyribonucleic acid (**Figures 5 and 6**). However, these agents can produce adverse effects such bone marrow toxicity, nephrotoxicity, myelodysplastic syndrome, liver dysfunction, and gastrointestinal disturbances.[102–104] Also, patients with a positive metaiodobenzylguanidine (MIBG) uptake can be treated with 131 I-MIBG therapy.[105,106] Other treatments with targeted pathways include sunitinib, bevacizumab (based on the vascular endothelial growth factor (VEGF) expression on NETs), and everolimus (inhibitor of mammalian target of rapamycin).[107]

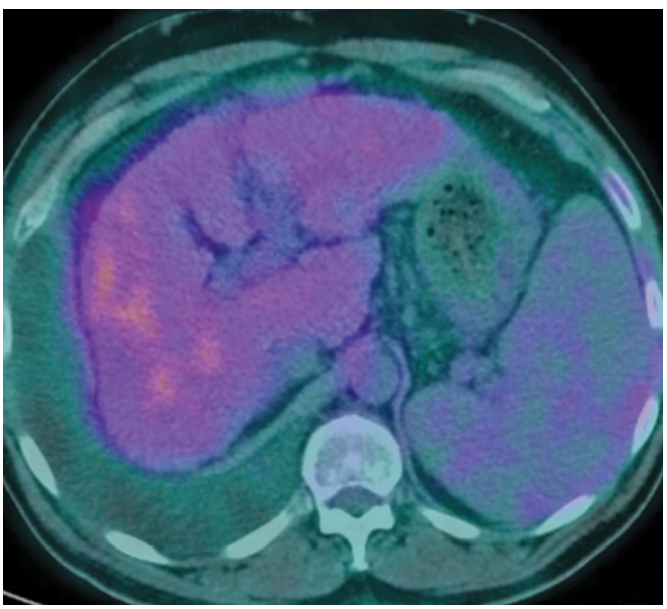

Figure 5. Positron emission tomography–computed tomography (PET-CT) of a patient with bronchogenic neuroendocrine tumor liver metastases prior to liver transplantation.

OTHER AGENTS

Interferon alpha is an alternative for patients with no response to somatostatin analogues, with some symptomatic response but no clear survival benefit. [86,87]

PREVENTION AND MANAGEMENT OF CARCINOID CRISIS

Carcinoid crisis is a life-threatening form of carcinoid syndrome that can be produced by tumor manipulation (during surgery procedures, biopsy, or patient palpation) or by anesthesia. It can be also seen after chemotherapy, hepatic arterial embolization, or radionuclide therapy. Carcinoid crisis develops when a large amount of biologically active compounds from the tumor are released in systemic circulation. It produces hemodynamic instability and symptoms such as flushing, diarrhea, tachycardia, arrhythmias, bronchospasm, and altered mental status.[108]

Octreotide before surgical procedures (in a dose of 300 mcg subcutaneously) specifically, in patients with a history of carcinoid syndrome, can prevent carcinoid crisis. Octreotide can also be used during a carcinoid crisis, in addition to plasma infusion, to restore hemodynamic instability, because typical fluid resuscitation is not efficient in this condition and the use of calcium or catecholamine can aggravate the clinical condition.

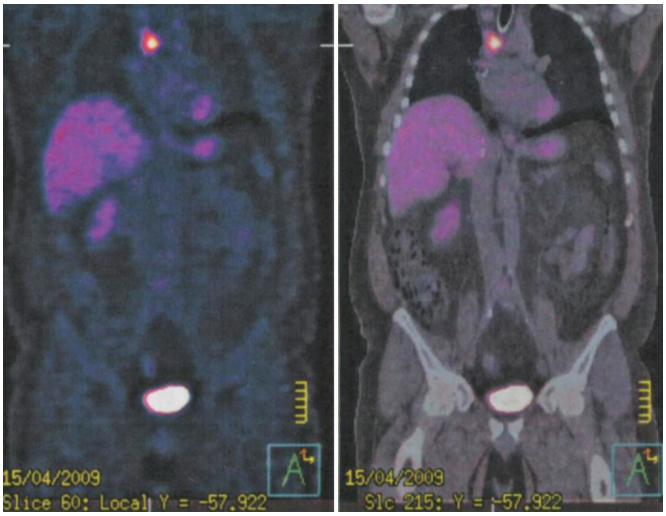

Figure 6. Positron emission tomography–computed tomography (PET-CT) demonstrating thoracic disease after liver transplant for neuroendocrine liver metastases. This patient was treated with 177Lu-[DOTA0, Tyr3] octreotate (DOTATATE) with satisfactory results.

SUGGESTED READING

Watzka, F. M. *et al.* Surgical therapy of neuroendocrine neoplasm with hepatic metastasis: patient selection and prognosis. *Langenbecks. Arch. Surg.* **400**, 349-358 (2015).

A retrospective single-center study with suggestions to improve patient selection for surgical resection of neuroendocrine liver metastases (NELMs). The authors propose that surgical resection of NELMs reduces symptoms and improves the survival in selected patients with a Ki-67 index less than 20%.

Mayo, S. C. *et al.* Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann. Surg. Oncol.* **17**, 3129–3136 (2010).

This multicenter international study demonstrates the efficacy of surgical resection of neuroendocrine liver metastases using a sample of 339 patients from eight hepatobiliary centers. On the multivariate analyses, they found that synchronous disease, nonfunctional tumors, and extrahepatic disease were independent factors for worse survival rates.

Mazzaferro, V., Pulvirenti, A. & Coppa, J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J. Hepatol.* **47**, 460–466 (2007).

A proposal of criterion for selection for liver transplantation in patients with neuroendocrine liver metastases (NELMs), based o n cumulative experiences on multicentric and institutional bases. Liver transplant for NELMs should be restricted to: age less than 55 years, low-grade tumor on histology, primary tumor drained by the portal system (pancreas and midgut), primary tumor treated with curative resection before transplantation, no extrahepatic disease, less than 50% metastatic liver involvement, and stable disease for at least six months. Exclusion criteria are also defined.

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