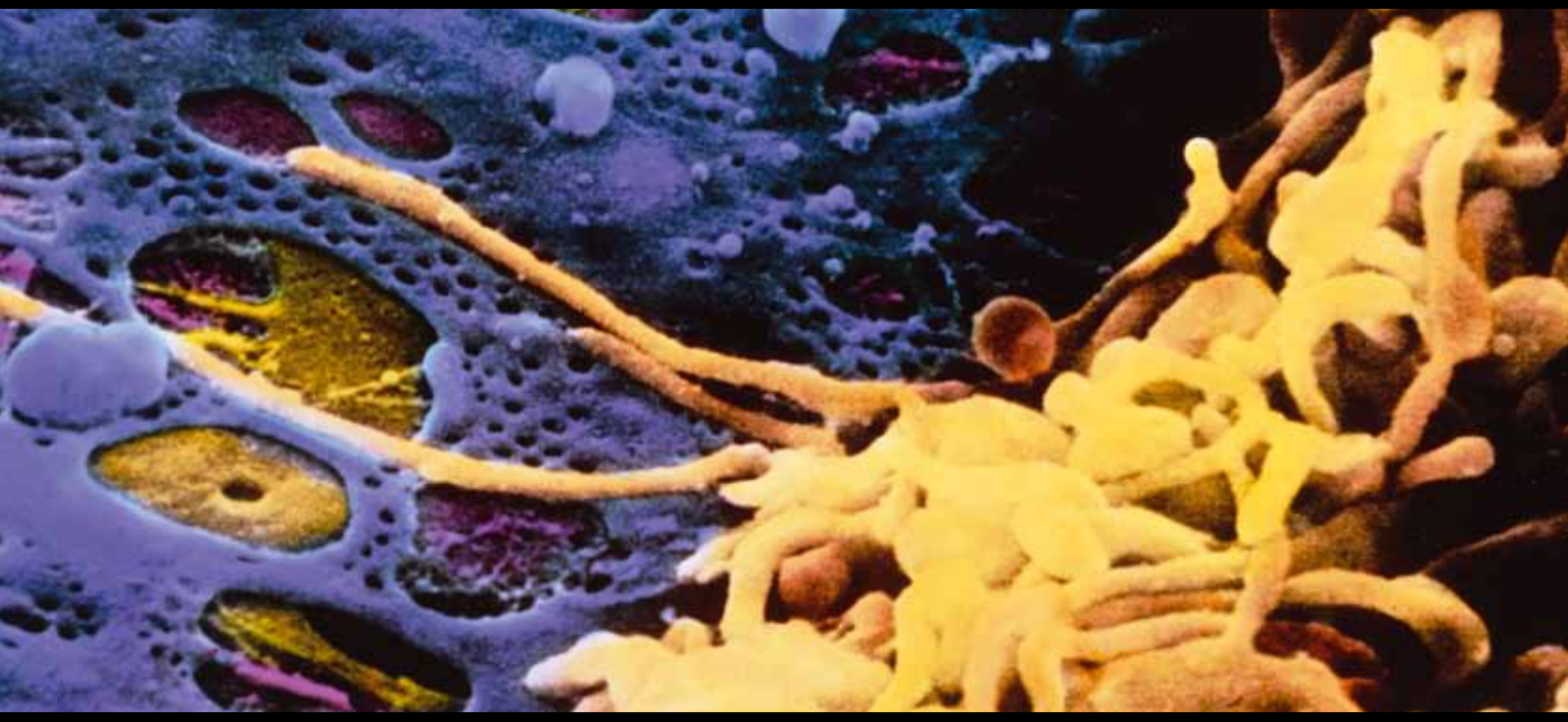
International Journal of Hepatology

Treatment of Liver Metastases in Patients with Neuroendocrine Tumors

Guest Editors: Dan Granberg, Wouter de Herder, Dermot O'Toole, and Larry Kvols



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Editorial Board

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Editorial

Treatment of Liver Metastases in Patients with Neuroendocrine Tumors

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Neuroendocrine tumours may originate from the lungs, thymus, stomach, gastrointestinal tract and endocrine pancreas. A majority of the tumours are malignant. Metastases occur to regional and distal lymph nodes, liver, bones, lungs, mammary glands, subcutaneous tissue, central nervous system and adrenal glands. Although most neuroendocrine tumours are relatively slowly growing, poorly differentiated neuroendocrine carcinomas are fast growing neoplasms with high proliferative activity.

A characteristic feature of many neuroendocrine tumours is the ability to produce and secrete various hormones and peptides, leading to endocrine symptoms that can be very disabling and cause substantial morbidity. Small bowel carcinoids, for example, produce serotonin giving rise to the classical carcinoid syndrome with flushing, diarrhea, right-sided heart disease and asthma. A prerequisite for the carcinoid syndrome to occur is usually the presence of liver metastases. Lung carcinoids rarely produce serotonin, but may instead secrete histamine causing an atypical carcinoid syndrome with generalized flushing, diarrhea, periorbital oedema, lacrimation and asthma. They may also produce adrenocorticotropic hormone or corticotropin-releasing factor, resulting in an ectopic Cushing's syndrome. Endocrine pancreatic tumours may as well secrete various hormones, such as gastrin, insulin, glucagon, vasoactive intestinal polypeptide (VIP) or somatostatin, resulting in the corresponding syndrome.

The treatment of patients with metastatic neuroendocrine tumours is based on primary tumour origin, tumour biology, stage and grade and includes debulking by surgery, liver embolization with particles, chemoembolization, radioembolization, radiofrequency ablation and peptide receptor radionuclide therapy (PRRT) with ^{90}Yttrium-DOTATOC or ^{177}Lutetium-DOTATATE. Medical treatment consists of biotherapy with alpha-interferon and somatostatin analogues, various chemotherapy regimens, angiogenesis inhibitors, tyrosine kinase inhibitors and mTOR inhibitors. In this special issue in the International Journal of Hepatology, focus is on the various specific treatment possibilities for patients with neuroendocrine tumours metastatic to the liver. There are two papers describing the role of surgery in these patients, and one clinical study reporting the results of liver transplantation. Surgical debulking should always be considered, and liver transplantation may in selected cases be an option. Because of the immunosuppression, it is however of utmost importance that every effort is made to exclude remaining tumour outside the liver before transplantation.

Three papers deals with hepatic arterial embolization, one of them reviews the role of hepatic arterial embolization for debulking of liver metastases. Another paper is about a clinical study and a review of radioembolization, which is a promising alternative for this patient group with possible long-lasting effect and few serious adverse effects. An important disadvantage (also with particle and chemoembolization) is that most patients with neuroendocrine tumours metastatic to the liver in addition have spread of the tumour to lymph nodes and/or other distant organs such as the bones, necessitating systemic therapy. In patients with normal bone marrow and renal function,

PRRT is thus often preferred to radioembolization, which however may be considered if the patient shows progression later after PRRT. A randomized clinical trial comparing the various embolization methods, particle embolization, chemoembolization and radioembolization, would nevertheless be highly desirable.

Three papers review the possible systemic therapies for patients with liver metastases from neuroendocrine tumours. This year, two new drugs have been approved for treatment of patients with metastatic endocrine pancreatic tumours, everolimus and sunitinib. This represents an important progress in the therapeutic arsenal for patients with neuroendocrine tumours. There is however still a need for more new drugs, and especially for patients with midgut carcinoids, in whom the therapeutic options are limited after progression. In addition, there is an urgent need to learn how to use, combine and sequence the various therapeutic alternatives, including chemotherapy, biotherapy, newer drugs and PRRT.

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Review Article

Treatment of Liver Metastases in Patients with Neuroendocrine Tumors of Gastroesophageal and Pancreatic Origin

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Well-to-moderately differentiated neuroendocrine tumors of gastroesophageal and pancreatic origin (GEP-NETs) with liver metastasis are a heterogeneous group of malignancies for which a range of therapeutic options have been employed. Surgical resection of hepatic metastases or hepatic artery embolization may be beneficial in patients with hepatic-predominant metastatic disease. Patients with "carcinoid" syndrome and syndromes associated with functional pancreatic NET (PNET) can be effectively treated with somatostatin analogs. On the other hand, the efficacy of systemic chemotherapy for these patients is limited. A placebo-controlled, double-blind, prospective, and randomized study showed that octreotide LAR improves progression-free survival in patients with advanced midgut functional "carcinoids." In patients with advanced pancreatic NET, randomized, placebo-controlled studies have recently demonstrated that treatment with the tyrosine kinase inhibitor sunitinib or with mTOR inhibitor everolimus is associated with improved progression-free survival. Based on these studies, octreotide LAR, sunitinib, or everolimus are now considered as first-line therapeutic options in patients with advanced NET. Future studies will likely further define the role of these agents in patients with carcinoid liver metastasis and pancreatic NET liver metastasis.

1. Introduction

Neuroendocrine tumors of gastroesophageal and pancreatic origin (GEP-NETs) are a heterogeneous group of tumors characterized by their secretion of hormones or vasoactive peptides often resulting in specific hormone hyperfunction syndromes. NETs have recently been shown to be more common than previously suspected. In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, the estimated age-adjusted annual incidence of NET in 2004 was 5.25 per 100,000 people [1].

The prognosis and management of GEP-NETs is guided by histological classification. As a general rule, tumors with a high grade (grade 3), a mitotic count of more than 20 per 10 high-powered fields, or a Ki-67 proliferation index of more than 20% represent highly aggressive malignancies with a short clinical course and poor survival outcomes. The approach for these tumors is similar to that for small cell lung cancer and is not discussed in this review.

The focus of this review is the well-to-moderately differentiated GEP-NETs. These tumors can be subclassified into two general categories: pancreatic neuroendocrine tumors (PNETs) and others, mostly arising in the intestine, and often associated with the "carcinoid" syndrome. The terminology of "endocrine tumor" is replacing "neuroendocrine tumor" in pancreatic neuroendocrine tumors. And carcinoid is often linked to the secretion of serotonin and other vasoactive peptites resulting in "carcinoid" syndrome. This syndrome is manifested by episodic flushing, wheezing, diarrhea, and eventual right-sided valvular heart disease. Syndromes associated with hormone-secreting PNET can be manifested in insulinoma, glucagonoma, vasoactive intestinal peptide (VIP)-oma, and gastrinoma.

The majority of PNET occurs sporadically, but these tumors can also belong to a number of inherited syndromes

associated with mutations in well-studied oncogenes and tumor suppressor genes. These syndromes include multiple endocrine neoplasia (MEN) types 1 and 2, von Hippel-Lindau disease, and tuberous sclerosis [2]. Patients with NET with such syndromes may represent subgroups particularly responsive to novel therapies targeting the underlying genetic defect or pathway.

GEP-NETs typically have an indolent natural history, even in the setting of metastasis. The treatment of patients with localized NET is primarily surgical. There are no data that demonstrate a benefit associated with adjuvant therapies. However, GEP-NETs commonly metastasize to liver, with up to 44% of patients developing neuroendocrine liver metastasis (NELM) over the course of their disease [3]. This review summarizes the current approach to NELM based on clinical trials in the past 10 years, emphasizing the differences between NELM arising from carcinoid and those from PNET.

2. Locoregional Therapies

2.1. Surgical Resection. Symptom control and improved quality of life and overall survival can be achieved by the reduction of circulating hormone levels via functional hormonal blockade, transarterial chemoembolization (TACE), or radiofrequency thermal ablation (RFA), thus obviating surgery. However, hepatic resection is often considered in patients with limited hepatic disease. If more than 90% of the tumor mass can be removed, these patients have an outcome similar to those with complete resection (resection of all visible hepatic tumors) [4, 5].

Mayo et al. [6] reported the outcomes of 339 patients from 8 major hepatobiliary centers who underwent surgical management for neuroendocrine liver metastasis (NELM) from 1985 to 2009. Major hepatectomy was performed in 45% of patients, and 14% underwent a second liver operation. Median survival was 125 months, with overall 5- and 10-year survival of 74%, and 51%, respectively. Disease recurred in 94% of patients at 5 years. Patients with hormonally functional NET who had R0/R1 resection benefited the most from surgery ($P = 0.01$). In a multivariate analysis, synchronous disease, nonfunctional NET hormonal status, and extrahepatic disease were independent predictors of worse survival ($P < 0.05$). Thus, while surgical resection for NELM is associated with prolonged survival, the majority of patients will develop recurrent disease. Patients with hormonally functional hepatic metastasis without prior extrahepatic or synchronous disease derive the greatest survival benefit from surgical management.

2.2. Radiofrequency Thermal Ablation (RFA). Mazzaglia et al. [7] reported a prospective trial of 80 RFA sessions which was performed in 63 patients with NELM. Tumor types included 36 "carcinoid", 18 pancreatic islet cell, and 9 medullary thyroid cancer. RFA was performed 1.6 years after the diagnosis of liver metastases. Median number of lesions treated was 6. The majority (49%) underwent 1 ablation session, and 14 (22%) had repeat sessions caused by disease progression. Fifty-seven percent of patients exhibited symptoms. One week postoperatively 92% of patients reported at least partial symptom relief, and 70% had significant or complete relief. Duration of symptom control was 11 months. Larger dominant liver tumor size and male gender adversely impacted survival ($P < 0.05$). Median survival times were 11.0 years after diagnosis of primary tumor, 5.5 years after diagnosis of NELM, and 3.9 years after first RFA. RFA, therefore, provides effective local control with prompt symptomatic improvement.

2.3. Liver Transplantation. If metastases are limited to the liver, orthotopic liver transplantation (OLT) is a viable treatment option [8]. OLT is currently offered to patients with unresectable metastases or for palliation of medically uncontrollable symptoms. Very few centers had reported experience representing more than 10 patients. Lehnert reviewed 103 cases who underwent OLT for metastases of NET in the largest review so far. Overall, 2-year and 5-year survival for all 103 patients was 60% and 47%, respectively, but recurrence-free 5-year survival did not exceed 24%. Three favorable prognostic factors were identified: age less than 50 years old, primary tumor location in lung or bowel, and pretransplant somatostatin therapy. In contrast, extensive abdominal operations were associated with poor prognosis. Thus, liver transplantation may be indicated in highly selected patients to provide immediate relief of otherwise intractable pain or hormone-related symptoms. OLT has no clear role in the routine treatment of patients with NET due to relatively high rates of tumor recurrence [9–11].

2.4. Transarterial Embolization (TAE)/Transarterial Chemoembolization (TACE). Hepatic arterial embolization is commonly used as a palliative technique in patients with hepatic metastases who are not candidates for surgical resection. Hepatic artery embolization is based on the principle that tumors in the liver derive most of their blood supply from the hepatic artery, whereas healthy hepatocytes derive most of their blood supply from the portal vein. Embolization response rates are measured either by a decrease in hormonal secretion or by radiographic regression and are generally greater than 50% [12, 13]. In one of the largest series of 81 patients underwent embolization or chemoembolization for tumors labeled as "carcinoids" (likely of intestinal origin), the median duration of response was 17 months, and the probability of progression-free survival at 1, 2, and 3 years was 75%, 35%, and 11%, respectively [12].

Objective tumor responses have been noted in 33% to 67% of patients (Table 1). The variation of objective tumor response is related to the heterogeneous nature of tumors, various combination of cytotoxic agents, uncontrolled concomitant use of somatostatin analogues, and the difference in hepatic tumor burden.

Table 1: Selected clinical studies of transarterial embolization (TAE)/transarterial chemoembolization (TACE) in metastatic NET.

Author (yr)	No. of patients	Disease	Therapy	Complete/partial response
Ruszniewski et al. [14] (1993)	24	Carcinoid/PNET	TACE	33%
Wängberg et al. [15] (1996)	40	Carcinoid	TAE	42.5%
Gupta et al. [12] (2003)	81	Carcinoid	TACE/TAE	67%
Strosberg et al. [16] (2006)	84	Carcinoid/PNET	TAE	48%
Marrache et al. [17] (2007)	38	Carcinoid/PNET	TACE/TAE	37%
Ho et al. [18] (2007)	33	Carcinoid/PNET	TACE/TAE	46%

Table 2: Selected clinical trials of cytotoxic chemotherapy in advanced PNET**.

Regimen	No. of patients	Tumor response rates (%)	Median PFS month	Complete/partial response	Author (yr)
Prospective studies					
Chlorozotocin	33	30	17	18	Moertel et al. [19] (1992)
STZ + 5FU	33	45	14	16.8	
STZ + DOX	36	69	18	26.4	
DTIC	50	34	NR	19.3	Ramanathan et al. [20] (2001)
Retrospective studies					
STZ + 5FU + DOX	84	39	18	37	Kouvaraki et al. [21] (2004)
TMZ various chemotherapy	53	34	13.6	35.3	Kulke et al. [22] (2009)
TMZ + Capecitabine	30	70	18	NR	Strosberg et al. [23] (2010)

** Several of the early studies often assessed tumor response and PFS by clinical and not imaging parameters.
PFS: progression-free survival, STZ: streptozocin, 5FU: 5-flurouracil, DOX: doxorubicin, DTIC: dacarbazine, TMZ: temozolomide, NR: not reported.

Recent research has investigated the use of ^{90}Y radioembolization to treat unresectable NELM. Kennedy et al. [24] reported that imaging response demonstrated stable lesions in 22.7%, partial response in 60.5%, complete response in 2.7%, and progressive disease in 4.9% of patients with only mild associated toxicity. The median survival from time of treatment was 70 months. Objective respond rate (complete and partial response) were observed in 50% of patients in a prospective studies, in which 32 patients were treated with ^{90}Y microspheres [25].

3. Systemic Therapies

3.1. Somatostatin Analogs. Most neuroendocrine tumors (>80%) express a high density of somatostatin receptors (SSTR 1–5). Native somatostatin has not been useful in clinical practice due to its short half-life (<2 minutes). In 1980, Bauer et al. synthesized a somatostatin analog called octreotide, constituting an octapeptide with 3 unnatural amino acids, whereby the compound became resistant to metabolic degradation and presented a half-life of 3 to 4 hours in circulation. This peptide binds with high affinity to SSTR2 and SSTR5 and, therefore, inhibits the secretion of peptides and amines from neuroendocrine cells. In an initial study, the subcutaneous administration of the somatostatin analog octreotide, administered at a dosage of 150 mg 3 times a day, improved the symptoms of "carcinoid" syndrome in 88% of patients [26].

Octreotide has been widely used in oncology for almost 3 decades and is the most effective drug in inhibiting clinical symptoms related to hypersecretion of amines and peptides in NET. A long-acting depot form of octreotide (octreotide LAR), which can be administered on a monthly basis, has gained popularity. Octreotide therapy results in remission or stabilization of tumor markers, such as serotonin and chromogranin A, in approximately 60% to 70% of patients [27, 28].

PROMID [29] is the first randomized prospective trial demonstrating a possible antitumor effect for octreotide LAR compared with a placebo in patients with well-differentiated neuroendocrine tumors of midgut origin. A total of 85 patients with inoperable or metastatic well-differentiated midgut neuroendocrine tumors (carcinoid tumor) were randomized to receive either octreotide LAR 30 mg monthly or placebo. Median time to tumor progression was significantly longer for patients receiving octreotide (14.3 versus 6 months). This study supports an antiproliferative effect in well-differentiated midgut carcinoid tumors, with stabilization being the most frequently observed therapeutic response. However, only less than 10% tumor mass in the liver along with resected primary tumors responded to treatment. There was no significant difference in time to tumor progression between octreotide LAR and placebo in

Table 3: Selected randomized trials of targeted therapy in advanced neuroendocrine tumors.

Regimen	No. of patients	Tumor response rates (%)	Median PSF (months)	% of NELM	Author (yr)
PNET					
Sunitinib 37.5 mg po qd	86	9	11.4 ($P < 0.001$)	71 (61/86)	Raymond et al. [35] (2011)
Placebo (+ best supportive care)	85	0	5.5	54 (46/85)	
Everolimus 10 mg po qd	207	5	11 ($P < 0.001$)	92 (190/207)	Yao et al. [36] (2011)
Placebo (+ best supportive care)	203	2	4.6	92 (187/203)	
Everolimus 10 mg po qd Everolimus 10 mg po qd + Bevacizumab 10 mg/kg every other week	GALGB 80701	Ongoing			
Carcinoid					
Octreotide LAR	42	2	14.3 ($P < 0.001$)	83 (35/42)	Rinke et al. [29] (2009)
Placebo	43	2	6.0	88 (38/43)	
Everolimus + octreotide LAR	187	Radiant-2 accrual completed	Final report pending		
Placebo + octreotide LAR	191				
Octreotide + bevacizumab	SWOG S0518				
Octreotide + placebo					

patients with larger tumor burden. The authors concluded that newly diagnosed NET with a low hepatic tumor burden and resected primary tumor were candidates for treatment with octreotide LAR.

The high rate of somatostatin receptor expression in NETs provides the rationale for peptide receptor radionuclide therapy (PRRT) as a treatment modality for patients with inoperable or metastatic disease. Several radiolabeled somatostatin analogs have been developed to treat patients with somatostatin receptor-positive metastatic tumors. The most frequently used radionuclides include yttrium (^{90}Y) and lutetium (^{177}Lu), which differ from one another in terms of emitted particles, particle energy, and tissue penetration. ^{90}Y emits β-radiation has a range of 12 mm, and ^{177}Lu emits both β-radiation and γ-radiation and has a range of 2 mm. ^{177}Lu-DOTA, Tyr^3-octreotate has since been utilized in the treatment of over 500 patients with GEP-NETs. Efficacy results, reported for 310 patients and 89% (276/310) presented liver metastasis, suggest an overall tumor response rate of up to 30%. However, all PRRTs using yttrium (^{90}Y) and lutetium (^{177}Lu) are not randomized, prospective studies and majority of patients are carcinoid [30–33].

3.2. Cytotoxic Chemotherapy. In a Phase II/III study of 249 patients with advanced "carcinoid" tumors, patients were randomized to receive either streptozocin/5-FU or 5-FU/doxorubicin [34]. The response rates were 16% and 15.9%, respectively. Although there was a slightly longer survival time associated with streptozocin/5-FU (24.3 versus 15.7 months) in this trial, over one-third of the patients treated with streptozocin developed renal toxicity. Thus, streptozocin-based regimens are not recommended in the first-line treatment of metastatic "carcinoid" tumors.

However, patients with advanced PNET may respond well to treatment with streptozocin and other alkylating agents. In a randomized trial, the combination of streptozocin and doxorubicin was associated with an overall response rate of 69% and a survival benefit, with median overall survival of 2.2 years [19]. A retrospective analysis of 84 patients with either locally advanced or metastatic PNET receiving a three-drug regimen of streptozocin, 5-FU, and doxorubicin showed that this regimen was associated with an overall response rate of 39% and a median survival of 37 months [21].

Temozolomide is an orally alkylating agent with a mechanism of action similar to streptozocin and dacarbazine. Retrospective studies suggest comparable progression-free survival (PFS) and overall survival (OS) between streptozocin and temozolomide-based regimens in patients with advanced PNET (Table 2). Prospective studies using

temozolomide-based regimens in patients with advanced PNET are ongoing.

3.3. Targeted Therapies for Pancreatic Neuroendocrine Tumors. Studies of targeted therapies in PNET have, to date, focused primarily on inhibitors of the vascular endothelial growth factor (VEGF) or mammalian target of rapamycin- (mTOR) signaling pathways. Two phase III randomized studies suggested that treatment with these agents is associated with improvements in progression-free survival (PFS).

3.4. VEGF Pathway Inhibitors. Bevacizumab which targets VEGF and three tyrosine kinase inhibitors: pazopanib, sorafenib, and sunitinib—all with activity against VEGF receptor (VEGFR)—have been evaluated in prospective trials of patients with advanced PNET.

Bevacizumab is a recombinant humanized monoclonal antibody that binds to and neutralizes the biologic activity of human VEGF-A. In a randomized phase II study conducted at M.D. Anderson, 44 patients on stable doses of octreotide were randomly assigned to 18 weeks of treatment with bevacizumab or pegylated interferon alfa-2b (PEG IFN). A rapid and sustained decrease was observed in tumor perfusion following treatment with octreotide and bevacizumab, as measured in functional computed tomography. Clinical activity was evident by a response rate of 18% and an improved PFS rate at week 18 (95% versus 68%; $P = 0.02$). Bevacizumab therapy therefore provides an advantage in objective responses, reduction of tumor blood flow, and PFS in patients with carcinoid compared to PEG IFN treatment [37].

NETs frequently express VEGFR-2 and platelet-derived growth factor receptor receptor-β (PDGFR-β). Sorafenib, a small-molecule inhibitor of the VEGFR-2 and PDGFR-β tyrosine kinase domains, is a rational targeted therapy to be evaluated in NET. Hobday, et al. [38] reported a phase II study in 2007 ASCO using sorafenib in patients exposed to prior interferon and prior or concurrent octreotide at a stable dose. Patients received sorafenib 400 mg orally BID. A total of 93 patients were enrolled: (50 carcinoid and 43 PNET). For patients evaluable for the primary endpoint, 4 of 41 (10%) carcinoid patients and 4 of 41 (10%) PNET patients had a partial response (PR). There were 3 minor responses (MR = 20–29% decrease in sum of target lesion diameters) in carcinoid patients and 9 MRs in PNET patients and this led to PR + MR rate of 17% for carcinoid patients and 32% for PNET patients. Sorafenib at 400 mg orally twice a day in this study demonstrated modest activity in metastatic NET.

VEGF is a key driver of angiogenesis in PNET. Tissue from malignant PNET also shows widespread expression of PDGFRs α and β, stem-cell factor receptor (c-kit), and VEGFR-2 and VEGFR-3. Sunitinib inhibits these kinases and delays tumor growth in a RIP1-Tag2-transgenic mouse model of pancreatic islet-cell tumors by reducing endothelial-cell density and pericyte coverage of tumor vessels.

Sunitinib was evaluated in a multi-institutional phase II study enrolling 109 patients with advanced NET. Patients received sunitinib, administered orally at 50 mg once daily for 4 weeks, followed by a 2-week off period. Partial responses were observed in 2% of the carcinoid cohort and 16% of the PNET cohort [39]. Based on the encouraging response rate in this phase II study, an international randomized phase III study was conducted to confirm the activity of sunitinib in PNET. The study was discontinued prior to a planned interim analysis after enrollment of 171 patients, 86 of them received sunitinib, and 85 received placebo. The trial was terminated early because of the risk of serious adverse events, disease progression, and death among patients receiving placebo. The early discontinuation of the study precluded the definitive conclusion on differences in PFS durations between the treatment and placebo groups. Nevertheless, analysis of the available data demonstrated that treatment with sunitinib was associated with a remarkable median PFS of 11.4 months, as compared with 5.5 months for placebo ($P = 0.0001$) [35].

Pazopanib is an oral tyrosine kinase inhibitor of VEGFR, PDGFR, and KIT with both antiangiogenic and antitumoral activity. Pazopanib was evaluated in a prospective study enrolling 51 NET patients (29 with PNET and 22 with carcinoid) on stable doses of octreotide-LAR. Patients received pazopanib at a dose of 800 mg daily. The response rate among patients with PNET was 17%; no patients with carcinoid experienced a radiographic response (by RECIST). PFS rate at week 24 was 76% (80% PNET and 71% carcinoid). Median PFS times were 12.7 and 11.7 months, for carcinoid and PNET patients, respectively. Encouraging PFS durations in both carcinoid and PNET patients in this study suggested that treatment with pazopanib and octreotide seemed feasible and associated with tumor regression in patients with PNET [40].

3.5. mTOR Inhibitors. mTOR is a serine-threonine kinase that participates in the regulation of cell growth, proliferation, and apoptosis. Signaling through the PI3K/AKT/mTOR pathway leads to increased translation of proteins regulating cell-cycle progression and metabolism. This enzyme also mediates downstream signaling from a number of pathways, including the VEGF and insulin-like growth factor (IGF) signaling implicated in NET growth. The inhibition of mTOR prevents phosphorylation of key cell-cycle control proteins, leading to G1 growth arrest.

Temsirolimus and everolimus are rapamycin derivatives which were evaluated in NET. Weekly intravenous temsirolimus was associated with a response rate of 5.6% in a study of 37 patients with advanced progressive NET. Outcomes were similar between patients with carcinoid and PNET [41].

Everolimus was initially evaluated in a single-institution study, in which 30 patients with "carcinoid" tumors of intestinal origin and 30 with pancreatic PNET received doses of 5 or 10 mg daily plus depot octreotide (30 mg every 4 weeks). The overall tumor response rate in evaluable patients was 17% in carcinoid and 27% in PNET [42].

In a follow-up international phase II study (RADIANT-1), 160 patients with advanced PNET and evidence of

RECIST-defined progression following chemotherapy were enrolled. In this nonrandomized study, treatment with everolimus was associated with an overall response rate of 4.4% and PFS duration of 16.7 months in those patients receiving octreotide. Among patients who did not receive octreotide, the response rate was 9.6%, and the PFS duration was 9.7 months [43].

A subsequent phase III study randomized 410 patients with progressive advanced PNET (RADIANT-3) to everolimus or placebo. This study demonstrated significant improvements in PFS (the primary endpoint) associated with everolimus as compared to placebo [(11 months versus 4.6 months ($P < 0.0001$)]. The overall tumor response rate associated with everolimus in this study was 5% [36]. A subgroup analysis of Japanese patients (23 patients received everolimus and 17 patients were in placebo arm) in the same RADIANT-3 study showed a significant 17 months improvement in PFS (19.45 versus 2.83 months) and an 81% risk reduction of progression or death (HR 0.19, 95% CI 0.08–0.48, $P < 0.001$) [44]. Phase III-randomized trials of biological targeted therapy in advanced neuroendocrine tumors are summarized in Table 3.

3.6. Combination of Target Therapies. Ongoing studies are evaluating combinations of targeted agents in patients with advanced neuroendocrine tumors. The combination of everolimus + bevacizumab was shown to be well tolerated and associated with antitumor activity (overall response rate 26%) in an initial phase II study enrolling patients with low- or intermediate-grade neuroendocrine tumors [43]. Other combination-advanced PNETs includes everolimus + temozolomide [45] and everolimus + octreotide [42].

4. Conclusions

Different therapeutic options have been employed for well-to-moderately differentiated NELM. Surgical resection of hepatic metastases or hepatic artery embolization can be helpful in patients with hepatic-predominant metastatic disease. Symptoms of hormonal excess, such as "carcinoid" syndrome and syndromes associated with functional PNET, can be effectively treated with somatostatin analogs. Treatment with the somatostatin analog octreotide has been shown to improve progression-free survival in patients with advanced midgut carcinoid tumors. Patients with NELM may also respond to treatment with streptozocin or temozolomide-based therapy but need to be reassessed using standard criteria of response. In patients with advanced PNET, randomized, placebo-controlled studies have recently demonstrated that treatment with the tyrosine kinase inhibitor sunitinib or with the mTOR inhibitor everolimus is associated with improved PFS. Initial phase II studies have also suggested activity associated with VEGF pathway and mTOR inhibitors in patients with neuroendocrine tumors of other origins including intestinal "carcinoids." Future studies will likely define the utility of combinations of these agents in the treatments of patients with NELM.

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Review Article

A Multimodal Approach to the Management of Neuroendocrine Tumour Liver Metastases

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Neuroendocrine tumours (NETs) are often indolent malignancies that commonly present with metastatic disease in the liver. Surgical, locoregional, and systemic treatment modalities are reviewed. A multidisciplinary approach to patient care is suggested to ensure all therapeutic options explored.

1. Introduction

Neuroendocrine tumours (NETs) are uncommon tumours that can arise anywhere within the body, but predominantly from the gastroenteropancreatic tract. Recent epidemiological evidence suggest that the incidence of all NETs is approximately 3–5 per 100,000 population per year with a prevalence of 35 per 100,000 population because of slow tumour growth [1, 2]. Though most NETs are nonfunctional, others secrete peptide hormones that can cause clinical syndromes, like flushing, diarrhoea, bronchospasm and palpitations seen with carcinoid syndrome. The majority of these tumours are indolent, slow growing malignancies, commonly presenting with metastatic disease. The most common site of distant metastases is the liver. Consequently, many therapies are focused at treating the primary and also the metastatic disease in the liver. Due to the indolent nature of most of these tumours, the 5-year survival of patients with metastatic disease at presentation is approximately 50%. There may have been some improvement in survival from medical and surgical therapies. New molecular-targeted therapies and an aggressive surgical approach to resection of primary and secondary tumours show benefit.

This paper focuses on management of liver metastases of NETs and covers both surgery, locoregional, and systemic therapy. In general, local therapies to the liver should be considered first if disease is confined to the liver. This allows systemic therapies to be given at a later stage if there is extrahepatic spread. Results for liver-directed and systemic therapy of neuroendocrine tumour liver metastases are summarised in Tables 1 and 2, respectively.

2. Liver-directed Therapies

Consensus guidance recommends surgery for liver metastases in well-differentiated NETs if complete resection or debulking of <90% tumour load is feasible [45]. However, intended curative surgery is only possible in less than 10% of patients who are diagnosed with hepatic metastases at presentation [3, 46–49]. The distribution of liver metastases affects survival; solitary metastases, isolated metastatic bulk with smaller accompanying deposits, and disseminated metastatic spread have 5-year survival rates of 100%, 84%, and 51%, respectively [50].

An aggressive surgical approach to resecting liver metastases is supported by significantly improved actuarial survival in series compared to nonrandomised controls [3–5]. A number of different surgical approaches are available depending on the distribution of metastases. If primarily unilobar metastases are present, a one-step approach can be adopted. In these cases, resection of the primary plus liver resection can be performed. A two-step surgical approach to bilobar metastases from luminal NETs with resection of the primary, limited resection of left liver lobe metastases, and right portal vein ligation followed by right hepatectomy has been proposed [6]. Overall survival and disease-free rates at 5 years were 94% and 50% with this approach. Other

Table 1: Summary of results for liver-directed therapy of neuroendocrine tumour liver metastases.

Modality author [Ref]	Intervention	Number of patients	Overall survival (5 years)	Median survivals (months)	Progression/disease-free survival	Clinical response	Biochemical response	Radiological response
Liver surgery								
Sarmiento et al. [3]	Resection	170	61%					
Touzios et al. [4]	Resection ± ablation	18	72%	>96				
Grazi et al. [5]	Resection	19	92% (4 yrs)					
Kianmanesh et al. [6]	Resection	23	94%		50% (5 yrs)			
Gomez et al. [7]	Resection	18	86%		66% (5 yrs)			
Scigliano et al. [8]	Resection	41	79%		3% (5 yrs)			
Osborne et al. [9]	Cytoreduction	61		Curative-50 (mean) Palliative-32 (mean)				
Musunuru et al. [10]	Resection ± ablation	13	83% (3 yrs)					
Mayo et al. [11]	Resection ± ablation	339	74%	125				
Liver transplantation								
Lehnert [12]		103	47%					
Olausson et al. [13]		15	90%		20% (5 years)			
Le Treut et al. [14]		85	47%					
Embolisation								
Ho et al. [15]	TAE or TACE	46		42	18 months			
Ruutiainen et al. [16]	TACE	57	50%		35% (3 yrs)			
Strosberg et al. [17]	TAE	84		36				
Dong and Carr [18]	TACE	123	36%	39 (mean)				
Ruszniewski et al. [19]	TACE	24				73%	57%	33%
Gupta et al. [20]	TAE or TACE	69 (Carcinoid) 54 (Pancreatic)			22 months 16 months			67% 35%
RFA								
Mazzaglia et al. [21]		63		46 (after RFA)		70%		
SIRT								
King et al. [22]		37		29 (mean)		55%	43%	50%
Kennedy et al. [23]		148		70				63%
Cao et al. [24]		58	47% (3 yrs)	36				34%
Saxena et al. [25]		48		35				55%

Table 2: Summary of results for systemic therapy of neuroendocrine tumour liver metastases.

Modality author [Ref]	Intervention	Number of patients	Overall survival (5 years)	Median survivals (months)	Progression/disease-free survival	Clinical response	Biochemical response	Radiological response
Biological Therapy								
Ducreux et al. [26]	Lantreotide	46						5%
Aparicio et al. [27]	Octreotide	35			11 months			3% (57% stabilised)
Rinke et al. [28]	Octreotide LAR	85			14.3 months			67% stabilised
Oberg and Eriksson [29]	IFN α	111		>80	34 months	68%	42%	15% (39% stabilised)
Arnold et al. [30]	Octreotide ± IFN α	109		32 versus 54 (combined)				1.9% (27% stabilised)
Fjällskog et al. [31]	Somatostatin ± IFN α	16					62.5%	19%
Chemotherapy								
Moertel et al. [32]	STZ + doxorubicin	36		26	20 months			69%
	STZ + 5FU	33		18	6.9 months			45%
Turner et al. [33]	5FU + cisplatin + STZ	79		31.5	9.1 months			33%
Sun et al. [34]	STZ + doxorubicin	85		15.7	4.5 months			15.9%
	STZ + 5FU	78		24.3	5.3 months			16%
Kouvaraki et al. [35]	5FU + doxorubicin + STZ	61	74% (2 yrs)		41% (2 years)			
Strosberg et al. [36]	Temolozomide + capecitabine	30	92% (2 yrs)		18 months			70%
Moertel et al. [37]	Etoposide + cisplatin	18		19	8 months			67%
Molecular-targeted therapy								
Raymond et al. [38]	Sunitinib	171			11.4 months			9.3%
Yao et al. [39]	Everolimus	410	34% (1.5 yrs)		11 months			
Yao et al. [40]	Bevacizumab	44			95% (18 weeks)			
PPRT								
Cwikla et al. [41]	DOTATATE Y-90	60		22	17 months	72%		23%
Kwekkeboom et al. [42]	177Lu-octreotate	131			>36 months			28%
Pfeifer et al. [43]	Y-DOTATOC or 177Lu-DOTATOC	69			29 months			23.6%
Kwekkeboom et al. [44]	177Lu-DOTA 0,Tyr3	310		46	40 months			30%

series report a range of overall survival and disease-free rates [7–9, 51]. A significant improvement in 3-year survival for surgical resection over medical treatment or embolisation has been demonstrated in a study limited by bias. [10]. The completeness of resection, in particular resection margin involvement, is thought to be more important than the number, localization, and size of liver metastases [7, 52, 53]. Histological grade and extrahepatic disease are predictive of overall survival [54, 55]. Disease has been shown to recur in 78–94% of patients at 5 years [3, 8, 11].

After surgery, patients with functioning tumours have prolonged partial or complete symptomatic response rates that can contribute to improved quality of life [11, 56, 57]. Patients with carcinoid tumours have reduced biomarkers (e.g., Chromogranin A and urinary 5-HIAA) after surgery that correlate with symptom relief and disease control [3, 58]. Some rarer functioning syndromes, like those related to PTHrP or VIP secretion, can be improved by debulking surgery [59].

There is no evidence from randomised clinical trials supporting liver surgery, either for curative resection or for debulking in nonresectable disease, over other treatment modalities. Liver surgery only achieved significance in improving survival in univariate but not multivariate analysis [60–62]. Neoadjuvant strategies for downsizing liver metastases or adjuvant chemotherapy following hepatic resection have not yet been subject to controlled clinical trials [63–65].

2.1. Surgery to Primary Tumour in Metastatic NETs. Recent guidelines recommend resection of the primary tumour and mesenteric lymph nodes in jejunum/ileum NETs [66–68]. Tumour mass reduction or debulking of primary jejunal and ileal NETs reduces the possibility of bowel ischaemia and obstruction from tumour and mesenteric lymph nodes mass effect even in the context of liver metastases. Resection of the primary tumour has been shown to be an independent positive predictor of survival ($P = 0.015$) and associated with a significantly longer survival than no resection (median survival 7.4 versus 4.0 years; $P < 0.01$) [62, 69]. Successful resection of mesenteric metastases and the desmoplastic reaction around the primary site are also associated with a significantly longer survival. Significant reductions in tumour-related symptoms are also seen after primary and mesenteric lymph node resections.

Aggressive surgery to primary tumours and resectable liver metastases in pancreatic NETs is recommended [67, 70]. Resection of pancreatic NETs has been suggested to be associated with significantly improved survival compared to those who did not undergo resection (114 months versus 35 months; $P < .0001$) though significant biases may exist in this study [71]. This survival benefit was demonstrated for patients with localized, regional, and metastatic disease with an adjusted odds ratio of 0.48. Independent predictors of survival after resection of pancreatic NETs include age, grade, presence of distant metastases, tumour functionality, and type of resection [72]. Current guidelines do not recommend surgery to the primary pancreatic tumour in patients with unresectable liver metastases [70, 73].

2.2. Transplantation. The role of orthotopic liver transplant is controversial given the demand for donor organs and a lack of clear selection criteria [74]. Patients with debilitating and poorly controlled hormonal syndromes from small intestine or pancreatic NETs are considered for transplantation as symptom relief is seen in 90% of patients following surgery [12, 13, 75–78]. Five-year recurrence-free rates vary from 25–50%. Overall five-year survival rates are around 50% but vary according to patient selection [13, 14, 79, 80]. Patients presenting with duodenal or pancreatic NET in association with hepatomegaly have poorer outcomes (12% versus 68% five-year survival rates) [14]. The presence of extensive extrahepatic tumour resected at the time of transplantation is associated with poorer median and five-year survival rates of ten months and 30%, respectively [12]. Important selection criteria include well-differentiated tumours, low proliferation rate (Ki-67 < 10%), and regular E-Cadherin staining [81, 82]. The Milan criteria for transplantation include age less than 55 years, low grade carcinoid NET, limited metastatic disease in the liver (<50%), previously resected tumours drained only by the portal system (pancreas and mid gut origin NETs), and stable disease for 6 months [83]. Combination treatment with chemotherapeutic agents, chemoembolisation, systemic radiopeptide treatment, and aggressive surgery for recurrence may lead to improved survival rates [84–86].

2.3. Embolisation. NET liver metastases are highly vascular with an arterial supply that if occluded will lead to ischaemia and necrosis. Normal tissue is supplied from the portal vein and preserved during embolisation of hepatic arteries. A catheter is guided to the hepatic artery or branch and material (gelfoam powder, microembospheres, and polyvinyl alcohol particles) released to occlude the vessel in bland embolisation. In chemoembolisation, cytotoxics (like cisplatin, mirplatin, gemcitabine, doxorubicin, streptozocin, and 5-FU) are injected prior to arterial embolisation in order to achieve higher concentrations and prolonged action in necrotic tissue [87–89]. Contraindications to embolisation include occlusion of the portal vein, severe liver dysfunction, and presence of biliary anastomosis. Relative contraindications include tumour burden, renal impairment, and heart disease (including carcinoid heart disease) [90, 91]. A postembolisation syndrome may occur with abdominal pain, vomiting, fever, and rise in transaminases.

Vascular occlusion can achieve reduced hormonal symptoms from NET syndromes, reduced tumour burden, and improved survival in patients who have tried medical therapy and who are not suitable for surgical resection [92–95]. Sequential hepatic artery occlusion can offer prolonged palliation for responsive patients even if performed later in their clinical course [90, 96, 97].

Median survival rates after transarterial embolisation (TAE) or chemoembolistaion (TACE) in patients with liver metastases is over 3 years with progression-free survival (PFS) of around 18 months [15–18, 98–100]. Clinical response rates of over 90% are seen following treatment [91]. Intact primary tumour, extensive liver disease, and bone metastases are associated with worse outcomes.

Embolisation of nonresectable liver metastases often results in disease regression in patients with carcinoid or pancreatic NETs [17, 19]. TACE appears to benefit patients with pancreatic NETs while TAE benefits those with ileal NETs [20]. A small randomized study of TAE versus TACE in all liver NETs has shown no difference in time to progression [101].

2.4. Radiofrequency Ablation (RFA). RFA of oligonodular liver metastases (fewer than 8) of less than 5 cm can result in symptomatic response in 70–80% of patients with hormonal syndromes for as long as 24 months [21, 63, 102, 103]. Electrical energy is delivered to tissues via a catheter, inserted percutaneously or laparoscopically, which leads to heating and cell death [104, 105]. Microwave RFA can reduce time required for this procedure. RFA can play an important role in the treatment of carcinoid metastases not suitable for surgical resection and refractory to TAE, improving symptom control, reducing octreotide dependence, and slowing progression in patients [106–108]. Limitations to using RFA include increased numbers and size of liver metastases as well as the detrimental cooling effect of blood flow from neighbouring blood vessels. Local recurrence has been identified in 21.7% of tumours on CT scans with a mean follow-up of 17 months. Recurrence can be predicted by tumour type and size, ablation margin, and blood vessel proximity [103, 109]. Median survival after starting RFA treatment is 3.9 years [21]. Although RFA may play a promising role in the treatment of liver metastases from NETs, its effect on survival and tumour progression needs to be explored in larger studies. In particular, studies are needed comparing surgical resection with RFA.

2.5. Selective Internal Radiation Therapy (SIRT). Radioembolisation of liver metastases can be achieved with Yttrium-90 resin microspheres in patients with disseminated and inoperable liver disease even if previous TAE or TACE has taken place [22, 110]. (90 Y) microspheres are injected through a percutaneously placed hepatic artery catheter via the femoral or brachial artery. Contraindication to SIRT is similar to those of bland embolisation, vascular involvement such as portal vein thrombosis, severe liver dysfunction, and large tumour burden. Long-term radiologic and biological responses can be achieved with radioembolisation with partial or complete response seen in 63% [22, 23]. Median survival varies from 36 to 70 months [23, 24]. Prognostic factors include radiographic response to treatment, tumour grade, and presence of extrahepatic disease. Patients with hepatic tumour burden of 20–50% by volume, well-differentiated tumour, female gender, and no extrahepatic disease benefit most from treatment [25]. There is no randomized evidence that radiologic and symptom response rates following SIRT are different from those seen with TACE and TAE.

3. Systemic Therapies

3.1. Biological Therapy. Over 70% of NETs express cell-surface somatostatin receptors that are targeted by synthetic somatostatin analogues. Patients with functional NETs can derive significant symptomatic benefit from the use of somatostatin analogues that suppress the secretion of peptide hormones. Octreotide can provide symptomatic response in up to 85% of patients and biochemical response in up to 70% of patients within weeks of commencement [111, 112]. Patients with NETs undergoing interventional procedures can experience severe symptoms related to the release of vasoactive hormones, like serotonin, that can cause a carcinoid crisis with bronchospasm, tachycardia, and labile blood pressure. This can be ameliorated through the use of octreotide infusions before, during, and after interventional procedures.

Some groups have reported an antiproliferative property of somatostatin analogues [26, 27, 112, 113]. Octreotide LAR has been found to significantly lengthen the time to tumour progression compared to placebo injections (14.3 versus 6 months resp.) [28]. The benefit was seen in both functionally active and inactive tumours. Patients with low hepatic tumour load and resected primary tumour benefited the most from treatment with octreotide LAR. Overall, survival was not an endpoint of this study, consequently; survival benefit from the use of somatostatin analogues has not been confirmed.

Interferon alpha 3–5 megaunits 3–5 times per week have been used with some symptomatic response, but no clear reduction in tumour size or survival benefit [29–31, 114, 115]. Interferon alpha should be considered as second-line biological therapy after somatostatin analogues.

3.2. Chemotherapy. Systemic chemotherapy has a role in the treatment of pancreatic and high grade NETs. Patient selection and individualized treatment are required to minimize toxicity, maximize response, and improve overall quality of life. The degree of differentiation and tumour grade of NETs can guide management [116, 117]. Poorly differentiated and high-proliferative tumours (from histological grading like Ki-67 and mitotic index) behave more aggressively but are more sensitive to cytotoxic therapy than well-differentiated and low-proliferative tumours (Ki-67 < 10%) [33]. Objective response to chemotherapy varies between 25–78% with progression-free periods between 4–22 months [32, 34, 37, 118–124]. Therefore, it is essential to ensure that chemotherapy is offered to patients who are likely to respond; those with pancreatic NETs, aggressive phenotypes, and high proliferation rates [125]. Biochemical and radiological progression in asymptomatic patients identifies those with rapidly progressive disease and an aggressive phenotype [67]. Response to cytotoxic therapy can be established from radiological-quantified reduction in tumour size, improved biochemical markers as well as improvements in quality of life as measured by health questionnaires [126–128].

Single-agent chemotherapy is seldom used because of limited response rates, toxicity, and poor survival rates. Newer agents like paclitaxel, temozolomide, topotecan, and gemcitabine are not markedly better than older agents like streptozocin, dacarbazine, 5 flourouracil, and doxorubicin when used as monotherapy [121, 126, 129–135]. In patients with pancreatic NET, combination chemotherapy

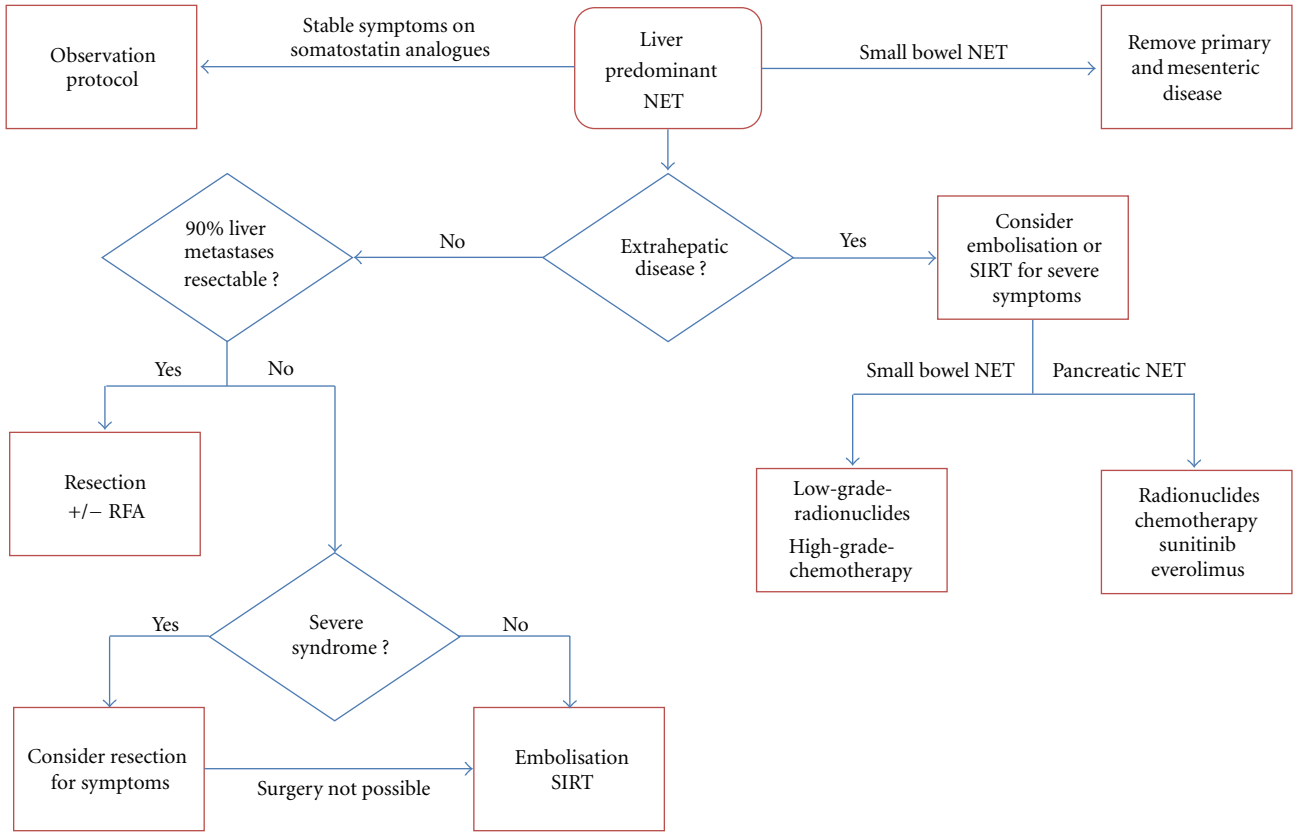

Figure 1

with streptozocin and doxorubicin is superior to streptozocin and 5FU in terms of response rates, time to progression, and overall survival [32, 136, 137]. Response rates from streptozocin and doxorubicin combination treatment vary between 30–70% [33–35, 138]. Recently, a retrospective analysis of capecitabine and temozolomide combination chemotherapy has demonstrated good response rates, superior to traditional streptozocin-based chemotherapy [36]. In 30 patients treated with capecitabine and temozolomide, response rates of 70%, progression-free survival of 18 months and overall survival of 92% at 2 years were observed. However, streptozocin-based therapy remains the standard chemotherapy regime for pancreatic NETs given the lack of data from randomised trials demonstrating benefit from other regimes [36, 116, 123, 139, 140]. Poorly differentiated or anaplastic NETs respond to a combination of cisplatin and etoposide, a regime used in small cell lung cancer [37, 118–120]. Despite chemotherapy, the prognosis remains poor in this group with a 2-year survival between 20–30%.

3.3. Molecular-Targeted Therapies. Novel systemic agents target the molecular mechanisms that are implicated in the pathogenesis of NETs [141, 142].

Sunitinib, a multitargeted tyrosine kinase inhibitor, has activity against a range of molecular targets, including VEGF receptors and platelet-derived growth factor receptors, and has been shown to have antitumour activity in pancreatic NETs [143]. Median PFS is significantly longer in patients treated with sunitinib over placebo (11.4 versus 5.5 months) [38]. Objective response rates and overall survival are also improved with sunitinib treatment. Frequent adverse events encountered include diarrhoea, nausea, vomiting, asthenia, and fatigue.

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has activity against pancreatic NET tumours through a mechanism of cellular apoptosis and antiangiogenesis [144, 145]. Median PFS is significantly longer in those treated with everolimus over placebo (11 versus 4.6 months) [39]. Severe adverse events like hyperglycaemia and anaemia were rare, with stomatitis, diarrhoea, and fatigue are more commonly seen.

Vascular endothelial growth factor (VEGF) is overexpressed in NETs and targeted by the ligand monoclonal antibody Bevacizumab [40, 146, 147]. There are reports of clinical benefit when combined with existing chemotherapy treatments [148, 149].

3.4. Peptide Receptor Radionuclide Therapy (PRRT). Somatostatin receptors subtype 2 are expressed in the majority of NETs and confirmed through uptake in octreotide scintigraphy or somatostatin-based PET imaging [150–152]. Beta-emitting 90 Y- and 177 Lu-labeled somatostatin analogues have been studied in patients with metastatic and inoperable disease [41, 42, 153–156]. The majority of patients develop

stable disease with the average time to progression of 40 months from commencing therapy. Partial and complete objective responses are seen in up to 30% of patients with median PFS of over 2 years [43, 157]. From diagnosis, there is a survival benefit of 40–72 months compared to historical controls [44]. Predictive factors include high tumour uptake on scintigraphy and limited liver metastases. Adverse events include bone marrow and liver toxicity as well as radiation-induced lose of renal function and gastrointestinal disturbance from the use of renoprotective agents [158, 159]. The addition of radiosensitisers like gemcitabine and capecitabine to PPRT may improve clinical outcomes [160, 161]. Alpha-emitting isotopes, such as actinum-225 (225Ac), have a higher cytotoxic activity than beta emitters and may be used in PRRT [162].

MIBG scans are also used to identify patients with metastatic NETs. 131 I-MIBG therapy is associated with significantly improved 5-year survival rates of 85% (non-randomized studies) as well as marked symptomatic and hormonal improvement [163–165]. Symptomatic response predicts improved survival.

4. Conclusion

There are a number of treatment modalities available in the management of neuroendocrine tumour liver metastases with a treatment algorithm outlined in Figure 1. Proactive surgical resection, with curative intent or for debulking (cytoreduction), has been shown to improve outcomes and should be pursued initially. In patients with more advanced disease or not amenable to surgical resection, locoregional therapies, like embolisation and SIRT, offer improved outcomes and may downstage disease. Newer systemic therapies, in particular PRRT and molecular targeted therapies, can play a role in patients with extrahepatic and progressive disease. Although there is a lack of robust evidence-based data in the management of patients with metastatic NETs, the future appears more positive with the range of treatment options available. An individualized approach to patient care is needed given the breadth of symptoms and disease, the lack of a validated treatment pathway as well as the indolent nature of NETs. Patient care should be managed under the auspices of a multidisciplinary team to ensure that all treatment options are explored both at diagnosis and follow-up.

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Review Article

Hepatic Arterial Embolization for the Treatment of Metastatic Neuroendocrine Tumors

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Neuroendocrine tumors (NETs) have a high predilection for metastasizing to the liver and can cause severe debilitating symptoms adversely affecting quality of life. Although surgery remains the treatment of choice, many liver metastases are inoperable at presentation. Hepatic arterial embolization procedures take advantage of the arterial supply of NET metastases. The goals of these therapies are twofold: to increase overall survival by stabilizing tumor growth, and to reduce the morbidity in symptomatic patients. Patients treated with hepatic arterial embolization demonstrate longer progression-free survival and have 5-year survival rates of nearly 30%. The safety of repeat embolizations has also been proven in the setting of recurrent symptoms or progression of the disease. Despite not being curative, hepatic arterial embolization should be used in the management of NETs with liver metastases. Long-term survival is not uncommon, making aggressive palliation of symptoms an important component of treatment.

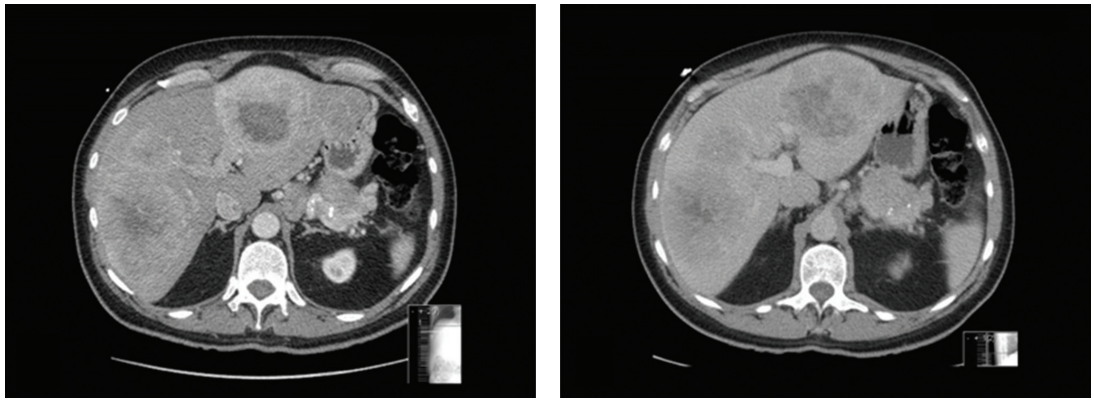
1. Introduction

Neuroendocrine tumors (NETs) consist of a heterogeneous group of neoplasms of varying presentation and prognosis. While a complete list of this family of tumors includes dozens of distinct histopathologic subtypes from multiple different organ systems, the majority of NETs are carcinoid tumors of the gastrointestinal tract and endocrine tumors of the pancreatic islet cells [1–3]. Primary liver NETs have been reported but are unusual and will not be discussed in this paper [4].

NETs are relatively rare, with an incidence ranging from 2.5 to 5.3 per 100,000 [3, 5]. The prevalence is significantly higher at about 35 per 100,000, indicating that many patients are alive with disease [3, 6]. However, these figures may not capture the full burden of NET disease, since conflicting nomenclature systems exist, making them difficult to classify and quantify [1, 3, 5–7]. Although some NETs are more aggressive in their behavior than others, all have the potential for distant metastases and should be considered malignant. In patients with resectable tumors without metastatic disease, surgery is considered the gold standard and is the only curative option. 5-year survival rates in patients with localized, nonmetastatic NETs undergoing curative resection range from 80% to 100% [2, 6].

While many NETs are nonfunctioning, these tumors are traditionally categorized by their classic patterns of symptoms arising from the secretion of various peptides and hormones [8]. For example, patients with gastrin hypersecretion from a gastrinoma tumor may present with severe peptic ulcer disease refractory to treatment. Insulinomas can cause severe hypoglycemia, while glucagonomas manifest with hyperglycemia and diabetes. Other NETs include VIPoma, characterized by diarrhea and hypokalemia, and somatostatinoma, presenting with cholelithiasis, diabetes, and steatorrhea. Carcinoid tumors of the GI tract frequently produce serotonin (5-HT), which can manifest as skin flushing, severe diarrhea, abdominal cramping, and electrolyte abnormalities [8].

The symptoms associated with functional NETs may be severe and debilitating and detract significantly from the quality of life of the patient; therefore, aggressive treatments to reduce symptoms have an important role in therapy [8]. Even in the setting of an unresectable primary tumor or widely metastatic disease, most NETs have an indolent course; 5–10-year survival with stage IV disease is not



(a) (b)

Figure 1: CT of bilobar hepatic metastases from a malignant NET in the (a) arterial phase and (b) venous phase. The characteristic enhancement of the tumor on arterial phase is apparent, as well as the relative darkening of the tumor on venous phase; the area of central necrosis is dark in both phases. Note the primary NET in the tail of the pancreas.

uncommon and makes the treatment of symptoms a fundamental component of patient care [3, 9–14].

2. Treatment of Metastatic Disease

Because the majority of NETs arise from the gastrointestinal tract and the pancreas, the liver is the most common site of metastases [15]. In patients with liver metastases, 75–80% will present with these metastases at the time of diagnosis (synchronous), while 20–25% of patients develop liver metastases during the course of treatment (metachronous) [8]. An estimated 80–90% of patients with liver metastases are inoperable at presentation [16]. Many primary NETs are small in size, and it is not unusual for the liver metastases to be of greater volume than the primary tumor. Given the high tumor burden often associated with metastases, symptoms can become significantly worse as the disease advances. In addition, many of the peptides and hormones produced by NETs are eliminated by metabolism through the liver. Therefore, it is only after liver metastases are present, and these compounds spill directly into the systemic circulation, that the phenotype of the tumor is fully expressed. As a result, symptom control can become increasingly important as metastases develop.

Surgical resection of hepatic metastases has been shown to reduce symptoms and is indicated for this purpose alone [2, 12]. In addition, some data indicate an improvement in overall survival as well, and therefore metastasectomy should be considered for resectable disease even in patients with nonfunctional tumors [10, 12, 17]. Meaningful improvements in symptom control and overall survival can be achieved even if complete resection of metastatic disease is not possible. However, available data suggest that debulking should only be considered if greater than 90% of the tumor burden can be resected [11, 18]. Two-step surgeries can be considered to increase resectability in bilobar disease [19].

While resection is preferred, excessive tumor bulk, tumor location, and other biological factors often preclude surgery. Even with resection, recurrence is common (50–60% at 5 years) and repeat hepatectomy may not be feasible [20, 21]. In these cases where resection is not possible or would not be tolerated by the patient's physiology, interventional radiology alternatives to surgery have been proposed, including radiofrequency ablation, hepatic arterial radioembolization with ^{90}Y, and hepatic arterial bland or chemoembolization. The goals of these therapies are twofold: to increase overall survival by stabilizing tumor growth, and to reduce the morbidity in symptomatic patients.

The radiologic appearance of liver metastases from NETs is distinct and has important ramifications for treatment. Compared to liver metastases that are of gastrointestinal origin, metastases from NETs derive a greater amount of their blood supply from the hepatic artery. As a result, when imaged during the arterial phase, metastatic NETs will typically appear brighter than the surrounding liver; and during the venous phase when the normal liver parenchyma is filled with contrast, NET metastases will appear darker than the surrounding liver. In other words, NET metastases typically "light up and wash out" (Figure 1) [22]. This pattern of enhancement is similar to that seen with hepatocellular carcinoma and is ideally suited for the arterial embolization techniques more commonly associated with that disease. Treatment response can be assessed using radiographic measures by examining the degree of enhancement of the lesions following embolization procedures (Figure 2).

3. Indications and Contraindications

Since surgical metastasectomy is the most effective treatment, only patients with unresectable liver disease or who are unable to undergo surgery should be considered for embolization procedures. Previous resection of the primary tumor is not necessary, although the disease should be stable and not at risk for complications such as bleeding or obstruction [13].

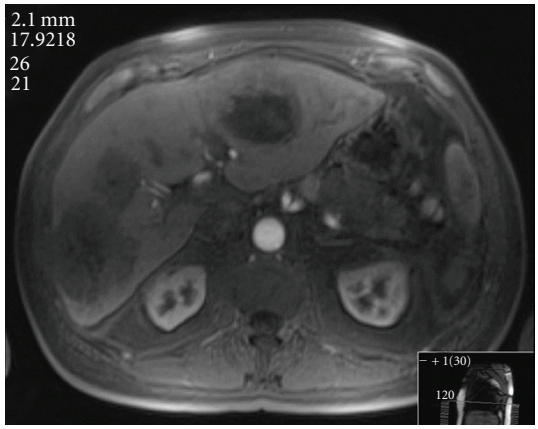


Figure 2: Post-TACE MR of bilobar hepatic metastases from the same patient in the arterial phase. Note the brightness of the aorta and lack of enhancement of the lesions compared to Figure 1, indicating the ischemia produced by the embolization.

Liver involvement greater than 75% is considered a relative contraindication to embolization, since these patients tend to have less response to treatment coupled with greater rates of complications [13, 23]. The presence of main portal vein thrombosis is a strict contraindication since hepatic arterial embolization relies upon the portal venous blood supply to rescue the nontumorous liver parenchyma. Therefore, hepatic arterial embolization in patients with complete portal vein thrombosis risks severe liver ischemia.

Embolization in patients with bilirubin levels greater than 2-3 mg/dL has also been reported to be unsafe [13, 24, 25]. Even though the liver parenchyma is relatively spared with arterial embolization, there is nevertheless an ischemic insult that results in temporary liver insufficiency. Patients with already borderline liver function may be tipped over into frank liver failure following embolization. Accordingly, patients with ascites should be carefully considered for embolization procedures since its presence suggests poor liver function [13].

Finally, patients with general contraindications to angiography, intolerance of contrast media, peripheral vascular disease, or coagulopathies should not be considered for embolization.

4. Hepatic Arterial Embolization Technique

Occlusion of the hepatic artery causes selective ischemia to the tumor, while the remainder of the liver parenchyma is rescued by the portal venous flow. As a result, the tumor is disproportionately affected by the ischemic insult, with relative sparing of the normal parenchyma.

While not curative, hepatic arterial embolization procedures slow tumor growth and prolong progression-free survival, until the eventual revascularization from collateral angiogenesis resupplies the tumor. One lobe of the liver is treated per session to minimize the risk of liver failure [25]. If both lobes of the liver are involved with tumor, the contralateral side can be treated approximately one month after the initial embolization.

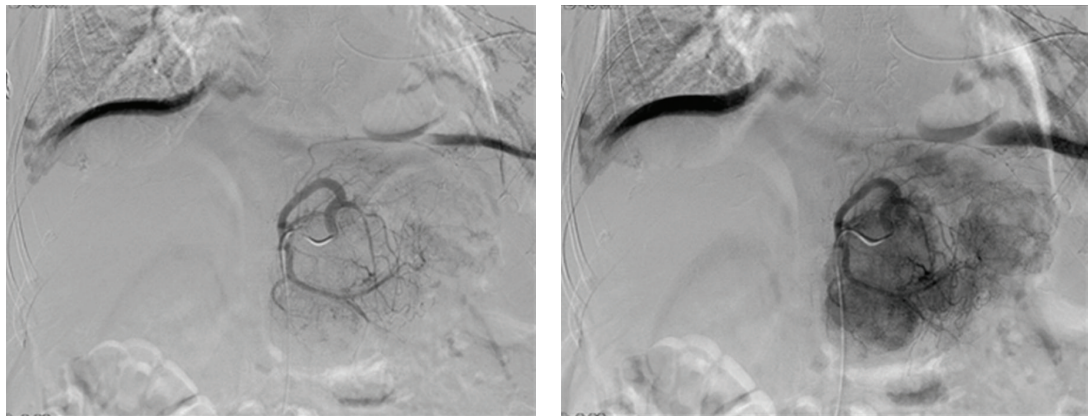
Three types of hepatic arterial embolization techniques are currently in use: transarterial bland embolization (TAE), transarterial chemoembolization (TACE), and embolization using drug-eluting beads (DEB-TACE). These procedures all involve percutaneous access to the femoral artery, followed by selective cannulation of the hepatic artery and its derivatives to the affected lobe. Prior to embolization, an arteriogram is performed to identify the vascular anatomy supplying the tumor (Figure 3). If femoral access is not available, the brachial artery can be used as an alternative, although this route is more technically challenging.

In bland embolization, catheterization is typically followed by the injection of 50 μm polyvinyl alcohol (PVA) particles, with or without ethiodized oil. These particles physically occludes blood flow through the selected hepatic artery, thereby inducing ischemic injury; if stasis remains unachieved, then larger 200–500-μm PVA particles can be used [26–29]. Other embolic agents currently employed include gelfoam, cyanoacrylate, tris-acryl particles, and embospheres [26, 28, 29].

Previous studies established that TAE is effective at reducing tumor size as well as decreasing tumor hormone production for palliation of symptoms [11, 25–34]. Systemic adjuvant chemotherapy following TAE was noted to prolong the duration of symptom relief, prompting the development of embolization coupled with chemotherapy [35]. TACE combines the use of embolic material with an initial infusion of a chemotherapeutic agent. However, it is unclear whether the addition of intrahepatic chemotherapy improves the efficacy of embolization techniques.

The literature has not consistently shown a clear benefit of TACE over TAE, and no randomized head-to-head studies have been performed. While select reports have found that patients treated with TACE experienced slightly longer progression-free survival (PFS) and greater overall survival (OS), other reports have not found any benefit of TACE over TAE [28, 31, 32]. It is likely that the efficacy of these techniques is largely due to the ischemia produced by the embolization itself, with only secondary benefits derived from the addition of chemotherapeutic agents.

In addition, there is no consensus on which chemotherapeutic agents for TACE are the most efficacious in the treatment of liver metastases from NETs. Doxorubicin, mitomycin C, streptozocin, vinblastine, gemcitabine, fluorouracil (5-FU), and cisplatin have all been used for TACE, and some regimens employ them in combination. The most common regimen described in the literature is a three-drug combination of doxorubicin (20–30 mg), cisplatin (50 mg), and mitomycin C (10–30 mg) mixed with 10 mL ethiodized oil [13, 27, 36, 37]. Doxorubicin alone with ethiodized oil is the second most common regimen described [38–40]. Lipiodol is an oily agent which is typically used during TACE to enhance chemotherapy retention within the tumor [38]. Lipiodol appears bright white on CT imaging and therefore interferes with assessment of tumor viability. Surveillance following TACE should utilize MRI imaging since lipiodol does not appear on MRI images.



(a) (b)

Figure 3: Arteriogram of the same patient with selective catheterization of the left hepatic artery from the femoral artery. Careful positioning of the catheter is important to minimize the risk of complications. Note the progressive tumor blush following the injection of contrast media.

A third chemoembolization technique, DEB-TACE, uses 500–700 μm embolic beads that are loaded with a chemotherapeutic drug, usually doxorubicin, which slowly elutes into the liver parenchyma over a period of 7–14 days [41–43]. The controlled release of chemotherapy allows for sustained, higher tumor levels of doxorubicin, while maintaining lower levels in the systemic circulation, which may decrease the incidence of systemic side effects. Studies have shown the OS and PFS in patients undergoing chemoembolization with DEB-TACE to be similar to TAE and TACE [41, 42].

Currently, all three techniques are actively in use, with no clear evidence for superiority of one approach over another.

5. Outcomes

Although there is a considerable amount of literature on hepatic arterial embolization treatments for metastatic NETs, most are retrospective reviews of smaller case series with historical controls; there are no randomized controlled trials. Due to the rare nature of NETs, prospective studies have not been feasible. Importantly, all methods of embolization have greater PFS and OS than no treatment or systemic chemotherapy alone [6, 11]. Most series include patients with both metastatic carcinoid tumors as well as pancreatic islet cell tumors in their cohorts. Patients with carcinoid NETs in general have longer OS and higher response rates than patients with pancreatic NETs, and as a result, outcomes should be interpreted accordingly [31, 32, 35].

One of the largest trials to date on the effects of embolization procedures is an analysis from Bloomston and colleagues on the outcomes of patients with metastatic carcinoid tumors undergoing TACE [36]. A cohort of 122 patients underwent 156 TACE procedures using a combination of doxorubicin (30 mg), mitomycin C (30 mg), and cisplatin (50 mg). The origin of the primary tumor was predominantly in the small bowel (47%), pancreas (21%), or lung (8%), with 14% of unknown origin. 81% of the patients presented with carcinoid syndrome, and the primary tumor had been previously resected in 75% of the patients. Interestingly, resection of the primary tumor did not prove to be predictive of survival. Following TACE, regression or stabilization of the hepatic metastases was observed in 94% of the patients, with a median duration of 19 months. Symptom improvement was reported in 92% of patients and was associated with a benefit in OS (41 months versus 8 months). Additionally, a lack of symptom improvement was associated with lack of radiographic response. PFS for the entire cohort was 10 months, and OS was reported to be 33.3 months with a 5-year survival of 28% from the date of the first TACE procedure [36].

Another large series by Swärd et al. examined 213 bland TAE procedures in 107 patients with metastatic carcinoid tumors. 106 of the patients had resection of the primary tumor, as well as prophylactic cholecystectomy [33]. Repeat TAE was performed in the setting of progressive disease, as demonstrated by two consecutive CT scans at least 6 months apart and a two fold increase in urinary 5-HIAA, a metabolite of 5-HT. Plasma chromogranin A levels, a general marker for NETs, were also recorded. Symptomatic improvement following TAE was reported in 71% of the patients, and an OS of 56 months from the date of embolization was shown for the group. Importantly, Swärd et al. were able to demonstrate a relationship between biochemical markers and survival benefit. Compared to patients who demonstrated no reduction in urinary 5-HIAA, patients with greater than 50% reduction experienced a 6-month gain in estimated survival, with an additional 6-month gain if the reduction was increased to 75%. In addition, increases in liver enzymes or chromogranin A both significantly correlated with reduced survival [33].

A more recent study by Pitt et al. compared the outcomes of 100 patients with carcinoid or islet cell tumors undergoing either TACE ($n = 49$) or TAE ($n = 51$) [28]. Particle embolization was performed with PVA, gelfoam, or embospheres; the chemotherapeutic agents used in TACE were cisplatin, doxorubicin, and mitomycin C. Both cohorts were similar with respect to age, gender, tumor type, and tumor burden. 67% of the TACE cohort underwent resection of the primary tumor, compared with 49% in the TAE cohort,

Table 1: Outcomes of hepatic arterial embolization in large published case series.

Author	Type of embolization	No. of patients/No. of embolization procedures	Survival	Comments
Bloomston et al. [36]	TACE	122/156	PFS: 10 months OS: 33 months 5-yr survival: 28%	Symptom improvement associated with increase in OS
Swärd et al. [33]	TAE	107/213	OS: 56 months	Increased survival with reduction in 5-HIAA; reduced survival with increased AST or chromogranin A
Pitt et al. [28]	TACE and TAE	100/229	TACE OS: 25.5 TAE OS: 25.7 TACE 5-yr survival: 19% TAE 5-yr survival: 13%	OS and 5-yr survival not statistically different between TAE and TACE; resection of primary tumor increased OS
Kamat et al. [23]	TACE and TAE	60/123	OS: 18 months PFS: 9 months	Patients had greater than 75% hepatic tumor burden; symptom improvement seen in 65%; major complication rate of 29%
Varker et al. [37]	Repeat TACE	27/54	OS: 28 months PFS: 5 months	Repeat TACE associated with similar OS and PFS, and lower complication rates compared to single TACE

although this difference was not significant. Response rates were 86% in the TACE cohort and 83% in patients treated with TAE and were not statistically different. Median overall survival from the date of the first procedure was also similar between the TACE and TAE groups, at 25.5 months and 25.7 months, respectively. In addition, 5-year survival rates for the TACE and TAE groups were not statistically different at 19% and 13%, respectively. Furthermore, the TACE and TAE groups exhibited similar complication rates (2.4% versus 6.6%, resp.) and mortality rates (0.8% versus 1.8%, resp.). In contrast to the study by Bloomston et al., resection of the primary tumor was significantly associated with an increase in overall survival: 73 months versus 28 months, respectively, from the time of diagnosis of metastatic disease. No other factors were found to be significantly predictive of survival, including tumor type, tumor burden, embolization type, and resection of liver metastases [28].

Patients with extensive liver tumor burden experience poorer response to embolization, as well as a greater rate of major complications. A major complication rate of 29% following embolization has been reported in patients with large volume disease [23, 31]. However, hepatic arterial embolization can still be of benefit in this group of patients. Kamat et al. demonstrated a median overall survival of 17.9 months and a PFS of 9.2 months using either TAE or TACE in patients with greater than 75% liver involvement. While only 44% of the patients demonstrated radiologic response, 65% showed improvement of symptoms, indicating that symptom relief can be used to guide therapy irrespective of radiologic findings [23].

6. Repeated Embolization

Despite embolization, most patients will exhibit disease progression as determined through both radiologic measures and the resumption of symptoms. These patients should be strongly considered for repeat embolization. Repeat embolizations are generally spaced 4–6 weeks apart to allow for the liver to recover fully [33].

The outcomes of patients undergoing repeat TACE have been reported in the literature, including a study by Varker et al. [37]. Although both radiologic and symptomatic responses were found to be slightly lower than for patients having their initial TACE (61% versus 82% and 77% versus 92%, resp.), this did not reach statistical significance. In addition, OS and PFS were similar between patients having initial versus repeat TACE. Of note, patients undergoing repeat embolization better tolerated the procedure and had a lower complication rate (11% versus 23%) than patients undergoing initial embolization [37]. These results indicate that repeat TACE is safe and effective in patients with progressive disease after initial embolic therapy and should be aggressively pursued to maintain disease control. A summary of the outcomes can be found in Table 1.

7. Complications

Both minor and serious complications as defined by the Society of Interventional Radiology standard criteria [44] are not uncommon among patients undergoing embolization. A review of the literature has shown the incidence of serious complications to range from 3% to 17% in most series [11, 13, 17, 25–34, 36–38, 45].

Postembolization syndrome (fever, nausea, vomiting, abdominal pain, and elevated liver enzymes) has been found to occur in the majority of patients but typically subsides within three days post-procedurally [11, 16, 27, 29–32, 38, 40]. There are anecdotal reports that the occurrence of postembolization syndrome correlates with the amount of tumor insult and that a robust physical response to embolization is in fact a positive prognostic indicator [46].

Hepatic failure, hepatic abscess, hepatorenal syndrome, sepsis, and severe hypertension occurring during embolization can all result from the local ischemia induced by

arterial embolization [11, 13, 16, 30, 31, 33, 36]. Patients with bilioenteric anastomoses or large tumors (greater than 5 cm) are especially at risk for hepatic abscess formation after embolization [47, 48]. Due to the risk of abscess formation, many physicians advise prophylactic antibiotic administration prior to the procedure [25, 27, 29, 36, 38]. Patients who develop a hepatic abscess can be treated with percutaneous drain placement and parenteral antibiotics; rarely liver resection may be indicated for persistence [30].

Cholecystitis and pancreatitis are both relatively common complications of hepatic arterial embolization. These events are thought to be due to reflux of embolic material into the cystic artery or pancreaticoduodenal artery respectively, causing ischemic injury to these organs. Careful positioning of the catheter tip into the intrahepatic portion of the hepatic artery, along with gentle infusion techniques, is thought to limit the incidence of these potentially serious complications [24].

Mortality following embolization procedures is rare in high-volume centers. In a study of 26 patients undergoing 62 TACE procedures, Kress et al. reported fatal hepatic failure in 2 patients (3.2%) within 30 days after embolization [38]. Similar 30-day mortality rates have been found by other investigators, ranging from 0% to 6%, the majority of which were caused by hepatic failure, acute renal failure, sepsis, and myocardial infarction [17, 27, 30, 31, 36].

As to be expected, both acute and chronic renal failure secondary to contrast media administration during arteriogram have been noted as a severe complication from TAE and TACE [23, 27, 38]. Finally, all hepatic arterial embolization procedures carry the potential complications which accompany femoral arterial catheterization, including groin hematoma, peripheral embolization, and arterial dissection [27, 30, 33].

Of note, patients having TAE have similar rates of complication compared to patients having TACE [28]. Additionally, DEB-TACE procedures have demonstrated comparable morbidity rates, with 30%–60% of patients experiencing elements of postembolization syndrome [42]. Both Gaur et al. and de Baere et al. reported mortality rates of 5% in patients undergoing DEB-TACE [41, 42]. Table 2 summarizes the characteristics of hepatic arterial embolization.

Table 2: Characteristics of hepatic arterial embolization for NET metastases.

Indications
Hepatic metastases of NET
Nonoperative candidates
Symptomatic and asymptomatic tumors
Contraindications
Main portal vein thrombosis
Bilirubin greater than 2-3 mg/dL
Hepatic tumor burden greater than 75%
Contraindications to angiography
Outcomes
Mortality 0–6%
Median OS 25–56 months
5-yr survival 13–28%
Common chemotherapeutic agents
None (bland embolization)
Doxorubicin
Mitomycin C
Cisplatin
Most frequent complications
Postembolization syndrome
Hepatic abscess
Hepatic failure
Cholecystitis
Pancreatitis
Indications for repeat embolization
Increase in tumor size or tumor enhancement
Progression of symptoms

8. Conclusion

Patients with NETs metastatic to the liver are often afflicted with debilitating symptoms that severely affect quality of life, and most patients with NETs ultimately die from progression in the liver. As a result, control of the hepatic tumor burden should be the primary goal in the management of patients with metastatic NETs. Surgical metastasectomy is considered preferable, although there are no randomized controlled trials comparing resection to nonsurgical therapies. In cases where resection is not feasible, interventional radiologic therapies such as hepatic arterial embolization can be used to control disease progression. The characteristic arterial enhancement of NETs can be taken advantage of, allowing selective embolization of the tumor while sparing normal parenchyma. Several modalities and chemotherapy regimens exist, and all have proven efficacy. Although not curative, hepatic arterial embolization can improve symptoms and reduce or stabilize tumor progression, prolonging PFS and OS, and should be the mainstay of treatment of patients with liver metastases from NETs. Embolizations should be repeated as needed to control symptoms and slow tumor growth.

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Review Article

Surgical Treatment of Neuroendocrine Liver Metastases

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Management of Neuroendocrine liver metastases (NELM) is challenging. The presence of NELM worsens survival outcome and almost 10% of all liver metastases are neuroendocrine in origin. There is no firm consensus on the optimal treatment strategy for NELM. A systematic search of the PubMed database was performed from 1995–2010, to collate the current evidence and formulate a sound management algorithm. There are 22 case series with a total of 793 patients who had undergone surgery for NELM. The overall survival ranges from 46–86% at 5 years, 35–79% at 10 years, and the median survival ranges from 52–123 months. After successful cytoreductive surgery, the mean duration of symptom reduction is between 16–26 months, and the 5-year recurrence/progression rate ranges from 59–76%. Five studies evaluated the efficacy of a combination cytoreductive strategy reporting survival rate of ranging from 83% at 3 years to 50% at 10 years. To date, there is no level 1 evidence comparing surgery versus other liver-directed treatment options for NELM. An aggressive surgical approach, including combination with additional liver-directed procedures is recommended as it leads to long-term survival, significant long-term palliation, and a good quality of life. A multidisciplinary approach should be established as the platform for decision making.

1. Introduction

Neuroendocrine tumors (NETs) are a varied group of neoplasms characterized by a relatively slow growth rate and the potential to produce and secrete a variety of hormones along with other vasoactive substances, giving rise to a variety of clinical syndromes. Neuroendocrine tumors are relatively uncommon with an approximate incidence of 1 to 5 per 100,000, but there has been a slow but steady rise in its incidence and prevalence [1, 2]. In the USA, the Surveillance, Epidemiology, and End Results (SEER) database showed a significant increase in reported incidence from about 1 in 100,000 in 1973 to 5 in 100,000 in 2004 [3]. Overall, the incidence is increasing at a rate of 3% to 10% per year [4]. This increase was likely caused in part by improvements in classification of these tumors, and the widespread use of endoscopy for cancer screening likely also contributed to the increase in reported incidence of gastrointestinal NETs [3].

Neuroendocrine tumors include carcinoid tumours, gastrinomas, insulinomas, glucagonomas, somatostatinomas, and vipomas [5]. Histopathologically, NETs are tumours of cells, which originate from the neuroectoderm and possess secretory granules. They can occur as part of multiple endocrine neoplasia type 1 (MEN type I) syndrome, or more often they occur in isolation. Anatomically, they are classified according to their site of origin as foregut (including lung), midgut, or hindgut tumours. Clinically, they can be classified as either functional tumors or as nonfunctional tumors [6, 7].

The natural history of NETs is highly variable, and clinical management is challenging. Over the past three decades, the understanding of neuroendocrine tumors has been improved significantly by the elucidation of its tumor biology, advances in surgical and perioperative care, and the development of novel diagnostic methods, but the survival of patients with NETs has not improved appreciably in either the USA or UK [1, 8].

About 85% of NETs originate from the gastrointestinal tract, and the majority of patients present at diagnosis with metastases. Liver is the most common organ involved, followed by bone and lung [9, 10]. Almost 10% of all liver metastases are neuroendocrine in origin [11–14]. Neuroendocrine liver metastases (NELM) occur in 50% to 75% of

small-bowel carcinoids, 5% to 70% of foregut carcinoids, and about 14% of hindgut carcinoids [1, 10]. Up to 85% of NETs have hepatic metastasis (Up to 87% present as synchronous lesions; about 10% as metachronous lesions), and they are potentially completely resectable in only 7% to 15% of patients [10, 15].

The presence of neuroendocrine liver metastases worsens survival outcome. There are many treatment strategies that have been attempted over the years for metastatic NETs. These include surgery, locoregional directed therapies such as radiofrequency ablation (RFA), hepatic artery embolization, and transarterial chemoembolization (TACE). These are often used in combination with other systemic therapy such as somatostatin analogues, various chemotherapy regimes, and most recently, peptide receptor radionuclide therapy (PRRT).

In this paper, we review the current literature and discuss on the surgical aspects of the management of neuroendocrine liver metastases. The spectrum of hepatic surgical procedures comprised complete resections of various extent (including hilar lymphadenectomy), palliative cytoreductive resection, and orthotopic liver transplantation (OLT). The aim of this paper is to collate the available and current information on the management of neuroendocrine liver metastases, to formulate a sound management algorithm, and to promote discussion regarding the role of surgical resection for NELM in these patients.

2. Surgery for Neuroendocrine Liver Metastases

There are more reports of patients undergoing surgery for NELM over the past decade than ever before; this is a testament to the increasing acceptance of the aggressive surgical attitude and its associated benefits towards management of NELM [16]. More than 2 decades ago, the Mayo Clinic, in their review of all their patients with carcinoid tumors treated between 1970 and 1989, fewer than 10% underwent cytoreductive hepatic surgery for metastases ($n = 37$) [17]. In 1986, Galland and Blumgart found only two candidates for suitable hepatic surgery among 30 patients with NETs [18]. Sarmiento et al. in a 2002 review paper on NELM, performed a literature search of the English language medical literature from 1973 to 1999, and this revealed a total of only 57 patients who undergone partial hepatectomy for NELM. This is in contrast to another more recent study from the Mayo Clinic group, they reported 170 patients who undergone surgical resection for NELM from 1977 to 1998 [19]. Another recent study comparing liver resection versus intra-arterial therapy for NELM involving nine institutions, they reported more than 300 patients who undergone surgery for NELM [20].

The gold standard for evidence-based clinical practice remains unbiased large prospective randomised controlled trials. A multi-institutional collaborative trial conducted over many years may be necessary to recruit patients to compare surgery versus other liver-directed treatment options for NELM, for example, RFA, TACE, and OLT, a study like this will require a minimum of 776 patients in order for it to be powered to detect a difference of 10% in survival rate (based on alpha of 0.05 and power of 0.8) [21]. In view of the highly selective nature of patients undergoing either hepatic resection or OLT, randomized controlled trials evaluating patient outcomes with these treatment modalities would likely be difficult to perform. However, it is important to highlight that due to the paucity of cases even in large institutions and the nonrandomized uncontrolled nature of these studies, there will be biases; the encouraging survival outcomes observed in surgically treated patients may be related to inherently favorable prognostic factors such as low tumor burden.

In the literature, many define curative resection differently. In some studies, curative intent is defined only with a R_0 resection achieved, whereas others classify resection as complete without referring to the margin status, and others defined a curative procedure when all visible gross disease was removed [22]. Despite the armamentarium of treatment options and an ill-defined optimal management protocol, surgical resection of neuroendocrine liver metastases (NELM), if achievable, is generally considered as the best option of both cure and palliation of symptoms [23].

3. Curative Liver Resection for Neuroendocrine Liver Metastases

In the principles of surgical oncology, curative resection is defined as the complete removal of tumour tissues with a clear resection margin on pathological examination (hepatic and extrahepatic R_0 status). Liver resection for metastatic disease has gained wide acceptance as a potentially curative option in patients with colorectal cancer [19, 24, 25]. With improvements in the safety of major hepatic resection and an operative mortality rate of about 5% in most series, there has been an increasing role of liver resection for a potential cure of metastatic disease from neuroendocrine tumors.

3.1. Results of Curative Liver Resection for Neuroendocrine Liver Metastases. Surgery for NELM is the standard against all other forms of liver-directed or systemic therapies. Due to the relative low incidence, the biological heterogeneity NETs, and NELM, there is a lack of prospective randomized studies providing level 1 evidence. Based on encouraging results from large retrospective studies and cumulative experience, radical surgery including resection of the primary tumour and the liver metastases has been the main treatment for potentially resectable advanced neuroendocrine tumours metastatic to the liver.

Patients with untreated hepatic metastases have a 5-year survival of approximately 20% to 40% [23, 26]. As a result, many studies have advocated aggressive surgery for NELM with the aim of extending survival (Tables 1 and 2) [19, 23, 26–33]. Due to the indolent nature of the disease, the overall survival is still very good after hepatic resection. This holds true even in stage-4 disease and notwithstanding a high post-curative resection 5-year recurrence rate of more than 40–70% in most series. The overall survival ranges from 46 to 86 percent at 5 years and 35 to 79 percent at 10 years [19, 23, 26, 29, 30, 32, 34–36]. The major studies of

Table 1: Case series of hepatic resections performed for neuroendocrine liver metastases published in the past 15 years. The following table summarizes the results of modern-day series of liver resections performed for neuroendocrine tumors liver metastases.

	Author	Year	*N* undergoing resection	Percentage of curative and palliative resections	Operative mortality (%)	Operative morbidity (%)	Symptom control (%)	Survival (% is for 5-year survival if not otherwise stated)
(1)	Que et al. [13]	1995	74	38% curative 62% palliative	2.7	24	90	73% at 4 years Similar survival rates between curative versus palliative resection
(2)	Dousset et al. [35]	1996	17	71% curative, 29% palliative	5.9	23.5	88	46% at 5 years (overall) 62% at 5 years (curative)
(3)	Ahlman et al. [16]	1996	54	22% curative, 78% palliative	0	NA	100	70% at 5 years
(4)	Chen et al. [26]	1997	15	100% curative	0	NA	NA	73% at 5 years
(5)	Chamberlain et al. [23]	2000	34	44% curative, 56% palliative	6	NA	100	76% at 5 years Differences in survival between curative/palliative resections are not reported
(6)	Grazi et al. [30]	2000	19	84% curative, 16% palliative	0	NA	NA	92.6% at 4 years
(7)	Sarmiento et al. [19]	2001	170	44% curative, 56% palliative	1.2	4.1	96	61% at 5 years; 35% at 10 years Differences in survival between curative and palliative resections are not reported
(8)	Yao et al. [32]	2001	16	100% curative	0	12	NA	70% at 5 years
(9)	Coppa et al. [36]	2001	20	100% curative	NA	NA	NA	67% at 5 years
(10)	Jaeck et al. [103]	2001	13	NA	0	NA	100	68% at 6 years
(11)	Nave et al. [33]	2001	31	32% curative, 68% palliative	0	13	NA	47% at 5 years 86% for curative resections, 26% for palliative resections
(12)	Dejong et al. [104]	2002	5	NA	0	20	NA	Median survival 59 months
(13)	Norton et al. [28]	2003	16	100% curative	0	19	100	82% at 5 years
(14)	Elias et al. [29]	2003	47	53% curative, 47% palliative	5	45	NA	71% at 5 years Similar survival rates between curative versus palliative resection
(15)	Osborne et al. [54]	2006	61	62% curative, 28% palliative	0	3.2	91	80% at 5 years (curative) 60% at 5 years; (palliative)
(16)	Reddy et al. [41]	2006	33	70% curative, 30% palliative	9	42	NA	75% at 3 years; Differences in survival between curative and palliative resections are not reported
(17)	Hibi et al. [43]	2006	21	100% curative	0	19	100	41% at 5 years
(18)	House et al. [37]	2006	26	100% curative	0	NA	NA	Median survival 78 months
(19)	Gomez et al. [34]	2007	18	83% curative, 17% palliative	5.5	22	100	86% at 5 years Differences in survival between curative and palliative resections are not reported
(20)	Landry et al. [105]	2008	23	NA	0	26	NA	75% at 5 years
(21)	Chambers et al. [106]	2008	30	NA	0	22	86	74% at 5 years
(22)	Ahmed et al. [107]	2009	50	NA	0	NA	NA	74.3% at 5 years

Comments: Operative mortality and morbidity refer to figures for patients undergoing liver resections. Survival date is stated for the entire cohort (curative and palliative resections), unless otherwise is stated. Symptom control includes both partial and complete response. NA means that information was not provided in original paper.

Table 2: Case series of hepatic resections with ablation performed for neuroendocrine liver metastases.

Author	Year	N undergoing resection/ablation	Operative mortality (%)	Operative morbidity (%)	Symptom control (%)	Survival
(1) Mayo et al. [39]	2010	339	NA	NA	NA	74% at 5 years
(2) Glazer et al. [42]	2010	172	0	22.1	NA	77.4% at 5 years 50.4% at 10 years
(3) Strosberg et al. [108]	2009	31	NA	NA	NA	75% at 5 years; median survival of 103 months
(4) Touzios et al. [27]	2005	19	5.2	42	95	72% at 5 years
(5) Musunuru et al. [31]	2006	13	NA	NA	100	83% at 3 years

Some studies [22, 65, 102, 109] are excluded in the tables as the data is not stratified to liver resections and thus no meaningful data can be extracted for liver resections.

liver resection for NELM are presented and summarized in Table 1. Patients in whom hepatic resection was achievable had a significantly better median overall survival and 5-year survival than those with unresectable hepatic disease [26, 30, 31, 37]. The median survival ranges from 52 to 123 months for patients who undergone resection of NELM [20, 38].

In the major series attempting curative resection for NELM, curative resection is achieved in a range of 22% to 84% (Table 1) [16, 30]. Sarmiento at al. reported one of the largest single center series on resection for NELM, they achieved complete resection in 44% of their patients. The main site of residual disease resulting in incomplete resection was the liver (96%). They reported a morbidity of 14% and an operative mortality of 1.2%. Not surprisingly, there is a significant difference in recurrence rate in patients with complete and incomplete resection (76% versus 91% at 5 years; $P = 0.0004$) The overall survival rate for the cohort of 170 patients at 5 and 10 years were 61% and 35%, respectively and median survival was 81 months. Notably, they did not detect a difference in survival rate in patient with or without preoperative endocrinopathy, although there was no mention of any quality of life measures [19].

Mayo et al. reported the largest and the only multi-institutional experience of surgical management of NELM. In this study of 339 patients, the majority underwent resection of the NELM (77.6%), 19.5% underwent resection plus ablation, and in 2.9%, ablation was the only liver-directed therapy performed. They achieved curative resection (R_0 status) in 53.7% of the patients. In their multivariate analysis, they found in those patients NET without hormonal function, presence of synchronous disease, and concomitant extrahepatic disease as negative prognostic factors. Patients with a hormonally functional NET who had R_0/R_1 resection benefited the most from surgery. In this study, they achieved an overall 5- and 10-year survival of 74 and 51% [39].

The differences in survival data must be interpreted appropriately as the criteria of resectability are ever evolving and there are major improvements in the safety of liver resection, this must be taken into account when comparing recent series to older studies [40].

It is important to highlight that even with an aggressive policy and available expertise, conventional partial hepatectomy is rarely possible, as approximately 90% of metastases are multifocal and bilobar [6]. Even in the scenario when complete resection of NLM is performed, early recurrence is more common compared to other common hepatic lesions such as colorectal metastases [40, 41].

The biological behaviour of NETs and their metastases is variable, patients with NELM from bronchopulmonary endocrine tumors are known to have the poorest prognoses as compared to other sites [42, 43]. Patients with NELM from a colonic primary seem to have a better recurrence free survival when compared to the rest of the other sites [42]. Other than tumor site, independent preoperative factors for a poor prognosis include tumor differentiation, pancreatic tumor, nonfunctional primary tumor, presence of multiple and/or bilobar liver metastases, and invasion of greater than 75% of the hepatic parenchyma [23, 29, 44].

There are studies comparing resection against other forms of therapy in an attempt to identify a subset of patients who will benefit the most from surgery and to individualize therapy regimes [45]. In a recent multi-institutional study analyzing over 700 patients comparing liver resection versus intra-arterial therapy (including transarterial chemoembolization, bland transarterial embolization, and drug-eluting beads or yttrium-90) for NELM, they found that although surgical management provided a survival benefit over intra-arterial therapy among symptomatic patients with >25% liver involvement, there was no significant difference in long-term outcome. In this study, liver-directed surgery includes resection and RFA or in combination. They concluded that asymptomatic patients with a large burden of liver disease benefited the least from surgery and nonsurgical liver-directed therapy like various forms of intra-arterial therapy may be more appropriate. They suggested that surgical resection of NELM should be reserved for patients with low-volume disease or for those patients with symptomatic high-volume disease [20].

Although there is no significant difference in disease incidence worldwide, most of the studies on NELM are from the West. There is only a single report from Asia reporting a case series of 21 patients reporting a similar results and conclusions. They report an overall 68% 3-year and a 41% 5-year survival rate for patients; those that achieved curative resection have a significantly better 5-year survival rate (73%

versus 0%, $P = 0.01$) compared to those who underwent a palliative resection [43]. The group from M.D. Anderson Cancer Center reported recently in their study of 172 patients undergoing surgery for NELM that they found that in Asians, on multivariate analysis, the recurrence free survival was significantly lower as compared to the rest of the study population [42].

There is no evidence for the effect of adjuvant treatment of radically operated patients [46]. Medical treatment is required only in the event that the tumour and/or its metastases cannot be completely resected.

4. Palliative Liver Resection for NET Liver Metastases

A distinguishing feature of these malignancies beside the ability to metastasize is the potential for unregulated endocrine activity. This fact complicates treatment but serves as one of the main rationale for roles of palliative surgery. Even when resection with curative intent is not feasible, either due to the presence of extrahepatic disease or extensive intrahepatic disease, there remains a role for surgery, though this remains less well defined. The goals of palliative surgery focus on retardation of tumor cell growth, relief of mass symptoms, symptoms of hormonal hypersecretion, prolonging survival, and finally achieving a good quality of life on the long term.

Some authors have defined cytoreductive hepatic surgery as resection of 90% of the bulk of the tumour, and this refers to the incomplete resection of tumor to reduce symptoms and facilitate the effect of nonsurgical strategies [47]. DebuIking surgery is defined as surgical resection with gross residual disease beyond the criteria of cytoreductive surgery. The Mayo Clinic group has recommended that palliative resection is justified if at least 90% of hepatic metastases are resectable, and the extrahepatic tumour bulk is limited [48]. This recommendation has also been advocated separately in the consensus report of the European Neuroendocrine Tumour Society [49]. Frilling et al. proposed that cytoreductive liver resections should be considered if there is no evidence of unresectable extrahepatic disease and less than 70 percent of the liver is involved by tumour [22].

In the palliative setting, where symptomatic control for quality of life and not extension of the survival is the primary goal, the risk-benefit ratio needs to be clearly ascertained in order to justify surgery as liver resection is not without its share of significant morbidity and mortality. If cytoreductive surgery can increase survival, then the application of operative interventions is doubly justified in a patient population that can survive many years with symptomatic disease.

Neuroendocrine tumor behavior and biologic characteristics exist to justify the application of cytoreductive therapy. In the majority of NETs, the tumors have a long doubling time, especially in gastrointestinal neuroendocrine tumors where hepatic and regional nodal metastases are the predominant site of spread. In the majority of metastatic NETs, metastases are limited to the liver. They are susceptible to chemotherapy and embolization, and the tumor volume correlates with magnitude of disabling endocrine symptoms. Crucially, the primary tumors are often resectable despite extensive metastases [50]. The survival of patients with gastrointestinal neuroendocrine tumors even with established metastases is longer compared with that of patients with other malignancies, up to 30 to 40% 5-year survival without treatment. Metastatic patients with gastrointestinal neuroendocrine tumors clearly have a better survival compared to patients with metastatic adenocarcinoma of the gastrointestinal tract [51, 52].

4.1. Results of Palliative Liver Resection for NET Liver Metastases. Proponents of aggressive approaches advocating partial hepatectomy, cytoreductive liver resection, and ablation cite numerous many retrospective institutional studies reporting palliation of symptoms and prolonged survival duration among patients undergoing surgery with curative or near curative intent (Table 1) [13, 17, 26, 53, 54].

However, to date, there have been no trials evaluating these criteria in a prospective fashion. Furthermore, these guidelines are neither universally accepted nor adopted, and the majority of the literature consists of heterogeneous cohorts, making interpretation and comparison of data difficult.

Advanced unresectable neuroendocrine tumours are associated with prolonged survival. Fifty percent of incurable tumors survive 5 or more years after diagnosis. Median survival of patients with unresectable hepatic metastases ranges from 3 to 4 years, and nearly 30–40% of these patients were alive at 5 years [52, 55].

Patients may suffer for prolonged periods from metastases-associated endocrinopathies, of which the severity of the endocrinopathy parallels the tumor volume [48]. Although there is an absence of a validated universal method for measuring and comparing symptoms and their response to therapy, the literature suggests that resection of neuroendocrine hepatic liver metastases can result in excellent palliation of hormone-related symptoms. In carefully selected patients, partial or complete relief of systematic endocrine-related symptoms can be achieved in more than 90% of subjects undergoing cytoreductive or palliative liver resection, with a correspondingly low morbidity and mortality [13, 19, 54]. Objectively, one study demonstrated a postoperative reduction in urinary excretion of the serotonin metabolite 5-hydroxyendoleacetic acid (5-HIAA) which correlated with the decrease in hormone-related symptoms of flushing and diarrhea [19]. As such, surgery for symptoms palliation alone is well justified.

After successful cytoreductive surgery, the mean duration of symptom reduction is between 16 to 26 months [13, 56, 57]. Unfortunately, recurrence or progression of symptoms can occur within 20–45 months, and the five year recurrence/progression rate ranges from 59 to 76% [19, 57].

More than a decade ago, Que et al. showed that initial symptomatic response is similar in patients with metastatic disease whether resected with curative or palliative intent, but recurrence of symptoms occurred earlier in patients undergoing resection with palliative intent (11.3 months versus 20.4 months). He further proposed that the duration

of response can be predicted by the completeness of resection and normalisation of hormonal markers in the immediate postoperative period [13]. Hibi et al. reported the only Asian series of liver resections for metastatic neuroendocrine tumours. Seven patients (33% of the cohort) underwent palliative resection. The resolution of symptoms after surgery was complete in five patients, partial in one, and one was asymptomatic preoperatively [43].

Sarmiento et al. have one of the largest single-institution series of hepatic resections for metastatic neuroendocrine tumours with 170 patients. This study included patients with curative resections, but majority of the patients underwent palliative resection (56%). They showed good response in 96% of patients with hormone-related symptoms, and all these patients had at least 90% of gross hepatic disease resected. In their series, symptom recurrence was 59% at 5 years, with a median time to recurrence of 45.5 months, although these were appreciably less severe and easily controlled with minimal doses of octreotide. They reiterated the recommendation that aggressive resection for palliation be pursued with a view to remove at least 90% of gross disease and suggested that the increasing availability and applicability of radiofrequency ablation would further increase the pool of patients who could potentially benefit from a combined ablative policy [19].

Notwithstanding the fact that metastatic neuroendocrine disease confined to the liver is compatible with prolonged survival, pain or debility due to hepatomegaly and symptoms from a variety of endocrinopathies from excessive hormone production can impact negatively on patients' quality of life [51, 58]. There is a paucity of data looking specifically at improvement in quality of life after surgery for NELM. One study by Knox et al. did demonstrate an improvement in quality of life as measured by Karnofsky performance score by the third postoperative month which was sustained for more than 4 years after surgery [59].

Radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), cryosurgery, and other ablative therapies have been used for palliation, although a Cochrane review in 2009 found no prospective randomized trials comparing the results of surgery to those of any other method in the palliation of metastatic neuroendocrine tumours to the liver [21]. Bergen and Osborne compared resection outcomes versus embolic treatment in symptomatic metastatic NET and reported that cytoreductive surgery for metastatic neuroendocrine tumors resulted in improved symptomatic relief in terms of high proportion of complete (69% versus 59%) as well as a longer duration of relief. There is also improved survival when compared with embolic therapy in this nonrandomized retrospective study. They recommended cytoreductive surgery should be pursued whenever possible even if complete resection may not be achievable [60].

5. Liver Transplantation for Neuroendocrine Liver Metastases

Liver transplantation has a selected role in unresectable NELM and is proposed for certain candidates with a 5-year overall survival of up to 70% and 5-year recurrence free survival of up to 50% [9]. In the largest meta-analysis of 103 patients, the 5-year survival rate was 47%, with only 24% of patients free of disease recurrence [61]. The largest series of liver transplants for NELM was the multicenter French study, coordinated by Le Treut et al. which reported on 85 cases with an overall survival of 47% and a recurrence free survival of 20% at 5 years [62].

Mazzaferro et al. proposed a set of guidelines for the selection of candidates for liver transplantation, now known as the "Milan criteria" (Figure 1 inset) [9]. These guidelines emphasized the requirement for a specific diagnosis of endocrine tumors and considered patients who had well-differentiated endocrine tumors with low-grade malignancy, established on the basis of mitotic and proliferation indices as eligible candidates for liver transplantation. In another consensus guideline by the European Neuroendocrine Tumor Society, patients with diffuse unresectable liver metastases or those with life-threatening hormonal disturbances refractory to medical therapy, liver transplantation may be a possible treatment option for these selected patients. Due to the slow-growing nature of NETs and their tendency to metastasize only to the liver, NETs remain one of the few indications for liver transplantation in metastatic disease, particularly if living-related donation is feasible. They commented that patients who are most likely to benefit from liver transplantation are those less than 50 years old who are free of extrahepatic tumor and have low expression of Ki-67 and E-cadherin [63]. The details and results of OLT for NELM are beyond the scope of this paper but in brief, several factors plague liver transplantation as an effective treatment option. Although liver transplantation has the theoretical advantage of removing all tumor burden in patients beyond the criteria for respectability, and advances in technique and improved perioperative care have made liver transplantation safer recently; early disease recurrence, significant morbidity and mortality, the absence of extensive experience, and shortage of donor organs all contribute to preclude orthotopic liver transplantation (OLT) as an effective option for most patients with unresectable NELM [64].

6. Combination Therapy

Palliation can also be achieved with a combination of treatment modalities. Surgery can be combined with other therapies, for example, antihormonal therapy, chemotherapy, immunotherapy, and interventional radiological procedures, either simultaneous or in stages. The role of adjuvant therapy and which modality will be optimal in complementing palliative surgery is not well established.

There is some data on the efficacy of a cytoreductive strategy combining both surgery and RFA in the same session (Table 2). Eriksson et al. showed that out of the patients aggressively treated with a combination of anatomical and nonanatomical resection with intraoperative and percutaneous radiofrequency ablation, 70.6% of those with carcinoid syndrome had partial or complete symptom response. They also found large tumor size, high preoperative Chromogranin A and 5-HIAA levels, and high Ki67 index to be risk factors for recurrence [65]. Musunuru et al. showed

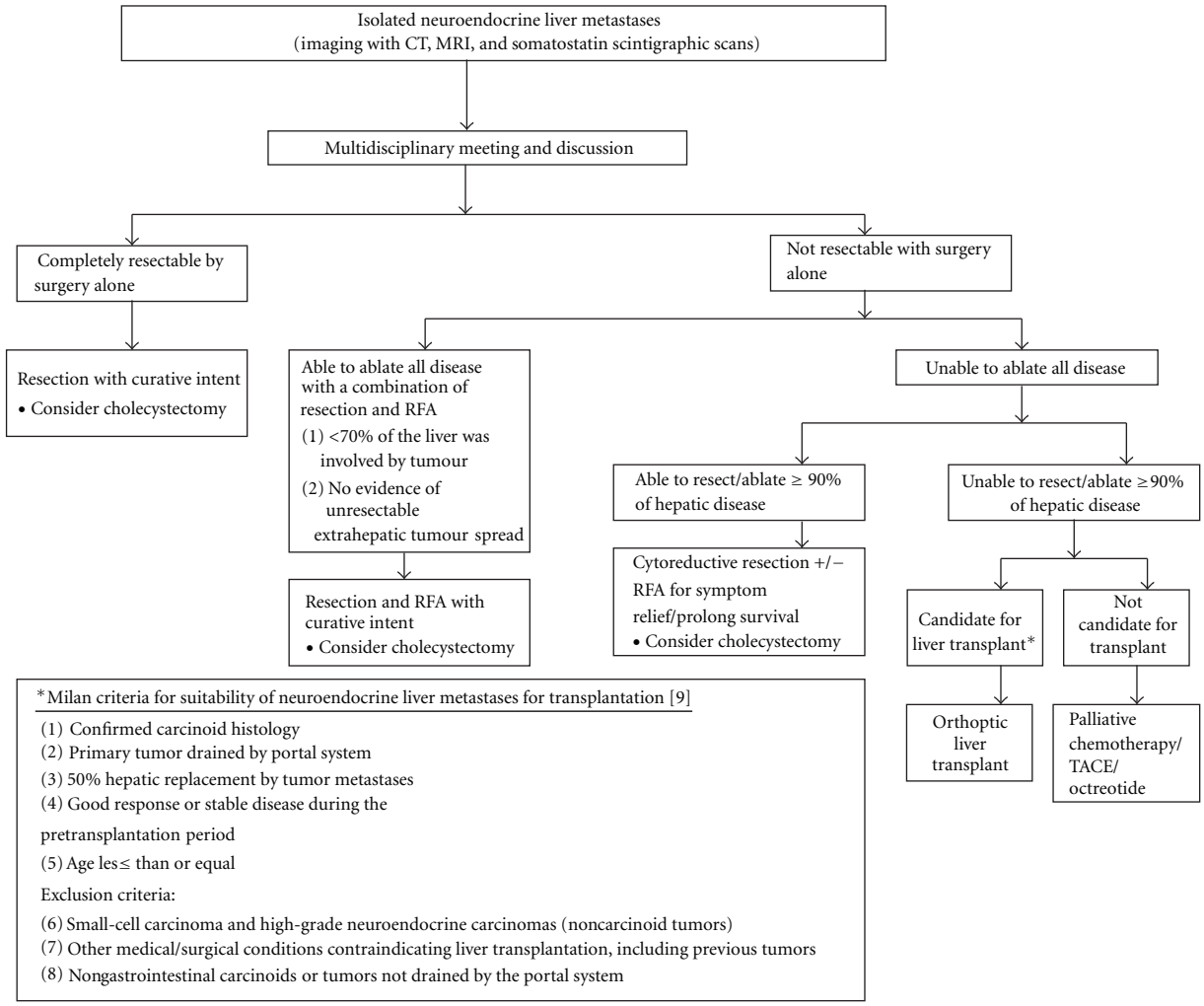

Figure 1: Proposed Algorithm for management of isolated neuroendocrine liver metastases.

that compared to either medical therapy alone, systemic chemotherapy, or transarterial embolization, a combination of surgery and RFA resulted in 100% symptom control and improved 3-year survival rate (83% versus 31%) [31].

7. Role of Prophylactic Cholecystectomy

The role of prophylactic cholecystectomy has been recommended by some authors when surgery is considered for an advanced neuroendocrine tumor [49]. The rationale for prophylactic cholecystectomy during partial hepatectomy for NELM includes (1) the fact that somatostatin analogs may induce gallstone disease in up to 50% of cases; (2) chemoembolization has a high risk for cholecystitis occurrence; (3) in the event that the hepatic lesions are not resectable and should the hepatic artery be ligated or embolized to control symptoms, necrosis of the gallbladder can potentially occur. Some authors cite these reasons to justify the minimal morbidity from the additional procedure [53, 66]. However, there are differing opinions, in the recent 2010 Nordic Guidelines, they commented that as the somatostatin-induced bile stones usually are asymptomatic, liver embolization techniques have improved considerably and the risk of complications to cholecystectomy is up to 3%; taking these points into consideration, they did not recommended prophylactic cholecystectomy.

8. Surgical Considerations

As neuroendocrine hepatic metastases are numerous and often large, surgical resectability is a primary concern. Once it has been established that curative or cytoreductive resection is indicated, resectability can be determined from two factors: anatomical feasibility and volumetric tolerance. A multidisciplinary approach involving in the minimum a liver surgeon and a dedicated hepatobiliary radiologist, a medical oncologist is recommended to validate the decision.

8.1. Resectability of Neuroendocrine Liver Metastases. The definition of "resectability" is determined by many factors including patient, disease, and technical factors. The principle lies in the technical ability to leave a remnant with adequate function for sustaining life but consistent with low perioperative morbidity and mortality and acceptable

long-term outcome in survival and quality of life. Relative contraindications to partial hepatectomy include significant medical comorbidities, rapidly progressing intrahepatic disease, and progressive or extensive extrahepatic disease. The golden rule for partial hepatectomy is to ensure enough liver parenchyma with a satisfactory blood supply (hepatic artery, portal vein, and hepatic vein), and biliary drainage remains after resection so that the patient does develop postoperative liver failure. Contraindications of liver metastasectomy are situations in which the tumors have invaded the biliary confluence or invaded the three hepatic veins or the portal bifurcation. Any scenario in which bilioenteric anastomosis to the remaining bile ducts cannot be constructed is also considered as a relative contraindication to resection. Fortunately, the growth pattern of NELM permits an aggressive surgical approach as the lesions are often discrete and the masses displace rather than invade or encase the major intrahepatic vessels or bile ducts. Some NELM have a miliary pattern with or without dominant tumors, however, these miliary metastases does not affect the resectability of the larger dominant tumors, and due to slow growth of the tumors, resection of dominant NELM can be considered for cytoreductive purposes for symptoms relief [50].

The ability of the nonpathological liver to regenerate after liver resection is good, and a remnant functional normal liver tissue as little as 20 to 25% may be sufficient [67, 68]. The ratio of remnant functional liver to the initial total liver tissue may be difficult to estimate because of the high number and size of metastatic nodules; the volume of these tumors should be excluded when determining the volume of the total liver. There are studies that utilize volumetric ratio without considering the total liver volume, but use percentage of total body weight instead [69]. It has been demonstrated that there is a risk of postoperative liver failure when the remaining functional liver ratio falls to less than 0.5% of total body weight. Multidetector computed tomography (CT) of the liver is usually applied to measure liver volumes. Most surgeons will not advocate surgery if the estimated volume of functional remnant liver is either less than 20–25% of the total liver or less than 0.5% of total body weight. Other than Child-Pugh scoring, Model for End-Stage Liver Disease (MELD) and liver function test, some studies have validated the use of indocyanine green clearance (ICG) as an objective adjunct in assessing liver function, in our institution, we use ICG selectively for patient with "borderline respectability" [70–73]. In patients with "borderline respectability", one safer option is to induce hypertrophy in the remaining functional liver via portal embolization to reduce the risk of postoperative liver failure. Compensatory hypertrophy of the contralateral lobe is generally observed in a period of three to six weeks. Some studies report a high feasibility rate for this strategy and report a mean gain in liver volume of over 40%, thus increasing the volumetric feasibility for resection of hepatic metastases from NETs [74, 75]. In patients whose NELM are bilobar, in line with aggressive approach, studies have reported the two-stage hepatectomy strategy as a useful alternative to portal embolization. This technique enables the successive treatment of the left lobar metastases followed by those in the right lobe, with ligature of the right portal vein in the first stage of the surgery to induce hypertrophy of the left lobe during the time interval between the two operations. In the second stage, a right hepatectomy is performed with the hypertrophied left lobe sustaining postoperative liver function [75]. Some authors suggest a core biopsy should be considered prior consideration for resection, in the situations when the health of the remnant liver is in doubt [42].

8.2. Role of Hepatic Lymphadenectomy in Neuroendocrine Liver Metastases. The role of hepatic lymphadenectomy in neuroendocrine liver metastases is not well established [76]. Most of the experience and data are extrapolated from colorectal liver metastasis (CLM), of which nodal involvement of the hepatoduodenal ligament is an independent predictor of survival following a curative partial hepatectomy [77–79]. The Mayo Clinic identified metastatic hepatoduodenal lymph nodes as an independent predictor of survival with an almost 40% increase in 5-year survival (18.8% versus 58.1%) in node-negative patients following hepatectomy for colorectal metastases [77]. A French study on lymph node metastases in CLM reported a superior 3-year survival of 38% in patients with nodal metastases limited to the hepatoduodenal ligament and retropancreatic region, versus no survivors beyond a year in patients with metastases to the common hepatic artery and celiac axis region following a hepatectomy; the authors concluded that a systematic regional lymphadenectomy should be performed in patients undergoing hepatectomy for CLM as it offers prognostic information, however, in the presence of metastases to common hepatic artery and celiac axis region, a hepatectomy may not be justified [80]. These data suggest that a regional lymphadenectomy is important in all patients undergoing a curative hepatectomy for malignant tumors for accurate prognostication, selection of patients for adjuvant therapy, and prospective evaluation of a potential survival benefit. However, there is little information on NELM, and there is no consensus if the CLM experience is translatable to NELM. Criteria for an adequate lymphadenectomy for NELM including the extent and minimum number of lymph nodes removed require further study.

8.3. Width of Resection Margins in Neuroendocrine Liver Metastases. Another point of contention in the resection of liver metastases is the optimal margin of resection. There is no clear evidence or consensus on the width of clear margins for NELMs. Generally for liver metastases, a positive resection margin predisposes to marginal recurrences and is an independent predictor of poor survival [81–84]. Most of the experience and data are accumulated from colorectal liver metastasis and extrapolated to other liver metastases from other primaries, for example, NETs. The optimal width of the resection margin is confounded by the different parenchymal transection techniques used at different centers [85]. The loss of a 5- to 8-mm tumor-free margin during liver resection confounds the issue of adequacy of pathologic margins and the use of contrast-enhanced intraoperative ultrasound may enhance the accuracy of resection margins [86, 87]. Comparisons of anatomic and wedge resections for CLM have demonstrated no difference in the rate of

positive margins, recurrence patterns, or overall survival [88–90]. Several series demonstrated that a positive resection margin is an independent predictor of poor survival following hepatectomy for CLM, further to this, some centers have demonstrated improved outcomes with more than 1 cm margins compared with narrower margins. The Memorial Sloan Kettering Cancer Center, in their review of 1019 patients after hepatic resection for CLM, reported a significant decrease in the median survival of patients with a positive margins of 1 cm or less, and that a resection margin of more than 1 cm was an independent predictor of survival [91]. In another report by Wakai et al. 95% of the intrahepatic micrometastases were noted within 1 cm of the advancing edge of the metastatic tumor deposit and a margin of 1 cm or more was associated with significantly improved survival [92]. In view of this, some have suggested that nonanatomic resection for CLM should at a minimum attain negative pathologic margins with the goal of a 1 cm margin. In contrast, some authors report that the width of the resection margin does not influence survival as long as it is negative [86, 92–95]. Complete resection is the goal of hepatectomy for neuroendocrine liver metastases as the rate of recurrence and the median time to recurrence are negatively affected by incomplete resection [13, 19, 23]. Agrawal and Belghiti have recently recommended a resection margin of less than 1 cm for noncolorectal liver metastases, that is, neuroendocrine liver metastases [96].

9. Perioperative Considerations

There have been huge improvements in surgical and anesthetic techniques and the perioperative management of these patients, these contributed to significant reductions in the morbidity and mortality rates after partial hepatectomy. Even in institutions reporting a significant percentage of complex hepatectomies, perioperative mortality is approaching 1% to 3% in patients without underlying liver dysfunction [97]. Perioperative morbidity and mortality rates for metasectomies of neuroendocrine tumors are similar to those reported for colorectal metastases [13, 98]. The surgery-related mortality of major series of hepatectomy for NELM ranges from 0 to 9% (Table 1) [74]. The reported overall morbidity rate ranged from 3% to 24% after partial hepatectomy for NELM (Table 1).

Patient selection is important for safe hepatic surgery. Patients with significant comorbidities should be reviewed by the anesthetic team for evaluation of preoperative risk factors related to general health status (American Society of Anesthesiologists (ASA) score) or associated diseases (e.g. right cardiac failure in carcinoid syndrome). Perioperatively or prior to any intervention, for example, radiofrequency ablation, all patients should receive 100–150 μg/h octreotide intravenously for 12 hours prior procedure [22]. Alternatively, preoperative preparation with 150 to 500 μg of somatostatin administered in the preinduction phase in the operating theatre prevents hemodynamic instability intraoperatively. Specific presurgery preparation may be necessary for individual tumors for example, for insulinomas, regular glucose monitoring and for gastrinomas, H_2-receptor antagonists or H^+-K^+ ATPase inhibitors are essential [50]. An endocrinologist consult preoperatively is recommended for patients going for surgery with functional NETs.

In general, the perioperative risk is not increased with specific endocrinopathies, with the exception of carcinoid heart disease. Surgical repair of carcinoid heart disease may be required prior to hepatic resection for symptomatic carcinoid syndrome in selected patients to reduce the risk of massive hemorrhage caused by intrahepatic venous hypertension from right heart failure [99].

Perioperative morbidity and mortality are directly related to the postoperative liver remnant function, the most important determinant of which is the extent of liver resection. In patients with tumors located adjacent to vascular structures or those with multiple lesions exist in separate distinct locations, this group of patients are likely to require large volume resections thus leaving small functional remnant liver as a result. Many strategies have been suggested to cope with this challenge; these include parenchyma-preserving, segmental approaches to resection, incorporation of concomitant wedge excisions or thermal ablations for small tumors outside the perceived safe field of resection, and the use of either preoperative portal vein embolization or staged resections to induce hypertrophy of the future liver remnant [100]. Besides liver-related complications, Glazer et al. also reported severe postoperative complications, for example, intra-abdominal fluid collection as an independent risk factor for perioperative mortality [42].

10. Discussion

The presence of liver metastases is a distinguishing feature of malignant neuroendocrine tumors and is the rate-limiting step on patient's survival [101, 102]. Based on available data (Tables 1 and 2), we advocate an aggressive surgical policy and propose an evidence-based surgical management algorithm (Figure 1). Surgery has a strong role in NELM and should be the treatment of choice if patients are fit and disease factors allow for it in both the curative, as well as palliative settings. Strategies to increase the limits of resectability, for example right portal vein embolization to induce hypertrophy of the remaining left lateral section before right hepatectomy or staged hepatic resections, can be considered especially in experienced centres. We propose that a multidisciplinary meeting should be the platform for decision making. In patients with curative lesions, curative resection should be the 1st line treatment, if cure cannot be achieved by surgery alone, ablative modalities, for example, RFA can be combined with surgery to achieve "cure". Adjuvant systemic therapies and local ablative treatment have a role in complementing surgery for disease control but the exact role of each is not well established and beyond the scope of this paper (Table 2). In the event, if curative intent cannot be achieved, cytoreductive surgery with or without ablation should be performed if at least 90% of the tumour load can be treated. If surgery and ablation cannot achieve this 90%, liver transplantation is a consideration, failing which best medical treatment should

be offered for palliation, for example, TACE, Chemotherapy, and octreotide.

A study from Germany further classified the different patterns of NELM; they defined type I as single metastasis of any size, type II as isolated metastatic bulk accompanied by smaller deposits, with both liver lobes always involved, and type III as disseminated metastatic spread, with both liver lobes always involved with virtually no normal liver parenchyma. With this classification, they found that the 3 types of NELM differ in behaviour and biology and are the only significant independent predictor of survival [22]. This study illustrates that although in general an aggressive therapy is recommended, individualization of treatment strategy should be tailored to each patient as some will benefit more from surgery for NELM than others [20]; a multidisciplinary team approach should be the platform for this decision-making process (Figure 1). The experts participating in such a team can comprise of endocrinologists, gastroenterologists, hepatobiliary surgeons, pathologists, diagnostic and interventional radiologists, medical oncologists, and nuclear medicine physicians.

Adjuvant therapy is currently not indicated in patients with completely resected NETs, and this need to be further studied in clinical trials [46]. Development of tumor repositories and clinical databases should help provide useful information to facilitate the development of future studies. Analysis of such data should also help identify patient subgroups at particularly high risk of recurrence and to validate scoring systems to help predict those patients most likely to benefit [23]. The development of standardized histopathological and staging criteria should also improve the selection of appropriate patients for clinical studies.

11. Conclusions

An aggressive surgical approach leads to long-term survival in patients with NELM. Although long-term cure can only be achieved in a proportion of patients with malignant NETs, significant long-term palliation can be achieved. This aggressive surgical approach can be recommended, keeping in mind that additional liver-directed procedures may be required or combined with surgery to achieve effectiveness for a good quality of life. A multidisciplinary approach in lieu of future prospective, randomized long-term followup studies should be established to identify the group of patients who will most benefit from surgery for NELM.

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Review Article

Surgical Treatment of Liver Metastases in Neuroendocrine Neoplasms

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Neuroendocrine neoplasms (NENs) are a distinctive entity, and nearly 10% of patients already have liver metastases at presentation. The management of neuroendocrine liver metastases (NEN-LM) is complex with differing patterns of metastatic presentation. An aggressive approach should be used to resect the primary tumor, to remove regional lymph nodes, and to resect or treat appropriate distant metastases (including liver tumors). Despite having an indolent course, NENs have a significantly reduced survival when liver metastases are untreated. Though a wide range of therapies are now available with a multimodal approach to the treatment, surgical treatment offers the only chance for a significant survival prolongation and/or improvement of symptoms and quality of life. A review of the existing surgical modalities for NEN-LM is discussed in this paper.

1. Introduction

Neuroendocrine tumors (NETs) consist of a group of neoplasms that arise from neuroendocrine cells dispersed throughout the body and show variable clinical course. The World Health Organization (WHO) classifications in 2000 and subsequently in 2004 did not address the diversity of these tumors. A histologic grading system based on Ki-67 labelling index was proposed by the European Neuroendocrine Tumour Society (ENETS) [1, 2]. The ENETS grading system (G1, G2, G3) has thus been incorporated in the new WHO 2010 classification [3]. It is now recognized that all neuroendocrine tumours are potentially malignant and hence characterized as neuroendocrine neoplasms (NENs). Intestinal NENs represent two-thirds [4], while pancreatic NENs represent about one-third of gastroenteropancreatic NENs (GEP-NENs) [5]. Besides regional lymph node involvement, liver is the predominant site of metastases [6]. Up to 75% of patients with small bowel NEN and 30–85% of pancreatic NENs present with liver metastases (NEN-LM) either at initial evaluation or during the course of their disease [7–9]. An additional 5–10% of NEN patients present with liver metastases with unknown primary tumor site.

In contrast with the traditional opinion that NEN represents an indolent disease, Touzios et al. [10] reported 5-year survivals range from 13–54% in patients with untreated NEN-LM compared to 75–99% in those without liver metastases [11–15].

2. Liver Metastases as a Prognostic Factor

Pancreatic NENs have a lower 5-year survival rate (30–60%) compared to intestinal NENs (60–90%) [16–18]. Liver metastases, however, are the most important prognosticator of survival in patients with NEN regardless of the primary site [19].

Two large population-based studies [7, 20] with 13715 and 4104 patients, reported that 12.9% of patients already had liver metastases at initial diagnosis regardless of tumor location and 5–10% of patients had metastases with unknown primary. Occasionally a primary neoplasm is not found elsewhere despite extensive investigations, raising the possibility that the hepatic lesion is the primary tumour [21]. This might be due to the low sensitivity of currently available imaging techniques, although this seems increasingly less likely with advances in technology such as helical computed

tomography (CT), endoscopic ultrasonography (EUS), and Gallium-68 PET CT.

Histological subtypes have an influence on treatment and survival outcomes. The reported overall survival ranges from 5.2 to 57% with different histological subsets of digestive NETs [7, 20]. A 95% survival at 20 years has been reported for patients with gastrinoma without liver metastases in contrast with 15% 10-year survival in the presence of bilobar hepatic metastases [22]. 5-year survivals of midgut and hindgut NET decrease by 10–20% and 50–60%, respectively, in the presence of liver metastases [23–26]. The new WHO classification (2010) emphasizes the importance of grades G1–3. Tumors with <2 mitosis/10 hpf and <3% Ki67 index are well differentiated and are labelled as G1 tumors, while well-differentiated tumors with 2–20 mitosis/10 hpf or 3%–20% Ki67 index are designated as G2. High immunohistochemical expression of Ki67 is a strong marker of poorly differentiated NETs, and tumors with >20 mitoses/10 hpf or a Ki67 >20% are labelled as G3 tumors [3]. Well-differentiated G1 tumors tend to be more indolent and are good candidates for liver-directed therapy, whereas poorly differentiated G3 neuroendocrine carcinomas (with or without liver metastases) are highly aggressive and patients (even with treated metastatic disease) have an expected survival time of 6–18 months [27, 28]. These tumors are not proposed for surgical resection and are usually confined to systemic chemotherapy (commonly Cisplatin and Etoposide combination).

3. Distribution of Hepatic Metastases

The pattern of distribution of liver metastases is an important determinant of prognosis [26, 29, 30]. Three different patterns of NEN-LM are identified that have an impact on the therapeutic approach: Type I: "restricted metastases," that is, the metastases are confined to one liver lobe or limited to two adjacent segments. This pattern is usually seen in 20–25% of the cases; the metastases are clearly resectable and can be dealt with by a standard anatomical resection; Type II: "dominant lesion with bilobar metastases" in which there is one dominant lesion but with smaller satellites contralaterally. Such bilobar patterns occur in 10–15% of the cases; the metastases may be potentially resectable and can still be approached surgically with a combination of ablative therapy on the contralateral lobe; Type III: "diffuse, multifocal liver metastases" are found in 60–70% of the cases and surgery is not a good option for these tumors [31, 32]. Type III tumors are clearly unresectable, and a cautious option of liver transplant may be considered for these tumors. Thus, the extent of hepatic involvement of metastatic NEN limits the benefit of surgery in a substantial majority of patients and standard resection alone is inadequate [33]. Nevertheless, it is evident that Type I NEN-LM are associated with favourable outcomes compared to the other two types [10, 30].

4. Diagnostic Work up for Neuroendocrine Liver Metastases

Combined anatomic and functional imaging studies provide tumor localization and assessment of posttreatment outcomes. Our current practice of evaluation is a Triphasic Triplanar CT scan with 1-2 mm slice thickness. A typical contrast enhancement in the arterial phase of the scans is characteristic due to the hypervascular nature of these tumors. However, depending on the tumor type, size, and location, the portal and parenchymal phases of contrast enhancement may also be important for improved detection [34–37].

Magnetic resonance (MR) imaging is complimentary and especially helpful in patients unable to receive iodinated contrast agents. One study [38] showed that MR imaging can detect more liver lesions, and a T2-weighted imaging may detect most lesions when contrast agents cannot be given.

Somatostatin receptor scintigraphy (SRS) has rapidly evolved as the gold-standard imaging procedure for NEN expressing somatostatin receptor subtype 2. Indium-labelled somatostatin analogues have been replaced by Gallium-labelled analogues that in combination with a PET-CT (68 Ga-DOTATOC PET/CT) increase the diagnostic sensitivity up to 30% higher than the conventional scanning. Moreover, SRS has resulted in a change in the clinical management in 33–77% of NEN patients in various studies [31, 39].

Beside the advantage of total-body imaging with the potential of simultaneous visualization of the primary tumour and metastatic deposits, SRS can possibly identify those patients who might be candidates for somatostatin receptor-based radiotherapy [39–41].

Plasma chromogranin A (CgA) is a widely accepted tumour marker with respect to diagnosis, prognosis, and monitoring of the treatment [42–45]. Though the sensitivity of CgA depends upon the NEN type and tumour burden, patients with NEN-LM tend to have significantly higher CgA concentrations than those without metastases [46]. Additional assessment of insulin, C-peptide, gastrin, pancreatic polypeptide, vasoactive intestinal peptide, glucagon, calcitonin, and somatostatin should be useful depending on the tumor functional status, clinical symptoms, and histological features.

A core needle biopsy and a histological examination with immunohistochemistry (IHC), Ki-67, and mitotic index of the primary/metastasis is essential for planning treatment. Tumour staging predicts the prognosis and tailors the therapeutic strategy [32, 47] particularly in patients who are not candidates for complete resection.

5. Liver-Directed Therapy

No optimal therapeutic strategies exist for treatment of liver metastases from GEP-NEN, and best strategy for treatment of NEN-LM is still poorly defined [48, 49]. Moreover, there is no randomized trial comparing surgery with nonsurgical treatments like RFA (radiofrequency ablation), TACE (transarterial chemoembolization), and medical treatment. In view of the infrequency of these tumours, multicentre clinical trials are needed in addressing the role of surgery.

5.1. Resection

5.1.1. Does Resection Benefit? Surgery is generally proposed to all patients with operable well-differentiated metastases

from digestive NENs regardless of the site of origin [32]. However, most NENs are detected after extensive liver metastases are present, and, consequently, only 10% to 20% of patients with NEN-LM are eligible for resection [50, 51].

The benefits of surgical resection for NEN-LM have been demonstrated in terms of overall survival and quality of life. Overall survival after hepatic resection has been reported in 46–86% at 5 years and 35–79% at 10 years in various series [52]. Complete resection (R0/R1) for both mid- and hindgut tumors is associated with better long-term survival [30, 53–56]. In many reported series of patients in whom hepatic resection was feasible, a median survival time was not reached during a followup of 27 months [56] up to 78 months [57] compared with 27 months [56] and 17 months [57] in those with unresectable tumours.

A recent multicenter study evaluating 339 patients who underwent surgical management of NEN-LM from 1985 to 2009 identified those who are likely to benefit the most by liver-directed surgery. It was observed that patients with hormonally functional NEN who had R0/R1 resection benefited the most from surgery [58]. Another large study [59] observed that R1 resections, unlike many other cancers, were not associated with a worse overall survival after liver resection for NEN-LM.

Resection is associated with a low mortality rate (0–5%) and an acceptable morbidity (close to 30%), and up to 95% of patients have shown symptom improvement in one large surgical series of 170 patients [56].

R0 resection rates have been reportedly between 20 and 57% in various series [31, 55, 56, 60–62]; however, among patients undergoing complete resection, long-term disease-free survival is reported in up to only 20 percent of patients [53, 63].

Such variability of clinical outcomes demands a meticulous case selection, and certain prerequisites should be considered prior to a resectional surgery [32, 52, 64]: (i) resectable primary tumor (previously resected or considered resectable synchronously), (ii) well-differentiated NEN-LM, (iii) possibility of R0 resection, (iv) exclusion of nonresectable extrahepatic disease, (v) reasonable performance status, and (vi) corrected or optimised carcinoid heart disease prior to aggressive liver surgery.

The presence of local recurrence including abdominal lymph node involvement is not an absolute contraindication for surgery if the removal of liver metastases and lymph nodes and/or the recurrence site(s) is planned [32].

In all cases in which the patients have carcinoid syndrome, specific perioperative treatments with somatostatin analogues are indicated to prevent intra- and postoperative carcinoid crisis [65, 66].

5.1.2. Recurrence after Resection and Impact of R0 Resection. Recurrence after an R0 resection is not uncommon, and 5-year local recurrence rates of up to 97% have been reported even when complete resection has been achieved [53, 55, 67, 68]. Recurrence depends mainly on the initial completeness of liver resection, and a thorough pre- and intraoperative assessment of small liver metastases is essential.

In a large series of 170 surgically treated patients, 5- and 10-year recurrence rate was 84% and 94%, respectively, with a median time to recurrence of 21 months. Only 44% of patients had a complete tumour resection in this series with a 5-year recurrence rate of 76% and a median time to recurrence of 30 months. In comparison patients who did not undergo a complete resection showed a 5-year recurrence rate of 91% with a median time to recurrence of only 16 months [53].

The prognostic relevance of R0 resection has been pointed out by Gomez et al. in their report of 18 resected patients who showed an overall 5-year recurrence rate of 34%. The five-year recurrence was only 10% in patients with tumour-free resection margins, in contrast to 75% when resection margins were involved [68]. Thus, an aggressive surgical approach does benefit irrespective of completeness or R0 status and has an impact on prognosis.

5.1.3. Resection Strategies in Synchronous and Metachronous Tumors. Unlike most malignancies, resection of the primary is beneficial for patients with NENs and should be considered in patients who have resectable metastatic disease [69, 70]. However, resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated [69].

In synchronous disease, liver surgery can be performed either as a one-step or a two-step procedure [32, 55, 71]. NEN-LM may be resected at the same time as the primary tumor with little additional risk if the metastases are unilobar [54, 55]. The main consideration however should be to perform a complete resection with acceptable morbidity rate. If major or complex liver resection is required, a two-stage surgery may be preferable in order to reduce the operative risk especially in patients with Type II metastases. A two-step surgery may involve at the first step a resection of metastases of the one lobe in addition to a resection of the primary and lymph nodes. Contralateral liver volume enhancement by portal venous embolization is an option with an aim to induce left liver hypertrophy followed by right hepatectomy or Lobectomy as a second step. Such an approach can in selected patients avoid or delay indications for liver transplantation [71]. For patients with unresectable liver metastases, a cholecystectomy is recommended to prevent ischemic complications of the gallbladder subsequent to chemoembolization and possible gallstones formation during somatostatin analogue therapy [54].

For metachronous liver metastases, a one-step procedure can be recommended as a low-risk approach to unilobar disease (<30% morbidity). For bilobar or diffuse liver metastases, a sequential approach including resection with or without ablative techniques, preoperative portal embolization, percutaneous treatments, or intra-arterial chemoembolization may be adopted [32, 72].

Overall, the effectiveness of the resection of unilobar and bilobar liver metastases depends on the operative techniques employed as well as the competence of the hepatobiliary surgeon. Intraoperative ultrasonography is essential in defining the extent of any known lesions and to detect any additional

smaller lesions missed during a preoperative diagnosis. Resectional surgery should be the first option before patient is considered for liver transplantation due to standard priority in listing.

5.1.4. Does Debulking Benefit? Several retrospective series have suggested that selected patients who undergo aggressive "debulking" of NEN-LM, in which the majority but not all of the disease is resected, have better quality of life and longer survival relative to those who do not undergo surgery [10, 30, 73–77]. Soreide et al. [78] found that patients with NEN hepatic metastases who underwent surgical debulking (planned repeat operations included) had a three- to fourfold longer median survival time compared with those who did not. However, complication and mortality rates were high (33% and 9%, resp.), and the duration of symptom relief in most cases was 6–24 months.

Incomplete debulking surgery (R2) has limited indications, yet it can improve the quality of life in selected patients for whom medical treatment has failed. However, in order to be efficient, the removal of at least 90% of the tumor volume is required [54, 56, 79, 80].

Thus, when complete resection of NEN-LM is not feasible or in the presence of unresectable extrahepatic disease, a tumor debulking strategy should be considered especially in patients with functional NENs with hormonal symptoms refractory to other treatments. Debulking can be a strategy for nonfunctioning NENs with local effects such as abutting the hepatic hilum (resulting in biliary obstruction) or obstructing the colon/duodenum [47, 81].

A combination of techniques, namely, resection and ablation or resection combined with other liver-directed therapy should be used to achieve complete tumor response when all liver disease cannot be resected.

5.2. Local Ablative Techniques. Radiofrequency ablation (RFA) has become the preferred local-ablative therapy in most centres, and its use has been shown to be effective in both relieving the symptoms of NEN-LM and achieving local control of the metastases [32, 82, 83].

Mazzaglia and colleagues reported the largest experience of ablation in patients with NEN-LM, encompassing a total of 452 lesions in 63 patients via 80 laparoscopic RFA sessions. Thirty-six patients were symptomatic from disease, and 94% experienced symptom relief after ablation for a median duration of 11 ± 2.3 months after RFA. The procedure-associated morbidity was 5%, and there was no 30-day mortality. Median survival was 3.9 years calculated from the first RFA session with a 2-year survival of 77% [84].

In yet another study of patients with 234 NEN metastases, 34 were treated with RFA. 80% of the patients reported a complete or significant relief from their symptoms, lasting for an average of 10 months and 41% of the treated patients showed no evidence of progression [85].

Tumor size poses a significant limit on the effectiveness of RFA. Though ablation may be used repeatedly within the same metastasis, it is difficult to fully eradicate with certainty tumors that are >3 cm in diameter, and a tumor >5 cm in diameter is considered to be unsuitable for RFA [86].

RFA has been shown to be a relatively low-risk procedure for treating liver tumors [87], and while the safety of RFA makes it an attractive method of treatment, the rate of tumor recurrence after therapy limits its effectiveness as a single therapy [86]. A recent study reported progressive liver disease in 80% of patients with NEN liver metastases treated with RFA [84].

5.3. Combination Techniques of Resection and Other Modalities

5.3.1. Resection Combined with Cryoablation. While liver resection for NEN-LMs provides the best chance of long-term survival, it is unfortunately not feasible in the majority of patients given the often widespread presentation of liver disease. Combining resection with local ablation can potentially expand the resection criteria and thus help improve survival [88]. In a recent study, forty patients with NEN-LMs underwent concomitant hepatic resection and cryoablation between 1992 and 2010 with a median followup of 61 months (for alive patients). The median progression-free survival and overall survival after hepatic resection were 22 and 95 months, respectively. Five-year and 10-year overall survival rate was 61% and 40%, respectively. While histologic grade was an independent factor associated with overall survival, presence of extrahepatic disease was associated with progression-free survival.

It thus appears that concomitant hepatic resection and cryoablation to achieve tumor debulking is associated with good survival outcomes in well-selected patients. This recent report suggested that such an approach may increase the number of patients with borderline resectable disease undergoing surgical management of advanced NEN-LMs [88].

5.3.2. Resection and Radiofrequency Ablation. Therapy with RFA alone is associated with higher recurrence rates compared to RFA plus resection, and in patients whose metastases are otherwise unresectable or difficult to access, the combination of resection and RFA provides the opportunity to achieve complete tumor removal [89–91].

Elias et al. [92] reported an overall survival rate of 84% at 3 years by incorporating a one-step combined approach of hepatectomy (for large or contiguous NEN-LMs) along with intraoperative use of multiple RFAs (for remnant metastases <2.5 cm). A mean of 15 ± 9 NEN-LMs per patient were surgically removed, and a mean of 12 ± 8 (median of 10) NEN-LMs per patient were RF ablated.

A combination of RFA along with parenchyma preserving liver resections seems to be the way forward while dealing with multiple bilobar liver metastases that are unlikely to be completely resected by surgery alone.

5.3.3. Resection and Chemoembolization. Chemoembolization is indicated for nonresectable multiple bilobar metastases, and in various studies 55%–100% of patients with malignant NENs treated by hepatic arterial embolization (HAE)/transarterial chemoembolization (TACE) have symptomatic improvement and 20%–80% have an objective

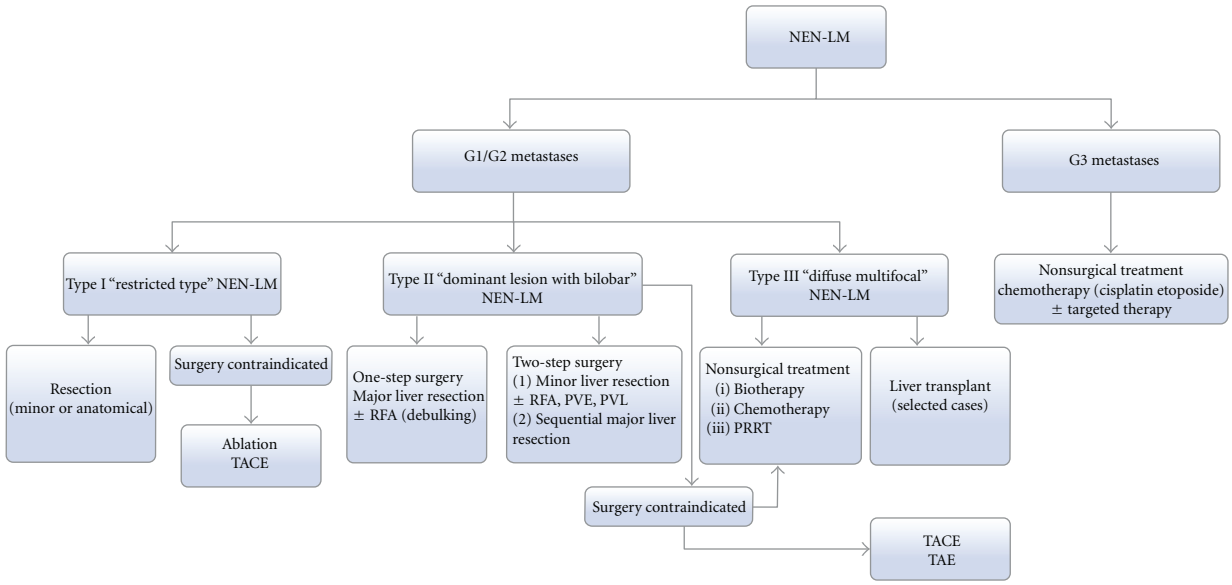

Figure 1: Suggested treatment algorithm for patients with NEN-LM. NEN: neuroendocrine neoplasm; LM: liver metastasis; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization; TAE: transcatheter arterial embolization; PVE: portal vein embolization; PVL: portal vein ligation.

response with tumor shrinkage. The mean duration of response ranges from 6 to 42 months [93–96].

Advances in major liver resectional surgery has resulted in further development of multimodal approaches for NELMs where surgeons and interventional radiologists have tried to work in multidisciplinary settings to evaluate whether TACE and surgery can have a synergistic action on overall outcomes of NELMs. Hepatic resection may be possible after cytoreduction of the tumor following TACE and other therapies [97]; however, the data on this subject is sparse.

5.4. Liver Transplantation. In patients with diffuse unresectable liver metastases or who suffer from life-threatening hormonal disturbances refractory to medical therapy, liver transplantation may be an option for carefully selected patients [32].

Primary tumor location has an impact on outcomes of liver transplantation. While the 5-year survival rate was 68% in patients with limited hepatic disease and nonduodenopancreatic tumours, it dropped to 12% in the case of hepatomegaly and primary tumour localized within the duodenum or pancreas [98, 99].

Majority of patients undergoing orthotopic liver transplantation (OLT) ultimately develop recurrent disease and reported 5-year recurrence-free survival ranges from 24 to 45% with an overall survival range of 36–57% [100–105].

Mazzaferro et al. could achieve a 90% overall survival and a 77% recurrence-free survival at 5 years by defining specific criteria for indication of liver transplant in the setting of NLM: (a) well-differentiated NENs (low-grade functioning or nonfunctioning), (b) a prior curatively resected primary tumor drained by the portal system, (c) ≤50% metastatic involvement of the liver, (d) good response or stable disease for a minimum of 6 months prior to transplantation, and (e) age ≤ 50 years [106].

An early disease recurrence, a considerable postoperative mortality, the absence of extensive experience, and lack of universal indications have precluded orthotopic liver transplantation as a good option for most patients with unresectable NEN-LMs [107]. Moreover, limited availability of donor organs in many regions has been a barrier to the widespread use of liver transplantation in general. Thus, the potential benefit of liver transplantation in patients with malignant NENs needs to be weighed against issues of perioperative morbidity and the ethical distribution of donor organs [32].

A modified algorithm for the treatment of patients with metastatic NETs based on ENETS consensus guidelines [32] is shown in Figure 1.

6. Summary

Surgical resection remains the gold standard especially in the treatment of well-differentiated NEN-LMs for symptom relief and long-term survival. In both synchronous and metachronous tumors, one- and two-step procedures may be undertaken, depending upon whether the liver disease is unilobar or complex.

Debulking resections are justified in functioning NEN and selective nonfunctioning NENs; however, removal of at least 90% of the tumor volume is necessary.

RFA can be used effectively as antitumor treatment and as a sole therapy for relieving symptoms in patients with NEN-LMs, but when combined with resection a better outcome is anticipated.

Liver transplantation needs to be carefully considered in specific liver alone bilobar metastases especially in (low-grade) well-differentiated NENs.

Surgical options are complimented by ablative techniques (RFA/cryoablation), nonsurgical liver-directed therapies (HAE/TACE/Transarterial radioembolization—TARE), and systemic treatment modalities (peptide receptor radiotherapy, cytotoxic chemotherapy, somatostatin analogues, and newer molecular-targeted treatments). A multidisciplinary team approach is necessary to customize therapy for each patient with NEN-LM.

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Clinical Study

Neuroendocrine Liver Metastases and Orthotopic Liver Transplantation: The US Experience

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Liver transplantation remains a controversial therapy for Neuroendocrine liver metastases (NLM), with coflicting suvival data reported. The aim was to assess the evolution of outcomes for patients transplanted for NLM in the US, both before and after the introduction of the MELD scoring system in 2002. The UNOS/OPTN database was reviewed to identify patients diagnosed with NLM who subsequently underwent a liver transplantation from 1988 to March 2011 ($n = 184$); Patient survival was determined using Kaplan-Meier methods and log-rank tests, and cox regression analysis was performed, using SPSS 15.0 (SPSS, Inc, Chicago, IL). The overall NLM patient survivals in the pre-MELD era were 79.5%, 61.4%, and 49.2% at 1, 3, and 5 years, respectively. After the introduction of the MELD score, NET/NLM patients had improved overall patient survivals at 1, 3, and 5 years of 84.7%, 65%, and 57.8%. Patients transplanted after 2002 had an improved survival outcome. Notably, the overall patient survival for NET is not significantly different when compared to the outcomes of patients transplanted for HCC, in the current era. This progress acknowleges the significant improvement in outcomes for NLM patients after liver transplantation and the potential for further gain in the survival of otherwise nonsurgical, terminal patients.

1. Introduction

Neuroendocrine tumors (NETs) encompass a broad group of neoplasms which originate from cells of the endocrine and nervous systems and are of similar indolent character. NETs are most commonly located in the gastrointestinal system, including the pancreas, but also arise from many other parts of the body. Patients with gastroenteropancreatic neuroendocrine tumors commonly develop liver metastases, which after protracted periods contribute towards morbidity and mortality [1–4]. In fact, the majority of patients with NET will have liver metastases discovered at the same time as diagnosis [4, 5]. The liver metastases associated with NET are typically multifocal and diffuse, compromising liver anatomy and function. With excess hormone production, these metastases can lead to debilitating symptoms, in addition to end-stage liver disease and death. Patients with neuroendocrine liver metastases (NLM) respond well to surgical resection, but, for patients who are ineligible due to widespread hepatic involvement, orthotopic liver transplantation (OLT) can be considered for curative therapy [4].

NLM is the only acceptable indication for OLT in the setting of metastatic malignancies, enabled by their slow growth rate and relatively low-grade malignancy. However, OLT for NLM remains a controversial therapy as there is conflicting actuarial data comparing outcomes of those transplanted to those who receive other therapies, as well as to others transplanted for different indications. In fact, the difference in 5-year survival between existing patient series can range as wide as 17 to 47%, with one series of 10 patients who received OLT for NET reporting a 90% 5-year survival [2, 6–11]. The lack of consistency in the data is partially due to the rarity of the disease and low incidence leading to small sample sizes. For example, only 14 OLTs were performed for NLM out of 28,665 OLTs performed in the United States in 2010 alone [6]. This is compounded with the wide variety of treatment options and algorithms making standardized and uniform protocols for this patient population difficult.

Surgery is the only potential for cure in NET/NLM patients, currently, and also serves to prolong survival in terminal disease. Complete surgical resection is an excellent therapeutic modality, with acceptable outcomes and minimal morbidity and mortality [12] though unfortunately is available to only 10% of the neuroendocrine cancer patient population [5, 7]. Excessive tumor burden in inaccessible locations precludes complete resection for the majority. Medical treatment options for patients who are not surgical candidates have evolved over the last two decades. This, along with the development of liver-directed therapies including ablative techniques, has expanded the treatment options for the majority of patients with NET/NLM [13].

For those patients in whom surgical resection is not indicated, symptomatic control and improved survival can be obtained with functional hormonal blockade, liver-directed therapies, and aggressive palliative treatments [8, 14]. Otherwise, OLT remains for the patients ineligible for surgical resection or refractory to medical therapies. Currently, patients with favorable biological features, including well-differentiated tumors with low proliferation index and overall stable disease without detectable extrahepatic metastases, may be potentially cured by OLT. Therefore, only a small subset of patients with NLM qualifies for possible OLT. Many transplant programs consider patients with NLM for OLT if several criteria are met: the patient is not a resection candidate, the primary disease is well identified and completely resected, there is no evidence of extrahepatic disease, the patient failed nonoperative therapies, and there is evidence of disease stability for at least a year [9–11, 14].

In an effort to assist in the selection of optimal NLM patients who would benefit from OLT, we aim to describe the outcomes of these patients, as well as, explore possible prognostic indicators to improve the allocation of a limited organ supply. Minimal selection criteria exist for this patient population and only recently are prognostic indicators being identified. It is our goal to further characterize this population in an effort to improve the outcomes of those to be transplanted in the future.

2. Materials and Methods

The United Network for Organ Transplantation/Organ Procurement and Transplantation Network (UNOS/OPTN) database is a national online database system to collect, store, and publish all OPTN data pertaining to patients waiting for and those who have received transplantation. This system has documented every organ donation and transplantation occurring in the US since 1986 [15]. The UNOS/OPTN database was queried for this study. All OLTs performed between September 1987 and March 2011 were reviewed. Of 108,924 OLTs in the database, 184 were identified to be secondary to neuroendocrine tumors. Since no UNOS/OPTN diagnosis code for neuroendocrine tumor exists, these cases were identified based on the diagnosis text field including "carcinoid", "glucagonoma", "gastrinoma", "insulinoma", "islet cell tumor", "pancreatic gastrinoma", "pancreatic islet cell tumor", "VIPoma", "Zollinger-Ellison's syndrome", "neuroendocrine tumor", or any combination of those names with "metastatic", "met", or "malignant". The OLTs performed under these classifications are due to an unspecified neuroendocrine liver metastatic disease. Demographic information was analyzed including age, gender, and ethnicity of recipient, along with age of donor. Additionally, recipient characteristics such as creatinine, international normalized ratio (INR), total bilirubin, and albumin at time of transplant, days on the waitlist, model for end-stage liver disease score, or pediatric model for end-stage liver disease score (MELD/PELD), body mass index (BMI), length of hospital stay (LOS) following transplant, and ascites, encephalopathy, or dialysis prior to transplant along with donor characteristics such as creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin, and operative variables including cold ischemia time (CIT) and warm ischemia time (WIT) were analyzed. The education level of the recipient, whether the recipient received multiple organs at time of transplant, whether the recipient had a prior OLT, or whether the recipient required retransplantation, were also included in the analysis. MELD/PELD scores were introduced in 2002 which changed the paradigm of organ allocation from the Child-Pugh Score and offered a more precise allocation model which accommodates for neoplastic disease. To assess the evolution of OLT outcomes for NLM, the survivals of patients transplanted before and after the introduction of the MELD/PELD system in 2002 were assessed and compared using the Kaplan-Meier and the log-rank tests. Outcomes of all patients transplanted for NET/NLM were then compared to patients transplanted for hepatocellular carcinoma and for nonmalignant indications to assess overall survival experiences of NET/NLM patients relative to other indications.

Time-to-event data were obtained from this database to estimate post-OLT survival. Specifically, the time variable was calculated as the length of time between transplantation and either death or last known follow-up. An observation was censored if the individual was alive at the last known follow-up. Univariate and multivariate analyses were performed by Cox's regression and proportional hazards model, and survival analysis was performed by the log-rank test and the Kaplan-Meier test. Variables in the univariate analysis with P value less than or equal to 0.200 were then tested in the multivariate analysis using a step-by-step approach. A P value less than or equal to 0.050 was considered statistically significance and indicative of independent prognostic factor. All statistical functions performed on SPSS version 15.0 (IBM SPSS, Chicago, IL, USA).

3. Results

3.1. Patient Characteristics. From 1988 to March of 2011, 108,924 liver transplantations were performed in the US, and, of those, 184 were performed for NET/NLM patients. Descriptive analysis of the sample reveals a slight majority of males at 54.1%, with an average age of 44.9 years (range 11–69 years), a mode of 56 years. Caucasians made up the majority of recipients at 86.5%. The mean survival time was 41 months, though ranged from 0 to 253.3 months at the

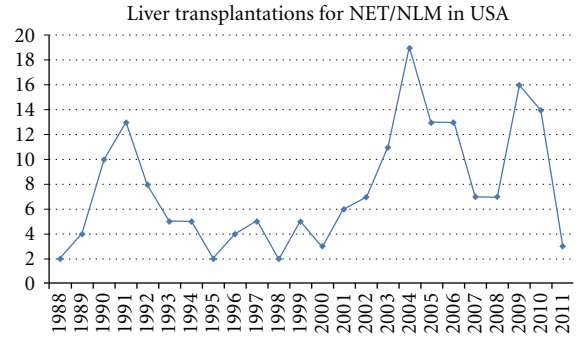

Figure 1: Liver transplantations for NET/NLM in USA. Note the significant increase in average number of transplantation which occurred after the introduction of the MELD/PELD score in 2002.

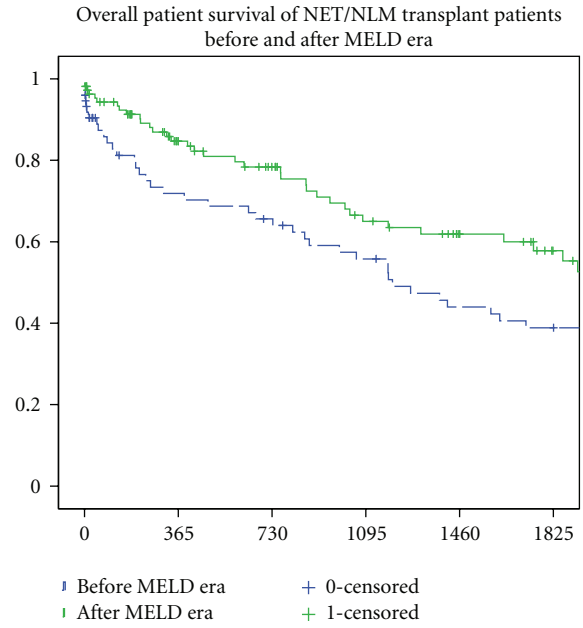

Figure 2: Overall patient survival of NET/NLM transplant patients in pre- and post-MELD era.

time this analysis was completed. Average length of stay after transplantation was 22.7 days, ranging 0–5.9 months. The first OLT for NLM included in the UNOS/OPTN database was performed in 1988. The number of OLT performed for the diagnosis of NET/NLM since then is separated into the year when the transplant occurred and is illustrated in Figure 1. Mean wait time on the transplant list for NET patients was 5 months. The larger majority of this subgroup received whole liver allografts, 89.7%, compared to split liver allografts. The LOS after OLT ranged from 15 to 52 days, with a mean of 23 days.

3.2. Introduction of the MELD/PELD Score. Figure 1 illustrates the distribution of liver transplantations which occurred annually since 1988. 74 transplantations occurred prior to the introduction of the MELD/PELD score in 2002. Transplants in the pre-MELD era averaged approximately 4 transplants a year between 1993 and 2001. In the post-MELD era, the average increase to 11.9 transplants annually for NET/NLM. (Please note that at the time this paper was written, 3 transplants occurred as of March of 2011.) The Kaplan-Meier and log rank tests were used to compare the survival experience of both the pre- and post-MELD subgroups and found a statistically significant difference graphed in Figure 2 ($P = 0.032$). Patients transplanted after the introduction of the MELD score had an improved survival outcome as compared to patients transplanted before 2002.

Overview of the patient sample reveals 86 patients who ultimately expired after transplantation for NET/NLM. Forty-six of those were listed to have died from recurrent and metastatic disease. The remaining causes of death are as follows: sepsis/infections (9), unknown (8), lung/kidney/multiorgan failure (7), hemorrhage (2 GI, 2 intracranial), lymphoproliferative disorder (3), graft failure (3), cardiac arrest (2), trauma (1), and hyperkalemia (1).

3.3. Patient and Allograft Survival. Patient and allograft survival of all NET/NLM patients ranged between 0 and 229.4 months. The mean overall patient survival was 91.9 months (7.5 years) ± 10 months whereas the median overall patient survival was 58.6 months ± 12.8 months. Overall patient survivals were 79.5%, 61.4%, and 49.2% at 1, 3, and 5 years, respectively (Figure 3). Allograft survival was 73.4%, 56.6% and 45.4% at 1-, 3-, and 5-year survivals, respectively, with an overall mean allograft survival of 83.9 months ± 9.3 months and overall median allograft survival of 47.1 months ± 8.2 months (Figure 3).

Kaplan-Meier log-rank analysis was also applied to overall patient survivals of patients transplanted for hepatocellular Carcinoma and for nonmalignant indications. These survival curves were then compared to all NET/NLM patients since 1988. NET/NLM patients had overall patient survivals of 79.5%, 61.4%, and 49.2% at 1, 3, and 5 years, respectively. This is compared to HCC patients, with 1-, 3-, and 5-year survivals at 85.8%, 71.1%, and 60.6%, significantly lower with a P value of 0.002 (Figure 4). Overall patient survival of those transplanted for nonmalignant indications was 85.2%, 78.3%, and 73.0% at 1-, 3-, and 5-year survivals, respectively, significantly better than patients transplanted for NET/NLM ($P < 0.00$) (Figure 4).

In light of the improved survival of NET patients transplanted after 2002, Kaplan-Meier log-rank analysis of overall patient survivals was also done for the three groups (NET/NLM, HCC, nonmalignancy) of patients transplanted after 2002. NET/NLM patients had overall patient survivals at 1, 3, and 5 years of 84.7%, 65%, and 57.8%. This is compared to HCC patients, with 1-, 3-, and 5-year survivals at 88.0%, 74.3%, and 64.4%. As opposed to transplants occurring prior to 2002, this difference in survival between HCC and NET/NLM patients is no longer significant ($P = 0.109$). Overall patient survival of those transplanted for nonmalignant indications was 87.1%, 79.5%, and 73.7% at 1-, 3-, and 5-year survivals, respectively, still significantly

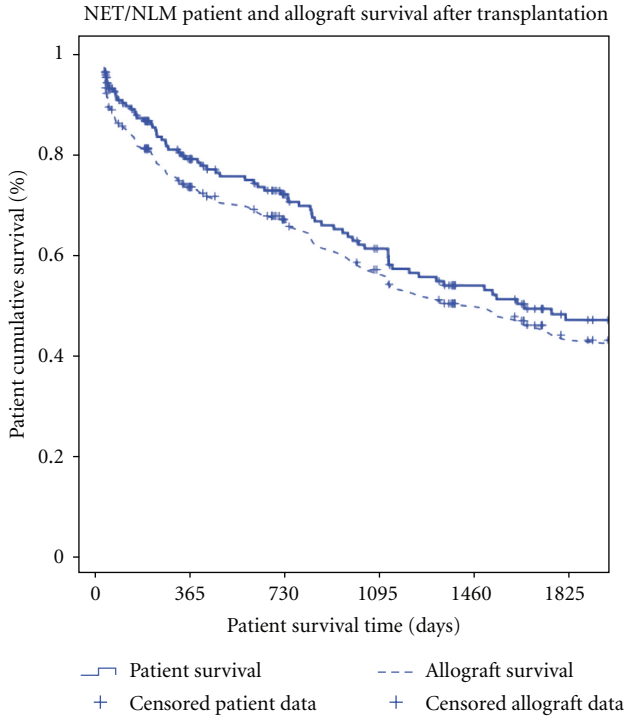

Figure 3: Neuroendocrine liver metastases: patient and allograft survival after transplantation, 1988–2011.

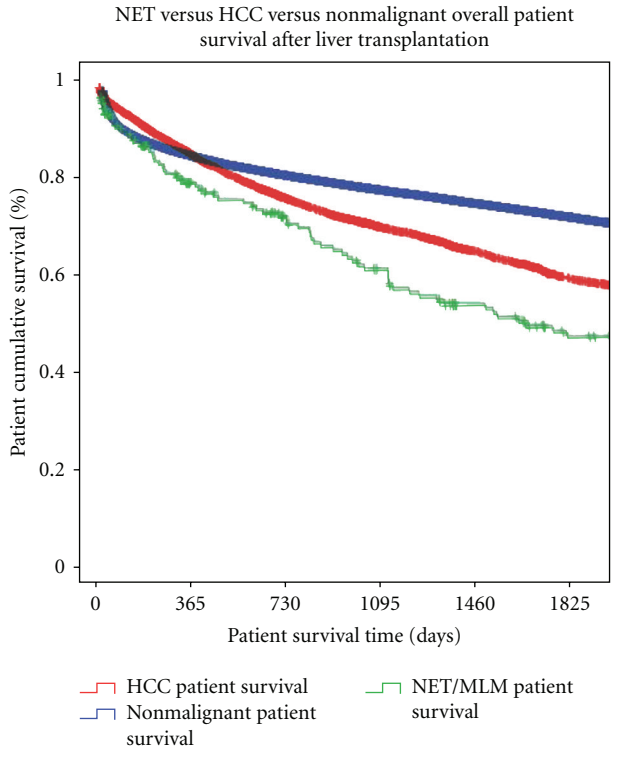

Figure 4: NET/NLM versus HCC versus nonmalignant patient survivals after transplantation, 1988–2011. NET/NLM versus HCC ($P = 0.002$); NET/NLM versus nonmalignant ($P \leq 0.00$).

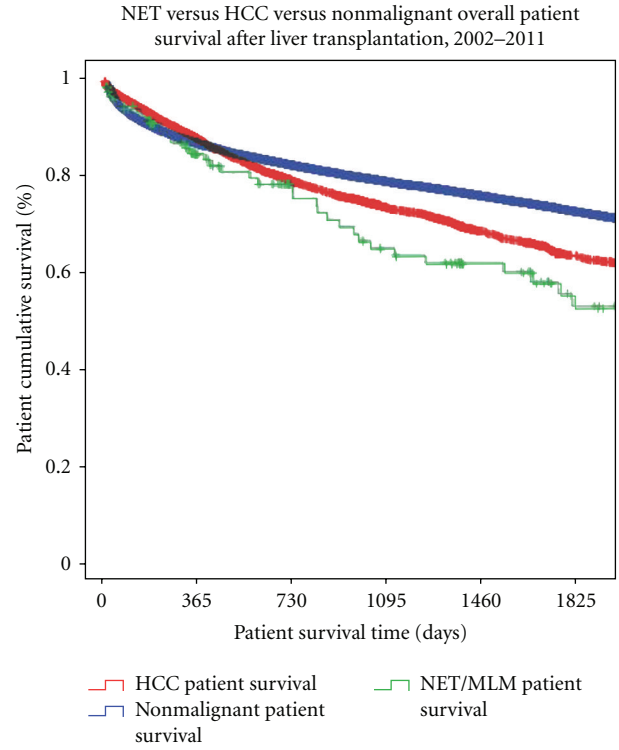

Figure 5: NET/NLM versus HCC versus nonmalignant patient survivals after transplantation, 2002–2011. NET/NLM versus HCC ($P = 0.109$); NET/NLM versus nonmalignant ($P = 0.002$).

better than patients transplanted for NET/NLM ($P = 0.002$) (Figure 5).

3.4. Univariate and Multivariate Analysis of Clinical Variables. Several recipient and donor predictors were analyzed in univariate analysis listed in Table 1. Of these variables, the following approached the P value cutoff for significance of <0.20 and were analyzed in the multivariate Cox regression model. Several prognostic factors were statistically significant after multivariate analysis (Table 2).

For all patients transplanted for NLM since 1988, a higher albumin serum level at transplant was significantly protective for patient survival ($P = 0.033$, OR = 0.45). A higher donor creatinine at transplant had a negative impact on allograft survival ($P = 0.00$, OR = 1.32), and, if the patient requires retransplantation, the patient also had worse allograft survival ($P = 0.004$, OR = 49.01; Table 2).

For patients transplanted for NLM *after* January 2002, multivariate analysis revealed that patient survival was deleterious for higher recipient total bilirubin ($P = 0.02$, OR = 1.06) and higher donor creatinine ($P = 0.004$, OR = 1.29) at time of OLT. A higher recipient albumin level at transplant portended a protective effect ($P = 0.011$, OR = 0.48) for patient survival. Allograft survival was negatively impacted if the patient required retransplantation ($P < 0.001$, OR = 35.9) and by higher recipient total bilirubin ($P = 0.02$, OR = 1.06) and higher donor creatinine at time of transplant ($P = 0.004$, OR = 1.31; Table 2).

Table 1: Clinical Variables used for univariate analysis with significance for patient and allograft survival. P values ≤ 0.2 were considered significant for multivariate analysis and marked in bold for clarity.

Univariate Cox regression		
Clinical variables	Significance for patient survival	Significance for allograft survival
Recipient variables:		
Age	.477	.454
Gender	**.168**	**.157**
Education level	**.174**	.304
Ethnicity	**.007**	**.024**
Body mass index	**.083**	**.043**
MELD/PELD	**.000**	**.006**
Days on waitlist	**.017**	**.033**
Previously transplanted	.782	**.079**
Patient requires retransplantation	.394	**.000**
Dialysis 1 week prior to OLT	**.006**	**.003**
Encephalopathy	**.052**	**.135**
Ascites	**.051**	**.088**
Multiorgan recipient	**.110**	**.095**
Type of allograft (Whole or Split)	.244	**.118**
Creatinine at OLT	**.021**	**.082**
Total bilirubin at OLT	**.008**	**.013**
INR at OLT	.546	.796
Albumin at OLT	**.000**	**.001**
Cold ischemia time	.574	.335
Warm ischemia time	.650	.692
Length of postoperative stay	**.001**	**.002**
Donor variables:		
Age of donor	**.097**	**.037**
Creatinine of donor	**.015**	**.067**
Total bilirubin of donor	**.099**	**.095**
AST of donor	.639	.882
ALT of donor	.447	.753

Table 2: Multivariate Cox regression results of clinical variables found to be significant ($P \leq 0.05$). *Signifies percentage of sample who required retransplantation.

	Range	Mean	P value	Change in OR
Transplants after 1988				
Patient survival				
Albumin at transplant	0.9–3.2	1.166	0.033	0.446
Allograft survival				
Patient required retransplant	n/a	7.6%*	<0.00	49.02
Donor creatinine	0.30–15.0	1.38	0.004	1.32
Transplants after 2002				
Patient survival				
Total bilirubin at transplant	0.10–69.60	2.64	0.02	1.063
Albumin at transplant	1.40–5.20	3.83	0.011	0.480
Donor creatinine	0.3–15.0	1.46	0.004	1.288
Allograft survival				
Patient required retransplant	n/a	4.5%*	<0.00	35.89
Total bilirubin at transplant	0.10–69.60	2.64	0.019	1.060
Albumin at transplant	1.40–5.20	3.83	0.006	0.455
Donor creatinine	0.3–15.0	1.46	0.004	1.308

4. Discussion

The use of OLT for NLM remains a controversial topic, in large part because of dismal outcomes, especially in early evaluations of smaller series of patients. Over time, these outcomes have slowly improved in further investigations, with a growing number of larger series done mostly in Europe. In our analysis of the USA experience for OLT due to NLM, we have found that 5-year survival outcomes are less favorable as compared to recipients of OLT for other causes, but in-depth analysis reveals remarkable improvement in the last decade. Of NET/NLM patients transplanted after 2002, with the introduction of the model for end-stage liver disease (MELD)/pediatric end-stage liver disease (PELD) scoring systems for organ allocation [16], the 5-year survival rate increased from 49.2% to 57.8% as compared to all patients transplanted since 1988. Notably, the overall patient survival for NET/NLM is not significantly different from the 1-, 3-, and 5-year outcomes of patients transplanted for HCC in the current era, since the advent of the MELD/PELD scoring system. This improvement acknowledges the potential for further gain in the survival of a patient population that would otherwise be considered for nonsurgical, palliative care. The outcomes are not significantly different from those of HCC patients, in whom liver transplantations are performed regularly. OLT serves as a reasonable effort in a patient group otherwise desperate for aggressive treatment options; the 5-year overall survival of patients with NLM on supportive care alone is reported to range between 0% and 46% [5, 7, 11, 17, 18] and the 5-year disease-free survival rate only at 24% [1]. Improvements in patient selection and evaluation, as well as surgical technique and postoperative care, have had a significant effect on this disease and its outcomes. As the majority of these transplantations occurred after 2002, our analysis shows that we are transplanting more patients with better outcomes over time. Olausson et al. [19] and Le Treut et al. [2] have shown that increased selectivity may be too specific, leaving out a number of patients who have already exhausted all other treatment options and who could otherwise benefit from this life-saving therapy. Olausson et al. transplanted 10 patients with expanded criteria, including a higher proliferation rate (measured by Ki67), large tumor burden, and higher age,

and were still able to show a 90% 5-year survival [19]. Le Treut et al. developed a selection tool based on the patient's primary tumor location and liver size (not tumor burden), which would have selected 70% of their 85-patient sample to benefit with a 68% five-year overall survival, inappropriately excluding only 2 patients [2]. Thus, the importance of precisely delineating the NET patient best suited for a liver transplantation becomes paramount.

Our analysis allows for greater precision in selecting the ideal NET/NLM patient for liver transplantation. From the inception of the UNOS/OPTN database, our research shows NET patient survival was affected significantly by albumin and total bilirubin, with higher albumin and lower bilirubin being protective. Allograft survival was negatively affected by the need for retransplantation and increased donor creatinine. While the need for retransplantation cannot be selected for, opting for patients with higher albumin levels, lower total bilirubin and donors with lower creatinine can improve both patient and allograft outcomes. While recipient creatinine level has been shown to be a prognostic indicator [3, 20], donor creatinine has not shown the same for liver transplantation recipients at this time. We hypothesize donors with elevated creatinine may have a poorer clinical picture, and thus the donor creatinine may act as a surrogate for the overall state of the liver allograft. Veering away from recipients with higher total bilirubin may help improve allocation efforts toward NET/NLM patients who would better benefit from organ transplantation. Our results corroborate with a large single-center series done by Le Treut et al. [2], finding age as not a significant variable in survival, and this counters a large multivariate analysis done by Lehnert [1]. Along with Le Treut et al., we found that the requirement for early retransplantation was associated with poorer outcomes and serves as a prognostic indicator [2]. However, our analysis found that overall survival of the UNOS/OPTN experience of those transplanted after 2002 is greater than that in their study, 57.8% versus 47%, respectively [2].

Therapeutic approach to liver metastases of NET must consider tumor distribution and bulk. Surgery is generally considered as first-line therapy, specifically liver resection [21]. While liver transplantation may occasionally provide for cure, it more often allows for symptomatic relief and prolongs survival. It is thus reserved for cases in which liver resection is not an option or for recurrent disease. Standard therapies to treat neuroendocrine liver metastases usually fall into the category of liver-directed therapies. This methodology exploits the dual blood supply to the liver, from the hepatic artery and portal vein, in order to control disease. Because of the higher recurrence rate of NET, these techniques are better considered debulking modalities than curative therapy [22]. General guidelines to dictate treatment options are dependent on tumor load, including location and number, as well as size and invasiveness [13]. For fewer lesions, local resection or thermal ablation is recommended. For higher tumor loads or recurrent disease, hepatic artery embolization and chemoembolization or radioembolization is used [23]. Other therapies are nonsurgical, non-liver directed therapies which includes chemotherapy and biotherapy and newer technologies directed at growth factors and peptide receptors, as well as regulation of micro-RNA pathways.

A weakness of this analysis is the inherent nature of the UNOS/OPTN database, as it focuses on clinical data pertinent to liver transplantation and not necessarily the disease process of the liver. The location of the primary NET and the histopathology have been shown to influence overall survival [4, 11], along with concomitant upper abdominal exenteration and presence of hepatomegaly [2]; however, these data points were not included in the UNOS/OPTN database as this database focuses on clinical variables as it pertains to liver transplantation, not necessarily the disease process leading to end-stage liver disease. Additionally, time of diagnosis, presentation of symptoms, production of hormones, and prior treatments utilized were also not available, though quite pertinent in describing this patient population. There is also evidence to suggest Ki67, and E-Cadherin status affects prognosis of NET patients [3, 10, 14, 19], but immunohistochemistry was not recorded. Lastly, recurrence rate and disease-free survivals would allow a more in-depth assessment of outcomes. These weaknesses are acknowledged, and, while whole generalizations cannot be made, it is important to note the breadth of this sample as it illustrates the transplant experience of a national, and thus larger, group of patients with the same rare disease, improving the power of the study. It is important to recognize that liver transplantation for metastatic neuroendocrine tumors is reserved for those with unresectable or refractory disease, both implying a usually dismal prognosis without further treatments. Survival time with patient status is present in all 184 patients of our sample and thus serves as reliable information on the survival experience of this rare and desperate patient population.

While OLT offers a potential for cure in these patients, long-term survival remains lower than the 5-year survival of patients transplanted for other diseases, both malignant and nonmalignant. Many have questioned whether the allocation of limited resources is warranted. Transplanting patients with malignancies has been argued to be justifiable only if the survival can be estimated to exceed 50% at 5 years [24]. Our analysis reveals that not only do NET/NLM patients meet this criteria and do relatively well after transplant but also they continue to improve over time and have survivals not significantly different from HCC patients who are transplanted. Considering the dismal prospects of a patient population that is otherwise without much hope of long-term survival and cure, the impact of these outcomes is compelling [5]. There is promise in the progress of our care for the NLM patient and liver transplantation, which offers us potential for improvement.

5. Conclusion

Understanding the limitations of the UNOS/OPTN database and its focus on transplantations and the associated patient and allograft outcomes, this analysis provides valuable

insight into patients with NLM and overall survivals after liver transplantation.

While the 5-year survival of patients after OLT for NLM is lower than that after OLT for non-malignant diseases, we argue that the overall survival remains reasonable, exceeding other estimations reported and is not significantly different from HCC outcomes. NET/NLM outcomes after OLT surpass that of patients with untreated NLM left to its natural progression. The significant improvement in outcomes after the introduction of the MELD/PELD scoring system reinforces the potential for gains in transplanting this patient population, who have already failed or exhausted the litany of therapeutic options dedicated to this disease process and who are otherwise facing fatal prospects. This data helps to characterize the NET/NLM patients who have benefited most from liver transplantation. Stratification of variables show requirement of a retransplant; decreased albumin level of the recipient and elevated donor creatinine influence the prognosis of the patient and the allograft after OLT in patients with NLM. In this era of transplantation, we argue the outcomes of liver transplantation for a carefully chosen subset of neuroendocrine tumor patients are acceptable and potentially life-saving.

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Review Article

Radioembolization in the Treatment of Neuroendocrine Tumor Metastases to the Liver

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Surgical excision remains the preferred treatment for resectable hepatic metastases of neuroendocrine tumors. In cases of more disseminated hepatic disease, transarterial radioembolization with Yttrium-90- (90Y-) labeled microspheres has been demonstrated as a viable option for symptom and locoregional tumor control. On an outpatient basis, radioembolization can be utilized from early line to salvage phases, in various combinations with systemic therapies. Review of available data shows encouraging safety and efficacy profiles for the intraarterial application of 90Y for the treatment of mNETs of the liver. Symptom control and decrease in somatostatin analog use can be achieved, as well as prolonged survival.

1. Introduction

After removal of the primary, isolated metastases of neuroendocrine tumors to the liver can be curatively approached by surgical resection with achievable disease-free survival of 42 to 46 months depending on the extent of metastases [1]. However, only 10% of metastatic liver disease cases are resectable [2]. Also, significant surgical morbidity and mortality as well as the unpredictable natural history of malignant neuroendocrine neoplasms has to be considered [2]. Consensus guidelines for digestive (neuro)endocrine tumors currently call for complete hepatic deposit resection or 90% debulking if feasible [3] since their introduction in the 1980s somatostatin analogs have significantly helped in symptom control of functional neuroendocrine tumors. Their effectiveness, however, tends to diminish over time due to tachyphylaxis and disease progression. An antiproliferative effect has been ascribed to somatostatin analogs on their own [4]. Additional labeling with radionuclides (e.g., 177Lutetium-DOTA-TATE) has shown response rates of 13–30% and median overall survival of 13–46 months along with significant clinical benefit [5–10].

Overall, metastatic neuroendocrine tumors have exhibited modest response to systemic chemotherapy. Streptozocin- and doxorubicin-based protocols achieve response rates of up to 16%. In more poorly differentiated NETs a 41.5% response rate has been seen with cisplatin/etoposide combinations [6–10]. Recently, 70% partial remissions with estimated overall survival of 92% at 2 years have been reported with a temozolamide/capecitabine regimen in metastatic NET of the pancreas [11].

Novel agents targeting diverse receptors are in various stages of development. Preliminary data for sunitinib, a multikinase inhibitor, for example, demonstrate a promising progression-free survival of 11.4 months versus 5.5 months for placebo.

2. Transarterial (CHEMO) Embolization (TA[C]E)

Retrospective studies have shown benefit to both TAE and TACE in the treatment of mNET with regard to tumor growth, symptom control, and biochemical surrogates. In the most recent large retrospective study of 123 treated patients undergoing an average of 7 chemoembolization cycles each, 62% partial response was seen with overall 3-, 5-, and 10-year survivals of 59, 36, and 20%, respectively, and overall mean survival of 5.47 years [12].

This result is corroborated by the 67% ORR (mean survival 33.8 months) in another large study employing TACE and TAE for the treatment of carcinoid hepatic metastases. A separate group of islet cell carcinomas in the latter study exhibited an ORR of only 34% (mean survival 23.2 months); in the former study 10 cases with insulin/glucagon secretion were subsumed in the study population [12, 13].

No consensus has been established regarding technique, embolizing, and chemotherapeutic agents in TACE. Overall, both TAE and TACE appear to elicit similar responses from NET liver metastases, suggesting relative primacy of the embolic effect [2, 14].

3. Transarterial Radiombolization (TARE)

Transarterial radioembolization (TARE) or selective internal radiotherapy (SIRT) with Yttrium-90 microspheres represents a further viable option in the treatment arsenal for nonresectable liver metastases of both functional and nonfunctional NETs. A number of retrospective as well as a few prospective studies demonstrate efficacy and safety combined with the convenience of an outpatient procedure that rarely requires hospitalization (Table 1) [15–25]. What is more, it appears that the primarily one-time treatments with TARE compare favorably to usually multiple procedures required TA(C)E regimens.

Two kinds of Yttrium-90 microspheres are currently approved for treatment of unresectable liver tumors on the European market: Yttrium-90 resin microspheres (SIR-spheres; Sirtex Medical, Sydney) with 20–60 μm diameter mounted with a radioactive load of approximately 50 Bq per sphere, as well as 20–30 μm glass microspheres (TheraSphere, MDS Nordion, Ottawa) with the higher radioactive load of 2500 Bq. SIR-spheres come with premarket approval (PMA) for unresectable hepatic metastases of colorectal cancer in the United States and may be utilized "off-label" for other tumors without prejudice under the using physicians discretion authority and responsibility. Therasphere has a humanitarian device exception for the treatment of hepatocellular carcinoma in the US which is more restrictive than PMA and requires an IRB protocol and limitations to hepatocellular carcinoma (HCC) only.

A phase II trial of Yttrium-90 resin microspheres in combination with systemic FU chemotherapy was conducted with 34 patients. While this represented first-line therapy for the majority of patients, 29% had failed prior liver resection and 15% had received earlier chemotherapy, with 59% also manifesting extrahepatic disease. Complete response was effected in 18%, partial response in 32%, and stable disease 15% of cases. Symptom improvement and Chromogranin A decrease at 6 months were seen in 50% and 41% of cases, respectively. 59% of patients remained alive at 37 $\pm$ 2 months, with 12 patients without hepatic recurrence at 33.3 $\pm$ 2.3 months [20].

Another prospective trial with Yttrium-90 resin microspheres involved ten patients with progressive or symptomatic unresectable hepatic spread of NET. 40% partial response was seen at 6 months and 2 out of 3 patients experienced symptomatic improvement, and average quality of life climbed to general-population levels by 6 months. Seven patients were still alive at 35 months followup, with the three intervening deaths attributable to progression of extrahepatic disease. Little toxicity was observed, with the authors noting comparable to better toleration of TARE compared to TACE [23].

Another study with Yttrium-90 resin microspheres also had quality of life as an endpoint and could demonstrate significant improvement of quality of life [18].

In a third prospective trial, 20 and 22 patients with mNET were treated with resin and glass Yttrium-90 microspheres, respectively, after the patient had previously undergone surgery (36%), ablation (19%), TA(C)E (14%), and symptomatic treatment (60%). ORR resulted in 50% and 54%, and stable disease in 44% and 38.5%, respectively. Projected median survival times were 28 and 22 months, respectively (not statistically significant difference), with the majority of patients alive at time of study publication [22].

The largest retrospective study to date reviewed a total of 148 patients in 10 clinical centers treated with Yttrium-90 resin microspheres in a primarily salvage setting of mNET. 70 months median survival with 63% ORR and 23% stable disease were demonstrated, with most deaths due to progression of extrahepatic disease. Toxicity was very low, no radiation-induced liver disease (RILD) was seen even in the 33 patients receiving retreatment of the same liver lobe(s) [19].

Repeated radioembolizations of both or single lobes were also performed in a minority of patients in other studies, with a few receiving a third treatment [19, 20, 24, 25]. No case of RILD was seen and an increased duration of tumor response in cases of hepatic mNET progression was recognized [18, 19, 24, 25].

4. Discussion

Overall, the available studies demonstrate effective and safe use of radioembolization for liver dominant disease in mNET. There is a positive effect on symptoms, quality of life, response criteria, and survival in various stages of progression, which is mirrored in the recommendations of the Radioembolization Brachytherapy Oncology Consortium [26]. A robust safety profile for radioembolization with Yttrium-90 microspheres was confirmed in two 2009 analyses [26, 27]. The overall incidence of RILD, in particular, was estimated to be 0.8% [26].

Evidence-based data for treatment decisions in inoperable mNET are not presently available. A recent overview of strategies for advanced enteropancreatic NET comprehensively presents the panorama of current and developing multimodal treatment options. In general, former wait-and-see strategies even in well-differentiated tumors with minor-to-moderate tumor loads will have to be reevaluated, as tumor progression, with median TTP of 6 months, is inevitable [5].

In order to relieve the common carcinoid syndrome consisting of diarrhea, flushing, hypertension, bronchoconstriction, right valvular heart failure and other endocrine effects, or effect medication sparing, at least palliative tumor

Table 1: Study outcomes of TARE for NET liver metastases.

Lead Author, Year	*n*	Prospective?	Treatment Phase	ORR	SD	Symptom Response	Survival
Arslan, 2011 [17]	10	No	?	80%	10%	NR	All alive at 4–28 mo
Cao, 2010 [15]	51	No	?	38%	27%	NR	36 mo
Saxena, 2010 [26]	48	No	?	55%	23%	NR	35 mo
Kalinowski, 2009 [19]	9	Yes	Refractory	66%	33%	Improved QoL	57% alive at 36 mo
Kennedy, 2009 [27]	148	No	Refractory/salvage	63.2%	22.7%	NR	70 mo
King, 2008 [22]	34	Yes	First-line*	50%	14.7%	50%	59% alive at 37 ± 2 mo
Murthy, 2008 [16]	8	No	Refractory/salvage	12.5%	50%	NR	14 mo
Rhee, 2008 [23]	20	Yes	Refractory	50%	44%	NR	28 mo
	22**	Yes	Refractory	53.8%	38.5%	NR	22 mo
Meranze, 2007 [24]	10	Yes	First-line	40%	60%	Improved QoL	70% alive at 35 mo
McGrath, 2007 [25]	26	No	First-line/refractory	58.3%	33%	NR	69% alive at 17.3 mo
Kennedy, 2006 [21]	18	No	First-line/refractory	89%	NR	NR	89% alive at 27 mo

*combined with 5-FU.
**with Yttrium-90 glass microspheres, all others with Yttrium-90 resin microspheres. Median survival in last column unless otherwise indicated. ORR: objective response rate (complete + partial response). SD: stable disease. NR: not reported. QoL: quality of life.

debulking, either surgically or with transarterial approaches, is necessary. Hepatic tumor burden debulking appears to improve survival as well [28–32]. 5-year survival rates for mNET are 50–59% according to national cancer registries [33, 34]. With intervention, 5-year survival reaches 72–100% in limited hepatic spread and 25–51% in more extensive hepatic spread [35, 36].

TARE (see Table 1) is at least comparable to TA(C)E in effectiveness [13, 14]. An advantage of the TARE protocol is the generally single treatment to achieve this effect, while TA(C)E is generally applied multiple times. This obvious patient comfort and quality of life advantage is compounded by the well-known lower severity of the "postembolization" syndrome (which in TARE's case represents radiation irritation) and reduced need for inpatient admittance. On the other hand, preparatory angiography mapping, embolization, and treatment simulation are a necessary first step in TARE workup.

It is conceivable that Yttrium-90 microspheres can be held in reserve, so to speak, for further repeated use to establish prolonged disease control. In this respect, it seems superior to repeated TA(C)E. For one thing further extended use of TA(C)E is limited by the sheer number of necessary repetitions, reducing patient days outside the hospital and thus quality of life. The extended use of TARE, on the other hand, would likely not reach the number of regular TA(C)E sessions. Similar advantages also apply to side effects and outpatient flexibility. Also, the degree of embolic effect could skew repeated treatment schemes to TARE's favor: while TA(C)E may "prune" the arterial tree to such an extent that agent delivery is impaired due to the larger particle size (100–300 μm versus 35 μm for TARE), the lesser embolic effect of TARE may keep the path to the tumor more reliably open. Further examination of the limits of dose and repeat application with regard to RILD could possibly enable attempts at treating even more advanced hepatic spread with radioembolization. An investigation of radiosensitizers, for example, capecitabine, to be concurrently used with TARE may also be warranted as this could represent another lever to further potentiate its effects [37].

Apparently disease control through radioembolization treatment is effective and long-lasting enough for most patients in the observed time spans to succumb to progressive extrahepatic disease. Thus, initiation/resumption of chemotherapy, possibly combined with extrahepatic local resection/ablation if necessary, appears reasonable.

Further considerations concern the endpoints surveyed in Yttrium-90 treatment studies. Morphologic response criteria (i.e., RECIST) may be misleading in TARE followups. Since the RECIST criteria were designed to reflect the response to systemic chemotherapy, the response to TARE is not gradual shrinkage but the creation of a necrotic tumor whose margins may not be well circumscribed in the baseline CT yielding a reading of progressive disease or mere stable disease. Collection of tumor marker data, for example, Chromogranin A, as well as functional parameters, for example, PET, may help to overcome some of these shortcomings. Emphasis should also be laid on formal measurements of quality of life in subsequent studies of TARE to better gauge this essential patient dimension.

Disclosure

Dr. Coldwell is a consultant to Sirtex, Inc.

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Clinical Study

Selective Internal Radiation Therapy for Gastrointestinal Neuroendocrine Tumour Liver Metastases: A New and Effective Modality for Treatment

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Background. Nonresectable neuroendocrine tumour (NET) liver metastases respond poorly to most widely available and used therapies. Selective Internal Radiation Therapy (SIRT) is becoming recognized as a new modality for selectively treating non-resectable liver tumours. This paper presents an experience of 14 patients with non-resectable NET liver metastases treated with SIRT. *Methods*. Between September 1997 and October 2009 14 patients with extensive NET liver metastases were treated with 2.0 to 3.0 GBq of ^{90}Yttrium microspheres. Repeat SIRT was undertaken in three patients after 16, 27, and 48 months, respectively. Responses were assessed clinically, biochemically, and with serial CT scans. Survival was measured from initial SIRT. *Results*. Some response was seen in all 14 patients. Carcinoid syndrome improved or resolved in 10/10 instances. 24-hour urinary 5-HIAA or serum chromogranin A levels fell dramatically in 5/7 patients following SIRT. Serial CT scans revealed partial response or stable disease in all 14 patients. Repeat treatment in three patients experiencing progression was associated with a further response. Median survival after SIRT is 25 months with 6 patients being alive (and 3 patients still asymptomatic), at 19, 22, 23, 23, 58, and 60 months. *Conclusions*. SIRT is an effective and well-tolerated treatment for non-resectable NET liver metastases capable of both alleviating the carcinoid syndrome and achieving significant tumour regression. Repeat treatment is an option and liver resection after downstaging may also become possible.

1. Introduction

Gastrointestinal neuroendocrine tumours (NET), previously known as carcinoid tumours, are rare tumours arising from neuroendocrine cells of the digestive and respiratory tracts with highest incidence rates being reported in black males (4.48 per 100,000) [1]. While most are well differentiated and relatively slow growing, they do vary considerably in their biological behavior ranging from benign to highly malignant. When they metastasize, they have a propensity to spread to the liver and to present clinically with carcinoid syndrome. The syndrome classically involves symptoms of episodic cutaneous flushing, diarrhea, bronchospasm, and, more rarely, signs of tricuspid incompetence. Symptoms arise in response to the systemic effects of vasoactive substances produced by the tumours which have escaped hepatic degradation. In those with carcinoid syndrome, there will usually be an elevated whole blood or platelet poor plasma level of serotonin and an elevated 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5HIAA), which is a metabolite of serotonin. Serum chromogranin A (CgA) levels can also be a useful marker of the disease.

Survival and quality of life for those with NET depends largely on the control of tumour growth and the suppression of carcinoid symptoms. Cure is unusual because metastatic deposits within the liver are usually widespread and seldom permit curative resection. Conventional approaches to managing those with NET liver metastases include (a) attempts to reduce tumour burden by resection, ablation, arterial emization, or chemotherapy, (b) chemical approaches to manage the carcinoid syndrome with somatostatin analogues, or (c) both. These antitumour strategies have not proven terribly effective. The mainstay for treating widespread liver

metastases has been transarterial embolization (TAE) or transarterial chemoembolization (TACE). While some patients respond well to such approaches [2], the benefit is usually relatively shortlived, and there remains a need for the development of new and more effective anti tumour strategies. In the absence of particularly effective anti tumour strategies most patients are simply treated with long-acting somatostatin analogues in an effort to control carcinoid symptoms, and with the hope these may have some anti tumour activity. However, in recent times, a variety of newer approaches have emerged and with encouraging benefit. Peptide Receptor Radionuclide Therapy (PRRT) with ^{111}Indium, ^{90}Yttrium, or ^{177}Lutetium labeled octreotide analogues is one such an approach [3]. Selective Internal Radiation Therapy (SIRT) with ^{90}Yttrium microspheres is another and is becoming recognized as an effective new tool in the management of a number of types of advanced liver cancer including NET [4–8].

We report our experience with fourteen patients with NET treated with SIRT with ^{90}Yttrium microspheres.

2. Patients and Methods

Fourteen patients with extensive NET liver metastases, considered unsuitable for hepatic resection or cryoablation, were treated at the Wakefield Gastroenterology Centre during the period from September 1997 to October 2009 and are the subject of this report. All were treated with SIRT on one (11 patients) or two occasions (3 patients) with or without a period of ongoing hepatic artery chemotherapy with 5-Fluorouracil. Prior to SIRT the patients were evaluated with CT scans of the chest and abdomen and a variety of standard blood tests. 24-hour urinary excretion of 5HIAA or serum CgA was also measured serially in some patients.

SIRT involved the delivery of 2.0, 2.5 or 3 GBq of ^{90}Yttrium microspheres (SIR-spheres, Sirtex Medical Pty Ltd, Sydney, Australia) into the hepatic artery either via a surgically placed hepatic artery port-a-cath or a percutaneous hepatic artery catheter inserted by the way of the femoral artery. The procedure, including the choice of dose, is a relatively straightforward one which has been described in detail elsewhere [6]. Great care needs to be taken to ensure all vessels arising from the hepatic artery which feed nonhepatic structures are either ligated or embolized. Prior to delivery of the ^{90}Yttrium microspheres a nuclear medicine scan is performed in which Tc99 labeled macroaggregated albumin (MAA) is injected into the hepatic artery to assess the likely distribution of the ^{90}Yttrium microspheres following their administration. The scan provides an estimate of any liver-lung shunt and also an indication of whether any inadvertent delivery of ^{90}Yttrium microspheres to foregut structures might occur. A liver-lung shunt of greater than 12% has been shown to be unacceptable because of the possible development of severe radiation pneumonitis [9]. Similarly, any indication of access to nonhepatic foregut structures (e.g., stomach, pancreas, or duodenum) is a contraindication to proceeding because of the risk of severe radiation damage to such structures. We deliver the ^{90}Yttrium microspheres to lightly sedated patients using a special delivery box, provided by Sirtex Medical Pty Ltd, over a period of approximately 10 minutes. Patients generally remain in the hospital for 48 hours following SIRT. No special radiation safety precautions are required during this period or following the return home.

Tumour responses have been assessed in three ways: (a) self-reported symptomatic improvement in symptoms of the carcinoid syndrome, (b) serial 24-hour urinary excretion of 5HIAA or serial serum CgA, and (c) serial CT scans performed at 3 to 6 monthly intervals. WHO and RECIST criteria were not used for reasons mentioned in the discussion. Rather CT evidence of tumour response was deemed to have occurred, providing index lesions reduced in size (partial response) or did not change in size (stable disease). Survival time is described in terms of time from SIRT.

3. Results

The fourteen patients included nine males and five females with a mean age of 58.8 (range 29–73) years. Ten had symptoms of carcinoid syndrome. Patient characteristics, symptoms and tumour burden are shown in Table 1. Although the primary site was not known in all cases, none of the patients were thought to have a pancreatic primary. One patient (patient 2) had received extensive previous treatment for her tumour including, multiple metastasectomies and TAE. Two patients (patient 6 and 9) were receiving long-acting somatostatin analogue, prior to SIRT. Six patients received whole-liver SIRT via a percutaneous hepatic artery catheter and eight received whole-liver SIRT via a surgically placed hepatic artery port-a-cath. The eight patients to receive SIRT via a port-a-cath also received ongoing hepatic artery chemotherapy with 5 FU (4 g every 4-weeks by continuous infusion over 4 days). In seven of the patients, this was given for between 6 and 12 cycles, but in the 8th it was given for only two cycles because of technical failure of the port. Three patients (patients 1, 5, and 6) had a repeat treatment with SIRT, 16, 27, and 48 months after the first treatment respectively. In all three patients the first SIRT had resulted in an excellent response and each experienced a further good response following the second SIRT. The others either had extrahepatic metastases at the time of liver progression or did not seek further SIRT. Patient 6 underwent a palliative extended right hepatectomy, some 16 months after her initial SIRT and some 28 months before her second SIRT. She died 79 months after the first SIRT with bony metastases and minimal liver disease.

There were no-treatment-related deaths or serious complications following either surgery or the SIRT. The SIRT was followed for some weeks with anorexia and lethargy in all patients but was otherwise well tolerated. In particular, there were no instances of early radiation hepatitis, radiation pneumonitis, or radiation gastritis. All patients were discharged within 48 hours of receiving SIRT. One patient (patient 5) developed slow and late signs of non-icteric liver failure and died 10 months after his second SIRT (37 months after his first SIRT). The cause of death was not clear but was not obviously related to the SIRT or tumour burden.

Table 1: Patient details and response to selective internal radiation therapy.

Patient	Gender	Age	Carcinoid syndrome	Liver Involvement	5HIAA response	CT response	Survival (months)
1*	Male	29	Yes	25–50%	Yes	Yes	34.2†
2	Female	49	Yes	>50%	n/a	Yes	26.9†
3	Male	70	No	>50%	n/a	Yes	11.9†
4	Male	64	Yes	<25%	Yes	Yes	110†
5*	Male	71	Yes	<25%	Yes	Yes	37†
6*	Female	46	Yes	>50%	Yes	Yes	79†
7*	Female	60	No	<25%	n/a	Yes	60
8	Male	52	No	<25%	n/a	Yes	58
9	Male	61	Yes	50%	n/a	Yes	16.4†
10*	Female	60	Yes	25–50%	No	Yes	21†
11*	Male	72	Yes	<25%	Yes	Yes	23
12*	Male	60	No	<25%	Yes	Yes	23
13*	Male	56	Yes	<25%	n/a	Yes	22
14	Female	73	Yes	<25%	n/a	Yes	19

† Deceased; * received hepatic artery chemotherapy.

Table 1 documents the responses noted in the fourteen patients. Carcinoid syndrome resolved or improved in all ten patients and a CT response (regression or stable disease) was seen in all fourteen patients. The CT scans before and after SIRT in patients 4 and 6 are shown in Figure 1. 24-hour urinary excretion of 5HIAA or serum chromogranin A levels fell in 6/7 patients in whom it was serially measured as shown in Figure 2. The fall was dramatic in five of the seven patients and was well maintained in all five. Median survival after the first SIRT is 25 months with 6 patients still alive (and 3 patients being asymptomatic), at 19, 22, 23, 23, 58, and 60 months.

Performance status as assessed by Karnofsky score was improved in all but one patient with advanced disease who did not do well following SIRT, despite CT evidence of a response. Mean Karnofsky scores improved from a value of 86.5 prior to SIRT to 93.5, 3–6 months following SIRT.

4. Discussion

Although the natural history of NET is generally regarded as relatively benign, metastatic disease does develop in a proportion of those affected. In a large study of 13715 carcinoid tumours from US databases some 12.7% had metastases at presentation [1] and a similar figure was reported from the ERG database of 2837 individuals [10]. Furthermore, while those with metastatic NET do have a more favorable prognosis than those with most other types of metastatic tumours, cure remains extremely unusual. Thus, although 5-year survival following recognition of liver metastases is achieved by some, most will succumb from the disease in this timeframe. Godwin reporting on the large ERG database noted that the 5-year survival for patients with distant spread from NET was only 18%. Another more recent report showed mean survival of those with carcinoid syndrome at only 38 months [11].

The use of regular long-acting somatostatin analogues has had an important and significant impact on the management of both functioning and nonfunctioning NET. The analogues octreotide and lanreotide are now widely used to control symptoms in those with symptomatic NET tumours and excellent control can be expected in around 75% of patients, although escalating doses may be required. Patients with symptoms refractory to one formulation may respond to another [12]. Biochemical responses are also seen with the somatostatin analogues but less often (i.e., 40–50%) than the symptomatic responses [13]. There is recent data from the PROMID trial and others that long-term use of octreotide LAR appears to have anti tumour effects which may stabilize disease or even achieve partial regression [14]. Previous reports have also suggested that tumour regression or stability can be achieved by use of somatostatin analogues alone [15, 16]. In the PROMID trial the anti tumour effects seemed to be most pronounced in those with low-volume hepatic disease. For all of these reasons, somatostatin analogues have become central in the contemporary treatment of metastatic NET.

Anti tumour approaches have involved a variety of modalities over the years with varying, but not usually predictable or reliable benefit. These include systemic chemotherapy, TAE, TACE, and a variety of locally ablative therapies. Although systemic chemotherapy is commonly administered, particularly in symptomatic patients with advancing disease, results are generally disappointing. Many different agents including doxorubicin, 5-fluorouracil, streptozotocin, mitotane, docetaxel [17–19], topotecan, lomustine, and leucovorin with or without interferon alpha have been used but none have delivered response rates exceeding 15–20%, and generally only for short periods. Survival advantage is doubtful or small [20–23].

TAE and TACE protocols have been widely employed and can certainly achieve symptomatic and biochemical responses with tumour regression in many patients. Such responses may be seen in as many as 65% of instances [17–19], but are seldom sustained. Touzios et al. have reported that aggressive management of patients with carcinoid syndrome with chemotherapy, embolization, and locally ablative surgery or radiofrequency ablation can improve

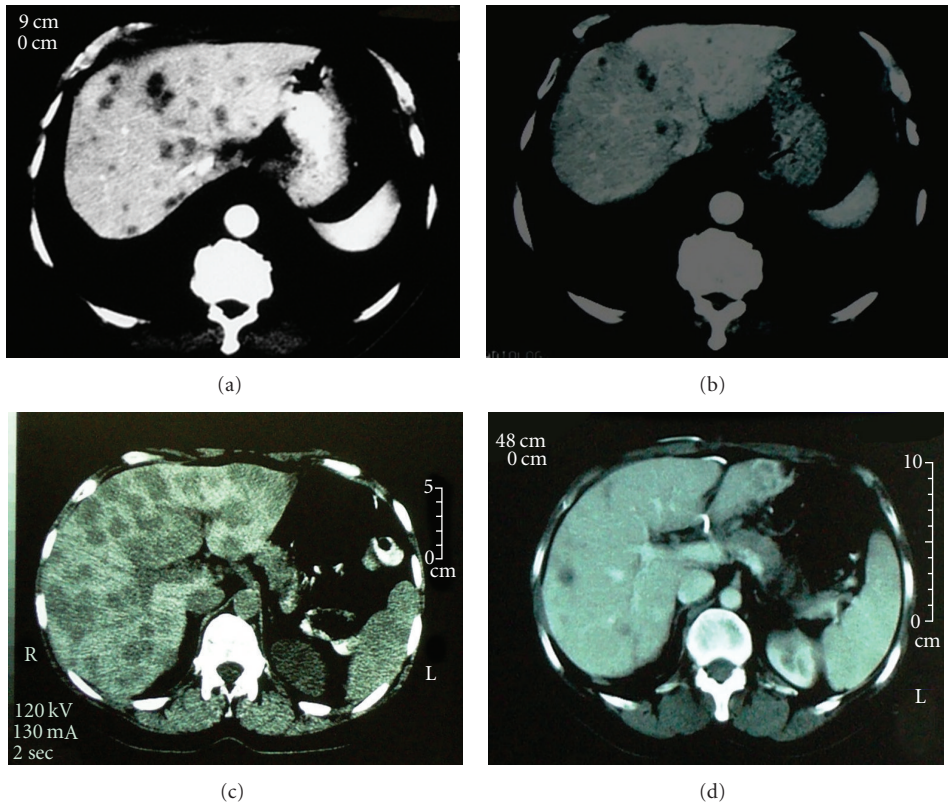

Figure 1: CT scans before and after SIRT. (a) patient 4 prior to SIRT, (b) patient 4 four years following SIRT, (c) patient 6 prior to SIRT, (d) patient 6 three months following SIRT.

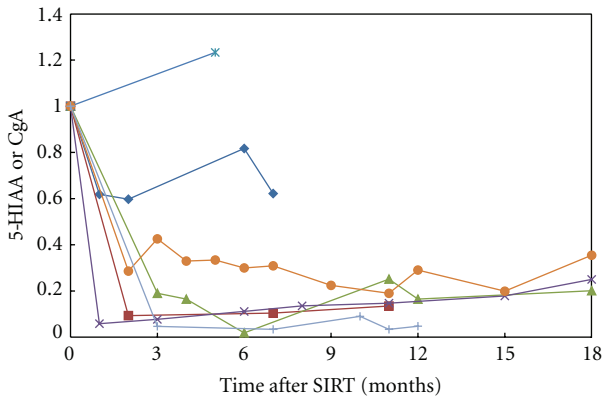

Figure 2: Graphic representation of serial 24 hr urinary excretion of 5HIAA or serum chromogranin in seven patients. Pre-SIRT values have been normalized to 1.0.

mean survival for this group to around 50 months with a 5-year survival to around 48% [24].

Peptide Receptor Radionuclide Therapy (PRRT) using a variety of radionuclide-(^{111}Indium, ^{90}Yttrium, or ^{177}Lutetium) labeled octreotide analogues has attracted growing interest in recent years [25] and is being actively investigated in many centres around the world. ^{90}Yttrium or ^{177}Lutetium appear more effective radionuclides because of higher energy and therefore greater tumour penetration. Symptomatic and biochemical responses are seen in a variable proportion of patients and partial response or stable disease are seen in up to 50% of subjects, at least for a period [26–29]. Renal, bone marrow, and hepatic toxicity have been a problem, but are becoming less so with use of alternative analogues and concomitant renal protection. Furthermore, a variety of different octreotide analogues are under investigation, in an effort to improve the affinity for the somatostatin receptors, and thereby the therapeutic index. It has been suggested, but not, established, that PRRT is more useful in managing small tumours [30]. However, only those patients with high affinity for the relevant analogue, shown by scintigraphy, are candidates for such therapy.

An alternative approach to targeted radiotherapy is Selective Internal Radiation Therapy (SIRT) using hepatic arterial delivery of ^{90}Yttrium microspheres as described in the present study. In our experience, we saw a response in all of our patients, based on symptomatic benefit (10/10), biochemical measurement (6/7), and at least stable disease on CT scanning (14/14). This was achieved without serious or significant toxicity. Median survival after the first SIRT is 25 months which compares favourably with alternative therapies. Furthermore, six patients are still alive at 19, 22, 23, 23, 58, and 60 months, with three being asymptomatic.

Hepatic arterial delivery of the microspheres delivers high doses of high-energy β radiation to liver tumours, with relative sparing of normal hepatic parenchyma. SIRT

with ^{90}Yttrium microspheres is emerging as a very effective modality for treating nonresectable secondary and primary liver tumours [4, 31–37] with many reports attesting to response rates of 80% and greater for both metastatic colorectal cancer and hepatocellular cancer. This particular vehicle for ^{90}Yttrium delivery has the advantage over octreotide analogues that it does not depend on the presence of somatostatin receptors, and it has a higher-therapeutic index. Furthermore, providing the SIRT is administered appropriately, there is a very low risk of extrahepatic toxicity, despite high doses being delivered. However, because the therapy is delivered via the hepatic artery, it is only suitable for liver-only or liver-predominant metastatic disease. By this technique, average doses of absorbed radiation by tumour are in the range 150–250 Gy while normal liver parenchyma receives average doses in the range 15–25 Gy, which are well tolerated by the liver [4, 38–40]. The principal adverse effect of SIRT relates to gastroduodenal ulceration from inadvertent delivery of microspheres to these structures which may occur in up to 5–10% of patients, depending on method of arterial delivery [33]. Fatal radiation hepatitis or radiation pneumonitis is very rarely seen with appropriate selection of cases and currently used dosing schedules.

We have previously conducted and published a study evaluating the utility of changes in tumour size (e.g., WHO and RECIST criteria) as a means to determine response following SIRT. In that study we demonstrated that changes in size, as conventionally assessed following chemotherapy are a very unreliable indicator of response to SIRT. We demonstrated and believe that providing tumours do not increase in size following SIRT, a response is likely to have occurred, and that tumour marker data, when available, is the most reliable and immediate indicator of response to therapy [41]. Based on this method of assessing response, all 14 of our patients with NET liver metastases responded positively to SIRT, and most for a protracted period of time. While it seems unlikely such a high response rate will be observed when larger numbers of patients are treated, the results certainly point to this being a valuable new treatment option.

At least three other reports of SIRT in metastatic NET tumours have been published and a number of other groups throughout the World have been using this approach with good results [7, 8, 42]. In a report on 34 patients from Australia, a symptomatic response was observed in 55% at 3 months and 50% at 6 months. Radiologic liver responses by RECIST criteria were observed in 50% of patients and included 18% complete responses and 32% partial responses. The mean overall survival was 29.4 ± 3.4 months [7]. In the second report from a number of contributing centres in the US, imaging revealed complete response in 2.7%, partial response in 60.5%, and stable disease in 22.7% with a median survival of 70 months [8]. In a report on 10 patients from Turkey a response rate of 90% was reported [42].

Our preference has been to deliver ^{90}Yttrium microspheres through a surgically implanted port in the hepatic artery because, in our experience, this permits whole-liver delivery of ^{90}Yttrium microspheres with less likelihood of gastro-duodenal ulceration than delivery through a percutaneous catheter because of the opportunity surgery presents for ligation of small arteries passing from the hepatic artery to the gastroduodenum [33]. In patients with a port, we also aim to follow the SIRT with 12 months of hepatic artery chemotherapy using 5 FU, as described for some patients in this report. While there is no clear evidence that this adds value to the SIRT in the setting of NET, it is accomplished with minimal, if any, side effects and may contribute to maintenance of a response.

5. Conclusion

Although metastatic NET is often thought of as having a slow natural history, active treatment is desirable, particularly in the presence of progressive disease or carcinoid syndrome. While a number of options including chemotherapy, TAE, TACE, and, more recently, PRRT have been used with some success, SIRT with ^{90}Yttrium microspheres is an emerging, simple, and effective alternative for selectively delivering radiotherapy to liver metastases. Our experience, and that of others, suggests this may be the treatment of choice for liver-only or liver-predominant NET. The time may be approaching for conducting a multicentre randomised trial comparing SIRT with TACE.

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Review Article

Multimodal Liver-Directed Management of Neuroendocrine Hepatic Metastases

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A preponderance of patients with neuroendocrine tumors (NETs) will experience hepatic metastases during the course of their disease. Many diagnoses of NETs are made only after the neoplasms have spread from their primary gastroenteropancreatic sites to the liver. This paper reviews current evidence-based treatments for neuroendocrine hepatic metastases, encompassing surgery, hepatic artery embolization (HAE) and chemoembolization (HACE), radioembolization, hepatic artery infusion (HAI), thermal ablation (radiofrequency, microwave, and cryoablation), alcohol ablation, and liver transplantation as therapeutic modalities. Consideration of a multidisciplinary approach to liver-directed therapy is strongly encouraged to limit morbidity and mortality in this patient population.

1. Introduction

Once considered extremely rare, neuroendocrine tumors (NETs), which include carcinoid tumors and pancreatic islet cell tumors, are increasing in incidence [1] and prevalence and likely remain underdiagnosed [2]. The disease course of these tumors is far from universally indolent, and metastatic involvement of the liver typically represents the greatest threat of morbidity and mortality posed by these malignancies. Regardless of their site of origin in the intestine, pancreas, or elsewhere, neuroendocrine carcinomas can compromise normal hepatic function when they spread to the liver parenchyma. Furthermore, midgut carcinoids, whose secretory peptides would ordinarily have been inactivated through enterohepatic circulation, can circumvent this first-pass clearance and then release vasoactive amines into systemic bloodflow, causing the carcinoid syndrome [3].

Pathologically, neuroendocrine carcinomas constitute a substantial fraction of noncolorectal metastases to the liver [4], and some of the techniques honed during management of oligometastatic colorectal disease have been applied to NETs. Survival after NETs metastasize to the liver is usually longer than the median survival times encountered in stage IV colon or rectal cancer and thus may provide a wider window of opportunity for intervention. However, the unique biology of NETs means that the principles applied to colorectal metastases cannot be fully extrapolated to management of this less common tumor type. For instance, neuroendocrine metastases tend to be more numerous and hypervascular, which may affect surgical decision making and lower the threshold for ablative approaches by interventional radiology [5].

2. Surgery

Surgery remains the treatment of choice. Neuroendocrine metastases are often well circumscribed and are less likely to encase or invade vascular and biliary structures than other malignancies which spread to the liver parenchyma, generally improving their resectability as a histologic group [5]. The aim of hepatic metastasectomy is removal of all gross tumor [6], but it is important to attempt cytoreduction, if feasible, even when total resection is not possible [7]. In the past, bilobar involvement or concerns about high recurrence rates meant many patients were not offered excisions of

their metastases. However, increasing experience with more extensive surgeries and the coupling of aggressive resections to favorable outcomes have expanded the modern criteria of operative eligibility [8].

Radiographic evaluation of the liver is mandatory for appropriate surgical planning. Although miliary dissemination of disease throughout the liver was considered unusual in the past [9], it is far from uncommon to encounter metastases of varying sizes in both hepatic lobes, and preoperative imaging and postoperative pathologic analysis alike can miss small lesions if the liver is not examined in sufficiently thin slices. An important study by Dromain and colleagues compared the relative sensitivities of MRI, CT, and somatostatin receptor scintigraphy (SRS, coupled to single-photon emission coupled CT) in detecting well-differentiated neuroendocrine metastases to the liver. 64 patients underwent each of these 3 imaging modalities in random sequence preprocedurally, and the pathology yielded by either liver biopsy or surgery was then compared to the radiographic findings. MRI detected 190 hepatic metastases missed by SRS and 69 missed by spiral CT. As such, liver MRI was recommended as the single most useful imaging modality in assessing the hepatic metastatic burden from NETs [10].

At least half of NET patients will have more than 50% of their liver replaced at the time metastases are first recognized [11], but the percentage of involvement of the hepatic parenchyma by tumor does not necessarily affect surgical outcome [12]. The resection of more than three segments of the liver is necessary in the majority of cases [13], with a goal of debulking 90% or more of the appreciable tumor burden [14]. In a retrospective univariate outcomes analysis by Saxena et al., of 40 patients undergoing concomitant resection and cryoablation, resection of 3 or more liver segments predicted for a poorer progression-free survival, but there was no difference in overall survival based on the number of segments resected [15]. In a separate retrospective single-institution series described by Saxena et al. of 74 patients undergoing resection of neuroendocrine metastases (of whom 38 underwent simultaneous cryotherapy), median postresection progression-free and overall survivals were reported at 23 and 95 months, respectively, with 40% postoperative 10-year survival; high histologic grade and extrahepatic disease were significantly associated with shorter survival [16]. 33 of the patients had their tumor necrosis status recorded as a binary variable; 9 of the 33 cases demonstrated tumor necrosis, which was significantly associated ($P = .047$) with poorer overall survival in univariate analysis. Suggested operative selection criteria (Table 1) thus include little to no extrahepatic disease, no indication of tumor necrosis, and well-differentiated (versus poorly differentiated) disease [15].

Operative planning must address the possibility of distant, nonprimary disease at the time when liver metastases are diagnosed. Among the available imaging modalities, octreotide scintigraphy may have the greatest utility in detecting or excluding extrahepatic disease [17]. This technique relies upon the binding of radiolabeled octreotide to the somatostatin receptor (especially subtype 2) expressed on the surface of the NETs in order to make tumors conspicuous during the nuclear medicine study. Pitfalls of this approach include high background uptake of the radioligand by abdominal organs, for example, the spleen, liver, kidneys, and gut lymphoid tissue, as well as variable tumor differentiation and receptor expression affecting homogenous binding of the octreotide at the site of disease [18]. There is also a lower limit of detection based upon tumor size, such that the radiolabeling most reliably highlights lesions at least 1 cm in diameter, so scintigraphy remains mostly adjunctive to other modes of disease visualization and is now seldom used without correlation to higher-resolution cross-sectional imaging [19]. A study by Montravers et al. of 30 French patients with well-differentiated NETs in the digestive tract suggested that histology should be factored into the selection of the optimal nuclear imaging modality. While they found that (111)In-pentetreotide scintigraphy did not differentially detect carcinoid versus noncarcinoid tumors (as defined by the 2000 WHO classification of NETs [20]), 18^{F}-fluorodihydroxyphenylalanine (^{18F}F-FDOPA) PET had a higher detection rate of carcinoid tumors, leading the authors to recommend PET over scintigraphy in the clinical contexts of detecting the primary carcinoid tumor, staging/restaging, and identifying otherwise-occult recurrences [21]. Focusing on the liver itself, Bechener et al. examined the relative utility of PET versus scintigraphy in assessing hepatic disease burden from both carcinoid and noncarcinoid NETs. In 17 patients later proven to have liver metastases, the sensitivity of ^{18F}-FDOPA PET was 81.3% versus 75% with scintigraphy, offering only a fractional benefit for the purposes of surgical planning. Moreover, the specificity of PET was lower than scintigraphy (85.7% versus 100%, resp.) due to false-positive hypermetabolism at the site of a metastatic lesion that had previously been embolized [22].

Carcinomatosis is a form of extrahepatic disease that can be particularly difficult to discern preoperatively, as tumor nodules usually have to be >1 cm in size to be reliably discernible on MRI, CT, or octreotide scintigraphy. Furthermore, the abdominal discomfort related to peritoneal involvement can be highly nonspecific and indistinguishable by history from pain related to the primary tumor. Ascites is a finding that raises the index of suspicion for carcinomatosis, but negative ascitic fluid cytology does not rule out peritoneal involvement. Minimally invasive staging laparoscopy can be particularly helpful in such cases and also allow visual

Table 1: Suggested eligibility criteria for resection of NET liver metastases.

No miliary disease on preoperative liver imaging (MRI or multidetector CT)
Little to no extrahepatic disease on preoperative nuclear medicine studies (^{18F}F-DOPA PET preferred over octreotide scintigraphy for carcinoid)
Well- or moderately differentiated neuroendocrine carcinoma (Ki-67 <20% and ideally, <15%)
Projected volume of residual functional liver >30%
No tumor necrosis

inspection of liver surfaces, adding to the assessment of the hepatic disease burden [23]. It should be noted that concurrent carcinomatosis is not an absolute exclusion criterion when considering patients for hepatic metastasectomy. In a multicenter French study, among 116 consecutive patients seen for digestive endocrine tumors, Vasseur et al. identified 9 patients with both liver metastases and peritoneal carcinomatosis; of the 5 deaths that occurred during their followup, 4 were related to the progression of liver metastases, and no death resulted from the peritoneal carcinomatosis. As such, the authors concluded (admittedly on the basis of a small sample size) that the presence versus absence of peritoneal involvement by the neuroendocrine malignancy did not affect survival, and that carcinomatosis should not detract from efforts to control more life-threatening liver involvement [24].

If there is concern that resection will result in insufficient residual liver volume, that is, <30% functional liver, portal vein embolization (PVE) can be performed about a month before surgery to induce hypertrophy of the parenchyma that will constitute the postoperative hepatic remnant [25]. Embolization of the right portal vein, for instance, can induce enlargement of the left hepatic lobe in cases where right hepatectomy is planned, especially if local ablative therapies will also be applied in the left lobe. The coupling of ablation (described in more detail below) to extended liver resection (±PVE) has expanded the eligibility of patients with bilobar disease to receive directed cytoreductive therapy.

In addition to preoperative imaging, closely evaluating the histologic characteristics of the NET constitutes an important step in surgical decision making. Tumor differentiation and the Ki-67 proliferative index are independent prognostic factors of survival and may influence the decision to pursue an operation. In a single-institution study of 63 consecutive patients presenting with NETs metastatic to the liver, Hentic et al. reported that the 18 patients with poorly differentiated NETs had a 5-year survival of 6%, markedly inferior to the respective 89% and 36% 5-year survival rates in cases of well-differentiated NETs with <15% and ≥15% Ki-67 indices. The median survival of the poorly differentiated cohort (who, by definition, had Ki-67 >20%) was 14 months, and only 1 of these 18 patients underwent resection (versus 15 of the 45 patients with well-differentiated NETs who proceeded to surgery). The authors concluded that, among their patients with well-differentiated NETs, Ki-67 carried more prognostic importance than the extent of liver involvement and postulated that an aggressive surgical approach likely explained the favorable survival rates in this cohort [26].

Although overall survival from NETs appears to worsen with hormonally active tumors versus their nonfunctional counterparts [1], survival after hepatic metastasectomy does not differ between functional and nonfunctional tumors [8]. While echocardiography is obviously an important component of preoperative assessment for carcinoid patients [27], it has been shown that even patients who have already progressed to carcinoid heart disease have slower declines in cardiac function and prolonged survival after resection of their hepatic metastases, so this subgroup should not be reflexively excluded from surgical consideration [28] (although perioperative consultation with cardiology is strongly advised). Indeed, NET patients with endocrinopathies may stand to experience greater symptomatic benefit and improved quality of life after their operations.

Outcome data from several trials examining neuroendocrine hepatic metastasectomy are summarized in Table 2. A 2009 Cochrane Database review of the published literature available at that time did not identify any randomized trials to compare surgical versus nonsurgical treatment of NET metastases to the liver, nor "any quasirandomised studies, cohort studies, or case-control studies that could inform meaningfully," but still concluded that surgery was apparently the mainstay of survival-prolonging management [29]. The tendency of the neuroendocrine tumors to reappear is a persistent problem [17] but should not create an attitude of surgical nihilism. Recurrence does not preclude the potential for initial cytoreduction to offer significant gains in symptom control and survival. The rates of recurrence seen at the site of resection may actually be lower in NETs than with other hepatic malignancies [6].

3. Hepatic Artery Embolization and Chemoembolization

Because liver metastases derive most of their blood supply from the hepatic artery, local devascularization offers a targeted approach that takes advantage of neoplastic hypervascularity, especially as healthy hepatocytes derive most of their blood supply from the portal vein. Selective tumor ischemia by occlusion of the hepatic artery, accomplished either through "bland" embolization using only particles of polyvinyl alcohol or through the augmented infusion of a chemotherapeutic slurry (such as doxorubicin/mitomycin) or microparticles [35], is an attractive strategy with which to diminish the NET metastatic burden and improve quality of life for patients who are not surgical candidates. The infusions are accomplished via a catheter inserted under fluoroscopic guidance into the celiac or mesenteric arteries and then advanced into the hepatic vasculature so that the interventional radiologist can select the downstream vascular territory to be embolized.

Response rates after embolization vary between 50 and 96% from study to study, depending partly upon which criteria of radiographic regression, symptom control, and/or biochemical improvement are used [36–40]. Median duration of response extends up to 18 months [5]. Low- and intermediate-grade neuroendocrine carcinomas are more likely to show a durable response to hepatic artery embolization (HAE) and chemoembolization (HACE), whereas the proliferative rate of high-grade neoplasms will usually outpace regeneration of normal hepatocytes, increasing the likelihood of recurrence and unfavorably shifting the procedure's risk:benefit ratio [41]. It is inevitable that, in spite of careful efforts to limit obstruction exclusively to the lesion's vascular supply, some normal hepatic parenchyma will be affected by embolization of even very distal vessels, and the "postembolization syndrome"—variably defined as the constellation

Table 2: Summary of outcomes from resection of neuroendocrine liver metastases. OS: overall survival; PFS: progression-free survival.

First author, publication year	No. of surgical patients	Median followup, months	Survival data	Predictors of survival
Mayo, 2011 [30]	339 [66 with simultaneous ablation]	26	Median OS: 123 months 5-year survival: 74%	Symptomatic high-volume [>25% liver involved] disease benefited most from surgery (versus intra-arterial therapy, $P < .001$)
Saxena, 2011 [16]	74 [38 with simultaneous cryoablation]	41	Median PFS: 23 months	Worse PFS with R1 (versus R0) pathologic margin status ($P = .023$)
			Median OS: 95 months	Worse OS from higher grade (well versus moderate versus poor differentiation, $P < .001$) and extrahepatic disease ($P = .021$)
Karabulut, 2011 [31]	27 [excluding subsequent liver transplants]	29	Median PFS: 15 months Median OS: 190 months	Margin status did not affect OS; in outcomes analysis including RFA and embolization, worse OS with male gender ($P = .04$), dominant metastasis >5 cm (versus <3 cm, $P = .04$), extrahepatic disease ($P = .03$)
Glazer, 2010 [32]	172 [120 with small bowel or pancreatic primaries; 18 had only RFA]	50	Median OS: 116 months 5-year survival: 77.4% 10-year survival: 50.4%	Increasing time interval from primary resection to hepatic metastases predicted for poorer survival ($P = .01$)
Sarmiento, 2003 [8]	170 [75 with complete resection]	Not reported (excluded <12 months followup)	Median OS: 81 months 5-year survival: 61% 10-year survival: 35%	No OS difference with or without endocrinopathy (60% versus 61% at 5 years, $P = .75$), no OS difference between carcinoid and islet cell (87 versus 66 months, $P = .058$)
Elias, 2003 [33]	47 [36 with concurrent extrahepatic resection]	62	Median OS: 91 months 5-year survival: 71% 10-year survival: 35%	Worse DFS with incomplete surgery (R2 versus R1 versus R0, $P = .003$), pancreatic origin ($P = .01$), bilateral liver involvement ($P = .01$); no factor predicted OS
Chen, 1998 [34]	15	27	5-year survival: 73% [versus 29% in 23 patients with unresectable disease]	Median survival not reached in resection group, but OS significantly longer than unresected ($P = .003$)

of elevated liver function tests, right upper quadrant pain, nausea/vomiting, and fever—should be anticipated with appropriate supportive care. A practice shift away from common hepatic artery occlusion or simultaneous bilobar treatment towards sequential, lateralized embolization of the left or right hepatic artery has decreased the incidence of fulminant hepatic failure after HAE and HACE [42, 43].

4. Radioembolization

Radioembolization is similar in principle to chemoembolization but uses radioactive microspheres of ytrrium-90 (^{90}Y) in combination with embolic agents [44]. Again, the hypervascularity of neuroendocrine metastases makes them amenable to this approach, as high-energy beta-particles can be preferentially delivered to heavily perfused tumors with relative sparing of normal liver parenchyma [41]. Theraspheres (MDS Nordion, Ottawa, ON, Canada) and SIR-Spheres (Sirtex Medical Limited, New South Wales, Australia) refer to proprietary radiopharmaceuticals that differ in the respective composition (nonbiodegradable glass versus biodegradable resin) and diameter (20–30 μm versus 20–60 μm) of their microspheres [44]. An MD Anderson study of 8 patients given SIR-Spheres for NETs (6 islet cell tumors, 2 carcinoids) delivered a median first radiation dose of 35.75 mCi. All 8 patients had disease that had previously been treated with HAE or HACE; the SIR-Spheres produced a partial response in 1 patient and stable disease in 4 patients, but 3 patients progressed [41]. The study provided proof of principle that the intermixture of radioactive and nonradioactive embolic agents does not preclude the possibility of response from neuroendocrine hepatic metastases, and higher response rates have been observed in other series; for instance, in a single-institution study performed upon 34 patients with nonresectable metastatic disease, King et al. described 50% or greater symptomatic and radiographic responses, with an 18% rate of complete response on imaging, and a mean overall survival of 29.4 months [45]. In the MD Anderson study, postembolization sequelae were considered more tolerable after radioembolization when compared to the after effects of HAE and HACE, but 3 patients developed abdominal pain

after the first ^{90}Y treatment that then prevented them from proceeding to a planned second treatment [41]. Another important distinction from HAE and HACE is that radioembolization patients should undergo preprocedural evaluation for hepatopulmonary shunts to ensure that no more than 20% of bloodflow is diverted to the lungs and to minimize extrahepatic delivery of yttrium [44]. Circulatory reflux into the gastroduodenal arteries also increases the risk of irradiation beyond target lesions in the liver. Pretherapeutic technetium-99m-(^{99m}Tc-) labeled macroaggregated albumin (MAA) scans can exclude these conditions [46]. Patients who are deemed untreatable on the basis of unacceptably high arteriohepatovenous shunting can actually have their shunts occluded through the temporary inflation of balloons within the hepatic veins, which may then enable radioembolization to occur more safely [47]. The risk of radiation pneumonitis and GI toxicity associated with radioembolization should be balanced against the potential benefit of the ^{90}Y beads as salvage therapy for unresectable liver disease, especially in NET patients for whom carcinoid syndrome is significantly detrimental to their quality of life [48].

5. Hepatic Artery Infusion

Hepatic artery infusion involves placing a pump inside the hepatic artery for the direct delivery of chemotherapeutic agents to the downstream vascular territories [44]. While this specialized technique is most often applied to the treatment of colorectal metastases, and even then only in tertiary care centers, it has rarely been used in the management of metastatic NETs, mostly as an adjunct to chemoembolization [49]. In a study by Christante et al., 77 patients with hepatic neuroendocrine metastases who progressed despite treatment with somatostatin analogues were treated either with HAI then HACE (59 patients), or with HAI alone (18 patients). The infusion regimen consisted of four monthly instillations of 5-fluorouracil. The overall response rate, measuring radiographic or symptomatic improvement, was 80%. Median progression-free survival was 19 months, with all patients initiating HAI when their hepatic disease first enlarged during octreotide therapy. However, the median disease-specific survival of 39 months was not clearly different from the outcomes of bland embolization or HACE without HAI [49]. Outcomes from various trials of intra-arterial therapy are reported in Table 3.

6. Thermal Ablation

Thermal ablative approaches to hepatic metastases rely on the cytotoxic effects of nonphysiologic temperatures that are focally induced within the liver by carefully placed probes. These instruments are designed to create extreme heat or cold, either of which can result in cell death, within a confined range of surrounding tissue. Radiofrequency ablation (RFA) and microwave ablation (MWA) are the most popular methods for inducing heat-related cell death [55]. Cryoablation, in contrast, produces damaging temperatures far below the freezing point of intracellular water. Ablation techniques can be applied in the setting of inoperable disease, or, at the surgeon's discretion, as a complement to resection, for example, to eradicate small foci of disease deep in the hepatic parenchyma with minimal disturbance to surrounding tissues and optimal preservation of residual liver.

In RFA, high-frequency current courses through an electrode, which is inserted in needle-like fashion into the target lesion under ultrasound or CT guidance, through percutaneous or laparoscopic approaches, or during laparotomy [55, 56]. Heat is generated after a change in the direction of the alternating current causes ionic vibration [57]. Intracellular proteins will denature and lipid bilayers will melt after fewer than two minutes above temperatures of 60°C, and the cells through which the radiofrequency electrical current passes directly can reach temperatures above 100°C, which boils the tissue and creates water vapor [58]; lower temperatures require longer exposure times, for example, eight minutes at 46°C are needed to induce coagulative necrosis of malignant cells through thrombosis of their microvasculature [58]. Beyond the zone of complete coagulation, tissue will be partly destroyed in a spherical distribution up to 0.8 cm in diameter. A single electrode can induce cell death up to 1.6 cm from the center of the tumor [59], and multiple electrodes can be deployed in an array to create a spherical burn beyond 5 cm in diameter [60]. Intraprocedural ultrasound can almost immediately assess the size of the necrotic zone to maximize the likelihood of adequate thermal damage to the site of known metastasis, which should, in theory, lower recurrence rates [61].

One of the largest prospective trials of RFA, which included 54 patients with unresectable hepatic metastases from carcinoid or islet cell tumors (as well as 9 patients with metastases from medullary thyroid carcinoma), and in which ablation was performed laparoscopically under ultrasound guidance, demonstrated a median survival of 3.9 years following the first ablation, and extrahepatic disease was not a criterion for exclusion. In measuring the diameter of the largest liver lesion targeted for ablation, 3 centimeters was an important cutpoint for predicting survival, with patients whose dominant lesions were at or above this threshold experiencing a median survival fewer than 3 years, whereas the median survival for patients with dominant lesions smaller than 3 centimeters had not been reached by the time the study concluded. Over 90% of patients reported postablation symptomatic improvement, and the median duration of symptom control was 11 months. Male gender was also significantly associated with poorer postablation survival, for reasons that were unclear [62].

In an even larger study, Mulier et al. performed a meta-analysis of 95 separate series describing the use of RFA in the control of liver tumors. The pooled data allowed the authors to examine the postablation outcomes of 5224 hepatic lesions of varying histologies. 11 of the 330 reported neuroendocrine metastases demonstrated recurrence, with a minimum follow-up period of 6 months, and this 3.3% rate of recurrence for NETs was the lowest among the different categories of pathology, that is, versus hepatocellular carcinoma and metastases from colon, breast, and unspecified

Table 3: Summary of outcomes for intraarterial therapy of neuroendocrine liver metastases. HAE: hepatic artery embolization; HACE: hepatic artery chemoembolization; HAI: hepatic artery infusion; OS: overall survival.

First author, publication year	No. of embolized patients	Survival data	Comments
Paprottka, 2011 [50]	42 [^{90}Y radio-embolization]	40 of 42 patients alive with mean followup of 16.2 months	36 of 38 symptomatic patients had clinical improvement within 3 months
Dong, 2010 [51]	123 [HACE]	Mean OS: 39.6 months 5-year OS: 36% 10-year OS: 20%	Baseline albumin <3.5 g/dL was a multivariate predictor for poorer OS ($P = .003$)
Kennedy, 2008 [52]	148 [^{90}Y radio-embolization]	Median OS: 70 months	No radiation-induced liver disease or failure, even with retreatment
Christante, 2008 [49]	77 [18 HAI alone, 59 HAI + HACE]	Median OS [HAI alone]: 26 months Median OS [HAI + HACE]: 39 months	All 10 patients with nonfunctional neoplasms and 15 of 16 patients with islet cell neoplasms died within 5 years
Strosberg, 2006 [53]	84 [HAE]	Median OS: 36 months	Fewer symptoms in 44 of 55 patients
Gupta, 2005 [54]	123 [74 HAE, 49 HACE]	Median OS [carcinoid]: 33.8 months Median OS [islet cell]: 23.2 months	Male gender predicted worse OS ($P = .05$) for carcinoid, bone mets predicted worse OS for islet cell ($P = .03$)

primary tumors. Indeed, in univariate analysis, neuroendocrine histology was a tumor-dependent factor significantly associated with a lower likelihood of local recurrence, along with smaller size (<3 cm versus 3–5 cm and >5 cm), a nonsubcapsular (versus subcapsular) location, and distance from a major vessel. When these factors were subjected to multivariate analysis, however, only a small size of the ablated lesion was significantly associated with lower recurrence, with Mulier and colleagues commenting that the minimum postablation followup of 6 months may have been a too short interval and thus underestimated the recurrence rate in NETs with a slower mean natural growth rate [63].

Microwaves are a nonionizing form of radiation that causes extremely rapid oscillation of the water within tissues, with dipolar reversals occurring a billion times per second. Friction from the fluctuation of intracellular water molecules generates heat, which in turn leads to coagulative necrosis [64]. The intratumoral temperatures of MWA are consistently higher than can be achieved with RFA [65]. Also, as opposed to the mostly passive conduction of heat in RFA, in which the "heat sink" effect of relatively cool nearby bloodflow can result in incomplete ablation of tumors close to the larger hepatic vessels, the MWA method involves active heating that may be more appropriate for targeting tumor sites next to major hepatic vasculature [55, 64]. As in RFA, a probe is placed into the target lesion under radiographic guidance or during open surgery. Multiple lesions can be ablated during the same procedure. The clinical experience with MWA has, to date, mostly involved treatment of hepatocellular carcinoma, but neuroendocrine tumors have been included in some series. Martin et al. described that, of 100 patients undergoing MWA for primary or secondary hepatic tumors at their institution during a 5-year period, 11 had neuroendocrine pathology. A 90% success rate for complete ablation was reported for carcinoid tumors, with no recurrences at the ablation sites. The authors noted that the multiplicity of lesions in metastatic carcinoid, as well as the intraprocedural difficulties of locating all the tumors seen on preprocedural CT, prevented achievement of a 100% complete ablation rate [65]. It is important to recognize that the majority of these patients had MWA performed under ultrasound guidance during open surgery, that is, concomitant hepatectomy and/or extrahepatic metastasectomy [65]. There is still a paucity of data comparing MWA (especially performed percutaneously) to RFA for management of NETs in the liver.

Cryoablation is the most mature thermoablation technique, having first been proposed in 1851 [66]. Cell viability is decreased at low temperatures, depending partly on the rate of cooling and the spatial relationship to ice formation around the cryoablation probe [67]. While cryogenic temperatures can both preserve and destroy tissue [68], the primary determinant of cell death is the depth of the lowest obtained tissue temperature, which should be -50°C to achieve necrosis in neoplastic tissue [69]. In addition to near-immediate mechanical injury caused during a freeze by ice crystals disrupting their membranes and organelles, cells can die during the thaw and postthaw periods due to disrupted vascular supply or due to cold-activated endonucleases triggering an apoptotic response [68]. However, malignant cells may be more resistant to lethal damage from freezing compared to hyperthermia [58], and some studies have reported higher complication and recurrence rates when cryoablation is compared against heat-based therapies [55]. Seifert et al. described a series of 13 patients with NETs who underwent hepatic cryotherapy; in each case, the cryoprobes were inserted under ultrasound guidance, and freezing was monitored until the ball of ice extended beyond the tumor for 1 cm in all directions. 12 of 13 patients had complete ablation of all visible tumors, with 2 recurrences at the ablation sites and 12 survivors at 1 year of followup. All 7 patients who had hormonally related symptoms prior to cryotherapy experienced palliative benefit. 2 patients developed a postprocedural coagulopathy requiring intra-abdominal packing

Table 4: Summary of outcomes for ablation of neuroendocrine liver metastases. DFS: disease-free survival; MWA: microwave ablation; NET: neuroendocrine tumor; OS: overall survival; PFS: progression-free survival; RFA: radiofrequency ablation.

Author, publication year	No. of ablated patients	Median followup, months	Survival data	Comments
Karabulut, 2011 [31]	68 [RFA]	22	Median PFS: 10.5 months Median OS: 73 months	No significant overall survival difference between RFA and resection
Akylidiz, 2010 [71]	89 [RFA; 78 with NETs of GI origin, 11 medullary thyroid cancer]	30	Median DFS: 15.6 months Median OS: 72 months	Liver tumor volume (>76 cc versus <30 cc, $P = .04$), symptoms (present versus absent, $P = .04$), extrahepatic disease ($P = .02$)
Martin, 2010 [65]	11 [MWA; 7 with concomitant hepatectomy; 6 with concomitant extrahepatic resection]	36	Median DFS: 8 months Median OS: 18 months	Zero recurrences at ablation site
Mazzaglia, 2007 [62]	63 [RFA; 24 with extrahepatic disease at time of 1st ablation; 9 patients with medullary thyroid cancer]	34	Median OS: 47 months after 1st RFA 5-year survival: 48%	Male gender [3x mortality risk of female] ($P = .04$), largest tumor >3 cm ($P = .03$)
Seifert, 1998 [70]	13 [cryoablation]	13.5	12 patients alive at the end of followup (up to 103 months)	All 7 symptomatic patients had subjective improvement
Shapiro, 1998 [72]	5 [cryoablation]	30	1-year survival: 60% 2-year survival: 40%	All 5 patients had relief of carcinoid syndrome

and the transfusion of clotting factors. The authors had not observed similar bleeding complications when applying their cryosurgical techniques to patients with hepatocellular carcinoma and speculated that the necrosing carcinoid tumors were releasing substances into circulation that disrupted the coagulation cascade. All patients demonstrated thrombocytopenia two days after the procedure [70]. In a larger series by Bilchik et al. of 17 patients undergoing hepatic cryosurgery for NETs, all patients demonstrated a transient coagulopathy, requiring transfusion of either platelets or fresh frozen plasma (with an average infusion of 4 units per procedure) [66].

Outcomes for various studies of ablative therapies in the setting of NETs metastatic to the liver are summarized in Table 4.

7. Alcohol Ablation

Ultrasound-guided injection of ethanol, otherwise known as percutaneous alcohol injection (PAI), into neuroendocrine metastases has been described in multiple series [75, 76], none of which were histologically exclusive to NETs. A 1994 report by Giovannini and Sietz included 5 NETs among 40 patients with various pathologies undergoing PAI, and complete necrosis rates in carcinoid tumors were inferior to the responses seen in colorectal metastases [73]. Nonetheless, PAI could be an advantageous technique over RFA when tumors are located next to large vessels that would be vulnerable to the "heat sink" effect, or in proximity to central bile ducts that tend to stricture in response to heat [5]. Lesions chosen for ethanol ablation are necessarily less than 5 cm in diameter and the cubic volume of alcohol injected requires modeling the target tumor as a sphere, but these estimations are more likely to be accurate when the radius is shorter, and very small metastases can be ablated with minimal collateral damage to the surrounding liver [5]. In a smaller study by Livraghi et al., in which 2 of 14 patients with liver metastases had neuroendocrine carcinoma, the patients demonstrated a complete response after ablation of 4 lesions smaller than 3.1 cm [74]. Thus, PAI is best used not as monotherapy but rather as an adjunct to newer ablative techniques when approaching tiny or inauspiciously located metastases [5, 75]. All of the ablation methods are summarized in Table 5.

8. Liver Transplantation

On its list of indications for orthotopic liver transplantation, the United Network for Organ Sharing (UNOS) includes "metastatic neuroendocrine tumors (carcinoid tumors, APUDomas, gastrinomas, glucagonomas) in persons with severe symptoms and with metastases restricted to the liver, who are unresponsive to adjuvant therapy after aggressive surgical resection including excision of the primary lesion and reduction of hepatic metastases." However, the published experience with liver transplantation for NETs remains limited, and fewer than 300 unique cases are described in the literature [80]. A meta-analysis of 20 studies encompassing 89 patients transplanted for metastatic pancreatic NETs

Table 5: Summary of liver-directed ablation modalities.

Ablation technique	Mechanism of tumor injury	Maximum size of target lesion	Comments/caveats
RFA	Heat	1.6 cm: single electrode 5 cm: array	Prone to heat sink from adjacent vessel, ↓ control for lesions >4 cm
MWA	Heat	2 cm: single needle 4 cm: parallel needles	Less prone to heat sink, but fewer supportive data than RFA
Cryoablation	Cold	4 cm: single needle 6 cm: multiple needles	↓ control for lesions >4 cm, risk of ↓ platelets and coagulopathy
Alcohol	Toxic	4 cm	Adjunctive only

Table 6: Summary of outcomes for liver transplantation for neuroendocrine metastases. OS: overall survival.

Author, publication year	No. of liver transplant (LT) patients	Survival data	Predictors of survival
Gedaly, 2011 [76]	150 [13 receiving another organ at time of LT]	49% 5-year survival [excluding multiple organ transplants]	Regardless of age, improved survival (>60% at 5 years) for patients waiting more than 2 months for transplant ($P = .005$)
Mathe, 2011 [77]	89	44% 5-year survival	Worse survival with recipient age >55 ($P = .0242$) and simultaneous LT-pancreas resection ($P = .0132$)
Rosenau, 2002 [78]	19	80% 5-year survival 50% 10-year survival	Ki-67 <5% and normal E-cadherin expression had 100% 7-year survival (versus 0% when Ki-67% >5% or aberrant E-cadherin expression, $P = .007$)
Le Treut, 2008 [79]	85 [34 with concurrent extrahepatic resection]	Median OS: 56 months	Exenteration ($P = .0034$), a duodenopancreatic primary ($P = .0018$), and hepatomegaly ($P = .0157$), all predicted for poorer survival

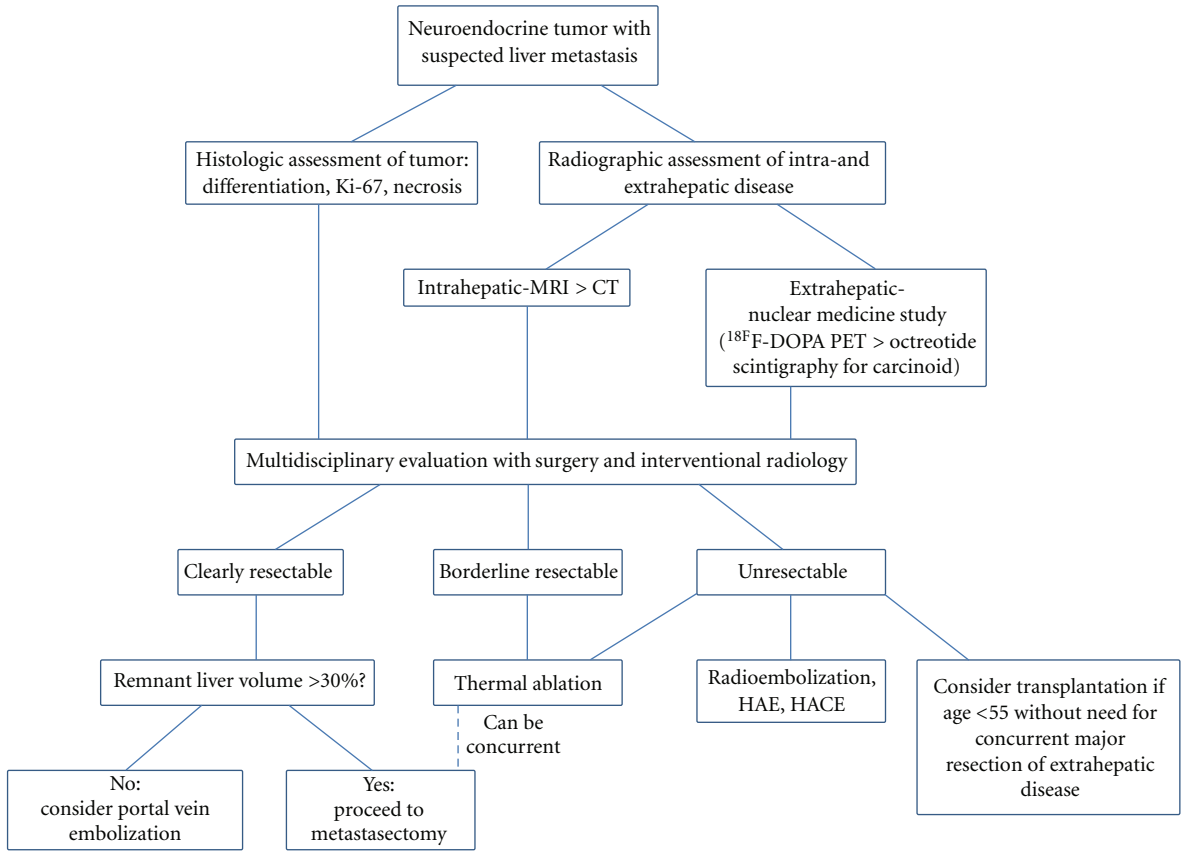

Figure 1: Liver-directed treatment algorithm for neuroendocrine hepatic metastases.

reported cumulative 1-, 3-, and 5-year survival rates of 71%, 55%, and 44%, respectively. Recurrence-free survivals were 84%, 47%, and 47% at the same respective time points. If patients were 55 years old or younger and were not undergoing simultaneous pancreatic resection, then their predicted 5-year survival was 61%. Conversely, a 0% 5-year survival rate was prognosticated for patients older than 55 who were undergoing resection of the primary pancreatic lesion at the same time as transplantation [77]. The largest single-center experience with liver transplantation for NETs reports a 10-year survival rate of 50% among 19 patients. 12 patients recurred, within 2 weeks to 48 months from the date of transplant. 3 patients had recurrence-free survivals beyond 8 years. 7-year survival was 100% in the 5 patients with Ki67 in less than 5% of their tumor cells and normal expression of E-cadherin, that is, positive membrane and absent cytoplasmic staining [78]. A multicenter French study pooled 85 cases of liver transplantation performed for NETs between 1989 and 2005. 34 of the patients underwent concurrent resection of extrahepatic disease, which in 7 cases required upper abdominal exenteration (resection of the pancreas, spleen, stomach, and duodenum, with 3 patients receiving en bloc composite liver-duodenum-pancreas grafts). Concomitant exenteration had the strongest association with death in multivariate analysis (RR: 3.72, 95% CI: 1.54–8.95, $P = .0034$), with 0% 3-year survival and a median survival of 1.5 months, whereas the median survival among all patients was 56 months. Excluding exenteration, the most important prognostic factors were a duodenopancreatic location of the primary tumor and hepatomegaly (≥120% standard liver volume in the explanted organ); the 23 patients with both of these attributes had a 12% 5-year survival versus 68% 5-year survival among the 55 patients with only one or neither of these factors [79]. Clearly, the decision to transplant a patient with neuroendocrine carcinoma metastatic to the liver requires careful consideration of numerous clinicopathologic variables, and mortality is higher in older individuals requiring concurrent disease resections. Outcomes for studies of liver transplantation for involvement by metastatic NETs are summarized in Table 6.

9. Conclusion

The unique tumor biology of neuroendocrine carcinomas presents disease-specific challenges when hepatic metastases occur [81], but some characteristics of these neoplasms lend themselves to management with liver-directed therapy. Medical oncologists should work in multidisciplinary fashion with surgeons and interventional radiologists to assess the potential utility of these organ-focused techniques in series with exciting advances in systemic management of NETs, such as peptide receptor radionuclide therapy (PRRT) [82] and promising chemotherapeutic agents like sunitinib [83] and everolimus [84]. It is beyond the scope of this review of liver-directed therapy to adequately address PRRT and chemotherapy, but, in conclusion, we propose the algorithm shown in (Figure 1) for approaching neuroendocrine hepatic metastases.

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Review Article

Treatment of Liver Metastases in Patients with Neuroendocrine Tumors: A Comprehensive Review

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Patients diagnosed with Neuroendocrine Tumors (NET) often are also diagnosed with Neuroendocrine Liver Metastases (NLM) during the course of their disease. NLM can cause significant morbidity and mortality, oftentimes much more than compared to patients with NET. Treatment options have been limited in the past, focusing on surgical resections, for which only a minority of patients are candidates. However, developments of new treatment modalities have progressed rapidly and patients with NLM now have significantly more options, including surgical-directed therapies; liver-directed therapies; and nonsurgical, non-liver-directed therapies. This review provides information about the roles of hepatic resection, orthotopic liver resection, radiofrequency ablation, hepatic artery embolization and hepatic artery chemoembolization, hepatic artery radioembolization and selective internal radiation therapy, peptide receptor radionuclide therapy, systemic chemotherapy, biotherapies including somatostatin analogs and interferon-α, vascular endothelial growth factor and mTOR targets, and microRNA-regulated pathways. Given these new options, the clinician can tailor therapy specific to the patient diagnosed with NLM, thereby giving the patient the best possible chance of prolonged survival.

1. Introduction

Patients with Neuroendocrine Tumors (NETs) often suffer from Neuroendocrine Liver Metastases (NLMs) causing significant morbidity and mortality. The excess hormone production, the multitude of hepatic lesions, and ultimate liver disease lend to the poorer prognosis. In fact, 46%–93% of patients with NETs will find NLMs involved at the time of diagnosis [1]. Patients with liver metastases have a significantly worse prognosis than those without liver involvement. The 5-year survival of patients with NLMs on supportive care is 0%–20% [1–3]. This dismal prognosis paints a much more stark reality for a pathological process often described as "indolent". Surgical interventions for NLMs have consistently been shown to have superior outcomes to nonoperative therapies. Resection alone is supported by favorable long-term outcomes in large retrospective trials [2]; however, complete surgical extirpation is an option for a very small percentage of the neuroendocrine cancer patient population [1]. Due to excessive metastatic tumor burden in difficult locations, surgical resections are limited to only 10% of these patients [2]. Treatment options for patients that are not surgical candidates have evolved over the last several years. Use of ablative techniques, as well as development of new medical therapies, has expanded the treatment options for the majority of patients with NLMs.

2. Surgical-Directed Therapies

Surgery remains the only potential for cure in patients with NLMs. Even in the setting of incurable disease, surgery offers the best chance for prolonged survival. In patients treated with resection, the five-year survival has been shown to be greater than 60% [4, 5] and even approaches 80% in some studies, with minimal mortality (<5%) and morbidity (<30%) [6]. A precise review of the literature available on patients who undergo liver resection for neuroendocrine

tumors is difficult due to the small number of patients who are candidates and the varied approaches to surgical treatment [7]. Historically, patients were selected to undergo palliative resection if greater that 90% of the tumor burden could be excised [8]. One of the earlier prospective studies concluded from their study of 47 patients that hepatic resection is indicated only when all gross disease can be removed safely. In this study, they determined that number, size, and location of primary tumor were less important than the completeness of resection. Patients that underwent a complete resection had a 5-year survival of 80%. However, the patients that underwent an R1 resection had a 5-year survival of 70% and R2 resection still had a 5-year survival of 60%. Although patients in this study were included only if it appeared that they could be completely resected, patients that had incomplete resection still did well [9]. Several other series have reported similar results [4, 6]. A more recent retrospective review of 74 cases demonstrated a greater than 60% 5-year survival in all patients that underwent resection [10]. Only 65% of these patients had all gross disease completely excised.

Although an aggressive surgical approach is considered to prolong survival and contribute to better symptom control, the criteria for patient selection are ill defined. In an effort to identify variables that have prognostic relevance to patients who undergo hepatic resection, a prospective review of 70 patients' outcomes was performed based on tumor grade. The tumors were categorized as low grade (<2 mitotic figures/50 hpf and no necrosis), intermediate grade (2–50 mitotic figures/50 hpf and/or focal necrosis), and high grade (>50 mitotic figures/50 hpf and/or extensive necrosis). The majority of the neoplasms were considered low grade (37) or intermediate grade (26). Only 7 were shown to be high grade. The overall 5-year survival rate was 61%. None of the patients with high-grade malignancy survived 5 years with a median survival of only 6 months [7]. The importance of tumor grade to patient's outcomes after resection has been confirmed by several investigations [10, 11].

Tumor size, number, and location have also been shown to influence postresection survival [4, 12]. In 2008, the ENETS proposed guideline for surgical resection based on the 3 distinct patterns of liver involvement: (1) "simple" pattern of metastasis located in one or two contiguous lobes (20–25%), (2) "complex" pattern where there is one major focus and other lesions are contained in the contralateral lobe (10–15%), and (3) "diffuse" disease in both lobes (60–70%) [13]. The type of surgical resection is based on the patient's overall medical condition, size, number, and location of lesions, and adequacy of remnant liver size/function. In patients with the simple pattern of disease, an anatomic resection is adequate to completely resect all disease. Patients with the complex pattern of disease can be treated with several different methods. An anatomic lobectomy can be performed for the majority of the disease and either a wedge resection or locally ablative therapy can treat the remainder of the tumors. Staged, multiple surgical procedures have also been shown to be beneficial with little increase in morbidity and mortality [13].

The majority of patients with "diffuse" disease are not candidates for resection. Cytoreductive surgery can be helpful for a small, select group of patients. It is usually recommended only in cases where >90% of the tumor volume can be excised or in very young patients [12]. In patients that are symptomatic, cytoreductive surgery has been shown to improve or alleviate their symptoms for a prolonged period of time. In addition, tumor debulking may also increase the effectiveness of medical therapy.

It has been estimated that less than 20% of patients with metastatic neuroendocrine tumors are candidates for hepatic resection [14]. Resection is not a viable option for the majority of patients with diffuse hepatic disease. Based on their slow growth and good response to resection, liver transplantation has been tried in an attempt to cure, prolong survival or control symptoms. Although many centers are reluctant to allocate liver allografts to patients with metastatic disease, liver transplantation for neuroendocrine tumors is one of the only accepted indications for transplant in the setting of metastatic disease. In 1998, Lehnert analyzed a total of 103 patients transplanted for metastatic neuroendocrine carcinoma. The overall 5-year survival was 47%, and disease-free survival was 24%. Tumor histology or location of primary did not appear to effect survival in this study. However, extent of surgery at the time of transplantation and age of recipient were significant prognostic factors for survival [15]. A more recent retrospective study was performed in 2008. 85 patients were identified who underwent OLT for metastatic neuroendocrine carcinoma in France. The overall 5-year survival was comparable at 47% and disease-free survival of 20% at 5 years. In this study, primary tumor location in the duodenum or pancreas was noted to be an indicator of poor prognosis [16]. This finding was not supported in several other investigations [2, 17]. One of the larger single center studies attempted to analyze tumor biology in relation to postliver transplant outcomes. These authors studied Ki-67, E-Cadherin, and p53. Based on evaluation of 19 cases, they demonstrated that patients with a low Ki-67 (<5%) and normal E-Cadherin staining did significantly better than patients with high Ki-67 or abnormal E-Cadherin expression. Expression of p53 did not appear to influence survival [18].

Analysis of the United Network for Organ Sharing database reveals that between November 1988 and March 2011, only 185 liver transplants were performed for metastatic neuroendocrine tumors in the United States. The overall 5-year survival was 57.8%. This is significantly worse than the 74% 5-year survival for all other patients. Although the long-term survival is not comparable to other patients with benign disease, most liver transplant programs will consider evaluating patients with NLMs. Many liver transplant programs will consider a patient with metastatic neuroendocrine for liver transplantation if the following criteria are met:

(1) not a resection candidate,

(2) identification and complete resection of primary malignancy at least one year prior to evaluation,

(3) no evidence of extrahepatic disease demonstrated on cross-sectional imaging or nuclear medicine scan,

(4) evidence of stability of disease for at least one year,

(5) failure of nonoperative treatments.

Liver transplantation for metastatic neuroendocrine tumors remains controversial. This radical treatment occasionally provides a cure, but the long-term survival is still significantly less than in patients transplanted for other diseases. It can prolong survival and provide symptomatic relief in a very small subset of patients. Patients that are younger than 50 years in the setting of low Ki-67 and E-Cadherin expression with symptoms that are difficult to control appear to benefit the most from liver transplantation.

3. Liver-Directed Therapies

NETs are predisposed to form highly vascular metastatic lesions in the liver and derive more than 90% of their oxygenation and nutrition from the hepatic artery. Thus, the hepatic artery offers a viable mode of introducing directed chemotherapy and/or creating an ischemic environment. This effectively starves the tumors of their nutrient and oxygen supply while sparing healthy hepatic cells, which derive the majority of their nutrient and oxygen supply from the portal venous system. Several ablative techniques have been developed that exploit the dual blood supply of the liver in an effort to control the disease process.

Defining the treatment best suited for the tumor load is dependent on number and location of the lesions, invasiveness and size of the tumor, physiology and effects of hormone secretion, and extent of metastatic disease within the patient. This is in conjunction with the ultimate goals of cure or palliation. Considering the rate of recurrence, liver-directed therapies have been considered more as debulking modalities. In a review of the literature, general guidelines for the treatment pathways are: for fewer nodular liver metastatic lesions, local resection or thermal ablation is recommended; for a higher-tumor load due to unresectable multinodular disease or recurrent disease after resection, hepatic artery embolization, hepatic artery chemoembolization, or radioembolization is warranted [19]. These modalities are also useful as "neoadjuvants" to decrease the size of previously unresectable metastatic disease. Unless 80%–90% of the tumor load is debulked, treatment does not serve useful as palliation therapy to prolong survival and improve symptom control [20].

3.1. Radiofrequency Ablation. Radiofrequency ablation (RFA) uses an image-guided technique, percutaneous, laparoscopic, or open, to provide local control with short-term symptomatic relief [21] by subjecting tumors to intense, destructive heat using an alternating electric current. This technique is amenable to patients with fewer liver metastases who are ineligible for hepatic resection. It is used as a single modality, often more than once, or as an adjunct to other NLMs therapies for debulking.

The largest study to date, with the longest followup, was done at the Cleveland Clinic [21], a prospective trial of 89 patients with NLMs who underwent 119 laparoscopic RFA sessions in total. Ninety-seven percent of the sample immediately felt improvement of symptoms after the procedure, where median disease-free survival was 1.3 years and overall survival at 6 years after RFA [21]. Of note, 22% of this sample developed local recurrence, with 63% developing new lesions and 59% developing extrahepatic disease.

Prior to that study, Mazzaglia et al. investigated a series of 63 patients who had a total of 452 treated NLMs lesions. Symptoms were controlled an average of 11 ± 2.3 months after RFA, with greater than 90% of symptomatic patients experiencing relief immediately after procedure. Mean survival extended 3.9 years after the first RFA treatment. Larger dominant tumor size (>3 cm) and male sex were significant variables negatively correlated with survival [22].

A United Kingdom group describes RFA of 189 lesions in 25 patients. Median survival of the group was 53 months from liver diagnosis. Of those with radiologic followup, 74% of patients were noted to have tumor load control at a median of 21 months after the procedure. This meant complete, partial, or static tumor response to RFA. Hormonal treatment has also been used as an adjunct to improve symptomatic relief, though not improve survival. Adjuvant octreotide has been shown to extend median symptom-free duration from 16 to 60 months [19]. It has not, however, been proven to increase survival.

Morbidity for radiofrequency ablation of liver metastases has been reported in the larger studies to be approximately 5% to 12%, with 30-day mortality at 0% to 1%. [21, 22] The complications can include carcinoid crisis, liver abscesses, biliopleural fistulas, bile leakage, and pleural effusion, as well as postablation syndrome, and liver failure.

3.2. Hepatic Artery Embolization and Hepatic Artery Chemoembolization. Capitalizing on the dual blood supply of the liver enables a transarterial approach to the hepatic lesions of neuroendocrine metastases. Hepatic artery embolization (HAE) induces ischemia within the tumor, using a variety of agents such as cyanoacrylate, gel foam particles, polyvinyl alcohol, and microspheres. Indications for HAE or hepatic artery chemoembolization (HACE) generally include unresectability with symptoms related to tumor bulk, excessive hormone production, and rapid progression of liver disease [3]. HAE has been shown to improve biophysical markers, palliate symptoms and reduce tumor burden by radiographic evaluation [2, 23]. Because of the observation that higher disease regression rate and longer length of regression with systemic chemotherapy after HAE was published [24], chemotherapy has been added to the embolic agents, and HACE is now generally favored over HAE. HACE, also known as transarterial chemoembolization, combines the hepatic artery embolization with the hepatic artery chemoinfusion where the microspheres are bound to chemotherapy agents, which are then injected into the hepatic artery to lodge downstream within capillaries. Not only do the emboli block the blood supply causing

ischemic necrosis, but the chemotherapy agents are localized within the region of the metastatic lesions, creating a much more concentrated effect (up to 20 times greater) than systemic chemotherapy alone [22] as well. Despite this theoretical advantage, little evidence has suggested a significant difference in the outcomes of hepatic artery embolization versus hepatic artery chemoembolization. In a review of the literature, HACE has shown a 5-year survival between 50% to 65% whereas HAE has a 5-year survival between 40% to 67% [24]. In one study of 100 patients with NLMs who received HACE or HAE, the authors found no difference in overall survival, median survival after diagnosis of metastatic disease, or median survival after first embolization [25]. On univariate analysis, the only predictor that significantly improved survival was concurrent resection of the primary tumor, which increased median survival from 28.0 months to 73.1 months [25]. Contrary to this study, Ho et al. reported results on 46 patients with NLMs who received HACE or HAE, and showed that there was no statistically significant survival benefit in a small subset of population that also had resection of the primary tumor, although mean survival after resection increased by a mean of 558 days [26]. Regardless, these therapies have increased versatility as reflected in a study of 48 patients and 123 treatment sessions which revealed HACE or HAE could even benefit carefully selected patients with a tumor load of greater than 75% liver involvement, so long as the patients did not have additional risk factors [27]. Having said this, a number of reports reveal worse outcomes for patients with greater than 50% liver involvement [28, 29]. This is tempered by the fact that extent of liver involvement did not serve as an independent prognostic indicator [3]. In order to mediate the complications arising from disease which takes up the bulk of the liver, it is recommended to divvy small portions of the liver for treatment during each session.

There are adjuvants to HACE or HAE in those patients with severely limited therapeutic options to improve otherwise bleak outcomes, and HACE or HAE can be used as adjuvant therapy to other treatments. Adding hepatic artery chemoinfusion (HAI) to HACE offers an increased probability of clinical benefits to those with unresectable, refractory disease, as presented in a study of 77 patients [30]. The response rate was 80% of islet and carcinoid tumors with a median progression-free survival of 19 months. 1- and 5-year survival rates were 78% and 27% [31]. Of the different types of neuroendocrine tumors, carcinoid tumors seem to consistently have better outcomes to the combination of HACE and HAI [21, 23, 30]. Although studies on patients with NLMs are limited, in one study of 32 patients with hepatocellular carcinoma, the authors found that there was no survival advantage in patients with preoperative HACE prior to surgical resection [32]. In fact, the recurrence-free survival rates were statistically higher, and cumulative recurrence rates were statistically lower at 1, 2, and 5 years compared between the two groups [32]. One study from Iowa on patients with NLMs showed that preoperative HACE followed by OLT can result favorably for the patients with progression-free intervals up to 29 months, but this was a small study, and statistical inferences could not be made due to the inclusion of only four patients [33]. Along a different treatment strategy, Hao et al. showed that survival improved when patients with hepatocellular carcinoma received combination therapy with HACE plus thalidomide versus HACE alone [34]. This improvement reached statistically significant improvement, resulting in median overall survival increases of 15 months [34]. Similarly, in an experimental model utilizing liver tumors in rabbits, favorable outcomes resulting in significantly decreased vascular endothelial growth factor and microvascular density levels were achieved when HACE plus antiangiogenic therapies were used [35]. However, tumor size was not significantly different between these two groups [35].

An important point of HACE or HAE is that response can be incomplete as the periphery of the tumor is spared from ischemia or chemotherapy. With proximal embolization of arterial branches feeding the tumors, peripheral hepatic collaterals reconstitute quickly, requiring repeated embolizations to complete the necrotic process [24]. Multiple sessions are usually needed.

As all other procedures, there are risks involved with liver-directed therapy through the hepatic artery. Liver abscesses, transient liver failure with or without encephalopathy, carcinoid crisis, pleural effusions, and postembolization syndrome (i.e., fever, abdominal pain, leukocytosis, and transient increases in hepatic enzymes and bilirubin) are some of the more common and worrisome. Relative contraindications for these procedures include coagulopathy, renal failure, portal vein occlusion, and liver failure.

3.3. Hepatic Artery Radioembolization and Selective Internal Radiation Therapy. Limited effective strategies exist for the treatment of inoperable, refractory NLMs. Interest in one particular liver-directed therapy is under further investigation for this indication: hepatic artery embolization (HAR), also known as selective internal radiation therapy (SIRT). SIRT acts by delivering microspheres of glass or resin, labeled by ^{90}Yttrium (^{90}Y) to deliver radiation directly into the hepatic artery. Rather than using peptides to localize the lesions, this therapy mechanically targets the metastases and lodges within the nutrient-supplying capillaries, thereby delivering radiation therapy. While this modality has been tested in a limited number of NETs patients, the results thus far have shown promise [31, 36–38].

Saxena et al. have been investigating the safety and efficacy of treatment with ^{90}Y radioactive microspheres for patients with unresectable NLMs. In this study, 34 such patients were treated with SIRT to achieve long-term responses with a mean overall survival of 29.4 ± 3.4 months, and radiological improvement in 50%. Biochemical marker levels of chromogranin A fell in nearly 50% of survivors by 30 months [31].

In one multicenter retrospective review by Kennedy et al., 148 patients with NLMs were followed after radioembolization with ^{90}Y [38]. This study reports favorable results with radiological response in 63.2% of patients, stable disease in 22.7%, and progression of disease in only 4.9% [38]. The authors state that one of the largest benefits of this treatment

is the stabilization of extensive disease allowing for longer survival periods [38].

Another recent publication investigated 48 patients who underwent similar treatment [37]. Radiographic and serology studies revealed median survival of 35 months with a followup of 41 months, and 55% of patients had complete or partial responses [37]. Less than a quarter of the sample had progressive disease [37]. Prognostic factors were assessed, and 6 of significance were found to influence survivorship: complete/partial response, low hepatic tumor burden, female gender, well-differentiated tumors, and absence of extrahepatic metastases [37]. This was important in identifying a subset of the NLMs patient population who would be best served by this newer technique.

The complications of radioembolization include abdominal pain, nausea, and fever. Radiation gastritis and duodenal ulcers have been described, and as all liver-directed therapies, the risk of liver failure is present. Of note, this promising modality of care, while approved for treatment of colonic cancer metastases to the liver, is still under FDA investigation for treatment of NLMs. Current literature suggests there is significant potential in SIRT/HAR as part of the armamentarium against neuroendocrine tumors and its hepatic metastases.

4. Nonsurgical, Non-Liver-Directed Therapies

Since NLMs is a rare disease, large-scale, randomized trials prove difficult, and although these therapies have been used in the treatment of NETs, not all have been specifically used in the treatment of NLMs. Due to the multiple therapies available, the effectiveness of one versus another is difficult to study, and many times nonsurgical, non-liver-directed therapies tend to be lumped together in studies that are available. Moreover, there continues to be a lack of consensus on a nonsurgical treatment algorithm; however, most agree that nonsurgical, non-liver-directed treatments of NETs and NLMs constitute palliative care. At least, one single-center study in the medical literature [12] has proven that aggressive treatment of NLMs with nonsurgical therapy can extend 3- and 5-year survival rates in patients to 76.4% and 63.9% as compared to previously stated survival rates of 39% [14] and 25% [39], respectively. With these encouraging results and the boom in treatment advancements, the older perspective of "wait-and-watch" treatment is considered antiquated.

4.1. Peptide Receptor Radionuclide Therapy. Peptide receptor radionuclide therapy (PRRT) is an upcoming option with enticing advantages, most useful in symptomatic patients with somatostatin receptor-positive tumors, who are not surgical candidates. Between 80% to 95% of gastroenteropancreatic, NETs express somatostatin receptors [40] as demonstrated by ^{111}In-pentetreotide scans (OctreoScan, Covidien-Mallinckrodt Imaging, Hazelwood, MO 63042) [41], so PRRT may be useful for a large percentage of NLMs, perhaps in up to 25% of patients [12]. PRRT utilizes the targeting of a molecule to specific receptors located on the surface of tumor cells. Once the molecule interacts with the receptor, it is internalized, thereby delivering specific and localized radiotherapy. This technique allows precise destruction of tumor cells [42, 43], with little interference of nontumor tissue, except for some exposure of renal, bladder, and bone marrow tissues [44]. ^{90}Y, ^{177}Lutetium (^{177}Lu), or ^{111}Indium (^{111}In) are radionuclides that are linked with a somatostatin analog: octreotide, octreotate, or lanreotide. The more the tumor expresses somatostatin receptors as compared to the surrounding tissue, the more effective the PRRT will be. Somatostatin scintigraphy can predict the effectiveness of PRRT: low uptake indicates 20% chance of effect on liver metastases, whereas high uptake indicates a 60% chance [45]. ^{177}Lu-DOTA^{0}Tyr^{3}octreotate seems to be the most effective PRRT, with a tumor response rate of 35% and tumor stabilization of 80% to 90% of NETs [44], versus ^{90}Y-DOTA^{0}Tyr^{3}octreotide with a tumor response of 4% and tumor stabilization of 70% [46]. After therapy with ^{90}Y-DOTA^{0}Tyr^{3}octreotide or ^{177}Lu-DOTA^{0}Tyr^{3}octreotate, median duration of results were 30 months and 36 months, respectively [45]. In one study with 310 patients, median overall survival rate from initiation of PRRT was 46 months [47]. Further, patients experiencing benefit after one round of PRRT who develop recurrent or progressive disease may benefit from a second round of PRRT [48].

Side effects of PRRT are rare and usually mild consisting most commonly of nausea and vomiting occurring within 24 hours of administration [41], and although anemia and transient toxicity grade 1 have been reported [12], long-lasting adverse side effects are extremely rare. Patients that seem to benefit the most from PRRT have strong radiotracer uptake on OctreoScan, at least as much as the liver [41]. Newer positron emission tomography (PET) imaging platforms such as ^{68}Gallium-DOTA^{0}Tyr^{3}octreotide-PET and ^{68}Gallium-DOTA^{0}Tyr^{3}octreotate-PET are increasingly used to evaluate tumors as they are even more sensitive to radiotracer uptake [40] and may be able to better predict responsiveness to PRRT [49]. Unfortunately, PRRT is not available in the United States until September 2011, when the first clinical trial will begin (http://clinicaltrials.gov/; Identifier: NCT01237457).

4.2. Chemotherapy. The use of systemic chemotherapy is less clear in the treatment of NLMs. Several chemotherapeutic agents have been used in multiple trials, but mainly in the study of NETs only, with limited success and restrictions from side effects and toxicities.

The usefulness of chemotherapy in the treatment of NETs seems to be related to primary tumor location and tumor grade [41]. Pancreatic NETs have been treated successfully with nitrosurea streptozocin (STZ) [41]. The greatest efficacy seems to be related to the use of STZ with other chemotherapy agents, including 5-fluorouracil and doxorubicin, but still only results in a median response time of 9.3 months [50]. Dacarbazine (DTIC) is another chemotherapy agent with proven effectiveness in pancreatic NETs, and in one phase II trial demonstrated a response rate of 34% [51]. The alkylating agent, temozolomide, has also shown promise in pancreatic NETs: a phase II study using

temozolomide and thalidomide showed a response rate of 45% [52], and a retrospective study of temozolomide and capecitabine showed a response rate of 70%, a median PFS of 18 months, and an overall 2-year survival of 92% [53]. Platinum-based chemotherapy regimens may be useful in patients with high-grade, poorly differentiated NETs, with response rates of 42% to 80% with the use of cisplatin and etoposide [54–56], and 78% with use of oxaliplatin-based regimens [57]. Even with increased response rates, median survival times are of short duration of 8 to 11 months [56]. Therefore, chemotherapy can be used as salvage treatment, but is generally not considered as first-line, nonsurgical treatment. Moreover, the presence of NLMs may be related to worse response to chemotherapy as compared to NETs [58].

4.3. Biotherapy

4.3.1. Somatostatin Analogs. Somatostatin exerts its affect by integration with one of five somatostatin receptors, $ssts_{1-5}$ [59], but due to a half-life of only two minutes [60], somatostatin analogs (SSA) have been developed. Newer formulations may be even easier to administer to patients due to a longer half-life of approximately two hours [61].

The principle use of SSA is in the symptomatic relief of NETs and NLMs, although it may be useful for other indications. The use of SSA produces a median biochemical response rate between 0% to 77%; and biochemical and radiographic tumor stability of 28% and 55%, respectively [61–71]. One review article found symptomatic and tumor response to octreotide, octreotide long-acting repeatable (LAR), lanreotide, and lanreotide slow-release depot (autogel) in 74.2%, 77.3%, 63.0%, and 67.5%, and in 57.4%, 69.8%, 46.6%, and 64.4%, respectively [72]. Another investigation demonstrated relief from flushing and diarrhea in 88% of patients after octreotide administration [61]. Interim data from the PROMID study with metastatic midgut NETs, showed a 66% reduction in the risk of disease progression and arrested tumor growth in 69% for a median of 14.3 months [73]. However, over 75% of patients in this study had limited liver involvement of 10% or less, and the response was highest in patients with relatively low tumor burden [73]. The greatest response rates have been witnessed with octreotide doses of 30 mg/day or greater or with lanreotide doses of 5 mg/day or greater [74]; octreotide doses greater than 60 mg/day likely do not have additive effect due to oversaturation of receptor sites [75]. Similar to PRRT, the level of uptake on somatostatin scintigraphy may be an indicator of patient's response to SSA therapy [44].

The newest SSA, pasireotide, is still in clinical development stages, but is promising due to binding of $ssts_1$, $ssts_2$, $ssts_3$, and $ssts_5$ [41], as compared to octreotide and lanreotide which bind to $ssts_2$ and $ssts_5$ only. Preliminary data indicate that pasireotide may be useful in patients with symptoms refractory to octreotide, possibly controlling symptoms in up to 27% of these patients [76].

Side effects are infrequent, but nausea, stomach cramping or discomfort, diarrhea, steatorrhea, cardiac abnormalities and arrhythmias, hypothyroidism, and hypoglycemia may occur [40, 41, 77]. Cholelithiasis may arise in up to 50% of patients due to inhibition of gallbladder contractility [41], but only a handful will develop symptoms requiring cholecystectomy [78].

4.3.2. Interferon-α. Interferons have multiple antitumor effects [79], and they may upregulate somatostatin receptors in NETs [80], thereby providing a useful combination therapeutic option. Interferon-α can ameliorate symptoms in 30% to 70% of patients [81, 82], and in some studies has shown promising results with tumor response rate or stabilization in up to 70% of patients [82]. However, the results of three randomized clinical trials involving interferon-α and octreotide have mixed results. Two demonstrated increased 5-year survival rate [70] and median survival time [83] in the combination group versus the octreotide-only group, 57% versus 37% and 51 months versus 35 months, respectively; but another trial showed minimal response rates [84].

The side effect profile of interferons may preclude wide utilization. Interferon-α can cause fevers, chills, myalgias, depression, and myelosuppression [41], and is considered inferior to SSA. However, in patients with progressive disease, combination therapy may be a viable option [85].

Others have examined the role of dopamine receptors and interferon-β [86] as other possible targets, but currently, neither of these targets seems promising at this time due to ineffectiveness and short half-life.

4.4. Newer Therapies.

Patients who have exhausted other therapies may find acceptable treatment through the use of newer treatment strategies. These interventions remain in the investigative process, including targeting vascular endothelial growth factors (VEGF), mTOR pathways, other growth factor receptors, antiproliferative factors, and antiangiogenic factors. Monoclonal antibodies against insulin-like growth factor-1 receptor (IGF-1R): AMG479, IMC-A12, and MK-0646, are currently in clinical phase II studies in patients with metastatic NETs (http://clinicaltrials.gov/, identifier: NCT01024387, NCT00781911, NCT00610129). Others are looking at genetic copy number alterations of tumor suppressor genes [87] and the detection and characterization of circulating tumor cells to reduce metastatic burden [88] as other possible avenues to treat NETs and NLMs.

4.4.1. Targeting Vascular Endothelial Growth Factors. NETs and NLMs frequently overexpress the vascular endothelial growth factor (VEGF) ligand and receptor (VEGFR) [89]. Tumor progression of NETs has also been associated with circulating levels of VEGF [41], therefore VEGF and VEGFR are promising targets.

In a study where patients on octreotide therapy were randomized into either treatment with bevacizumab, a humanized monoclonal antibody against VEGF, or interferon-α, 95% of patients receiving bevacizumab were progression-free after 18 weeks, compared to 67% of patients receiving interferon-α [36]. Bevacizumab is associated with reduction of tumor blood flow and longer

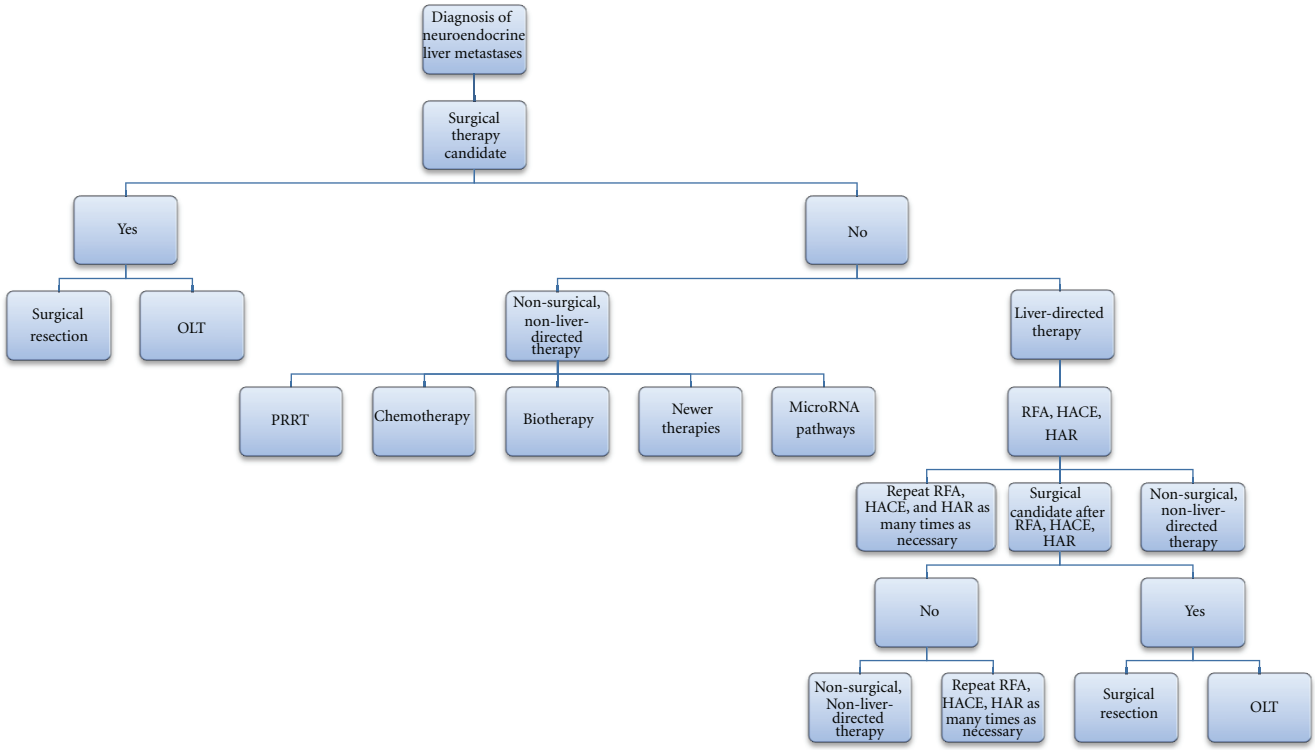

Figure 1: Algorithm for treatment of neuroendocrine liver metastases. The preferred treatment options involve surgical management, followed by liver-directed therapies, or a combination of these procedures. Nonsurgical, non-liver-directed therapies constitute palliative care.

progression-free survival (PFS) when compared to alternative treatments [36]. Currently, multiple clinical trials of bevacizumab are ongoing (http://clinicaltrials.gov/, identifiers: NCT00569127, NCT00137774, NCT00398320, NCT00227617, NCT00607113). Bevacizumab may cause hypertension and proteinuria [44], so optimal patient selection prior to treatment is mandatory.

Sunitinib is a tyrosine kinase receptor inhibitor currently approved in the treatment of renal cell carcinoma and gastrointestinal stromal tumors and inhibits VEGFR1, VEGFR2, and VEGFR3. Phase III trials resulted in median PFS of 11.1 months for patients on sunitinib versus 5.5 months for patients receiving placebo ($P < 0.001$) [40, 90, 91]. In Europe, sunitinib is approved for the treatment of unresectable or metastatic, well-differentiated pancreatic NETs with disease progression in adults [40]. Side effects of sunitinib include fatigue, asthenia, diarrhea, nausea, vomiting, anorexia, bleeding complications, mucosal inflammation, hypertension, anemia, granulocytopenia, thrombocytopenia, and hypothyroidism [40].

4.4.2. Targeting mTOR Pathway. The mammalian target of rapamycin (mTOR) pathway is central to the control of cell growth, protein synthesis, and apoptosis and is activated in NETs [40]. Two mTOR inhibitors have been developed and approved for use in renal cell carcinomas [92], everolimus, and temsirolimus, and have been studied in NETs [41, 93–95]. Everolimus has a potential in conjunction with octreotide LAR [93] and as a monotherapeutic agent with a response rate of 20%, a median PFS between 11 and 16 months in three separate phase III trials [41, 96], and with stabilization of disease in 70% with low- to-intermediate grade NETs [93]. Side effects of everolimus include stomatitis, rash, diarrhea, fatigue, infections, non-infectious pneumonitis, anemia, lymphopenia, hypercholesterolemia, hyperlipidemia, and hyperglycemia [40].

4.5. MicroRNA-Regulated Pathways. MicroRNAs are small, noncoding RNAs that can function as gene regulators by posttranscriptional processes, such as inducing mRNA degradation or repression of translation [97–100]. MicroRNAs are usually downregulated in cancers [97–100] and have been studied for possible therapeutic interventions. One study identified microRNA-133a, -145, -146, -222, and -106 to be important in primary NETs, whereas microRNA-183, -488, -19a+b were found to be important in metastatic NETs [97]. Further, the same group determined that decreasing levels of microRNA-133a has an important role in the development, progression, and possible metastasis of midgut carcinoid tumors [97]. A different study identified microRNA-142-3p, -142-5p, -155, -146a, and -483 as up-regulated in pancreatic NETs as compared to normal tissue [101]. This study also found that microRNA-210, -431, and -424 were up-regulated in metastases as compared with tumors, suggesting that certain microRNAs could be used to predict the probability of metastasis [101]. Another study

showed that anti-microRNA-182 targeting had a therapeutic effect against melanoma liver metastasis, which may be extended to other tumors [102].

Additional studies are warranted in this area pertaining to microRNA-regulated pathways, but already possible therapeutic targets have been identified by researchers including the high-mobility group A proteins, HMGA1, HMGA2, and the microRNA family let-7 [103, 104]. These targets will be useful as better strategies evolve to care for patients with NLMs and extend their survival.

5. Conclusion

The treatment modalities available to a patient diagnosed with liver metastases due to NETs are vast. The options range from surgical treatments, to locally liver-directed therapies, to systemic approaches (Figure 1). However, most, if not all clinicians, agree that the treatment must be tailored specifically to the patient. Generally, surgical therapies are preferred as they can give the longest disease-free interval. Yet, not all patients with NLMs are candidates for surgical therapy, and in the case of an elderly asymptomatic patient with a slow-growing NETs, the patient may not desire surgical therapy. Liver-directed treatment can also produce great results, extending the lifetime of the patient without riskier surgical interventions. Moreover, liver-directed therapies may clearly benefit a patient who is symptomatic from their tumor or may even allow that patient to be a candidate for surgical treatment in the future. Lastly, nonsurgical, non-liver-directed therapies are considered palliative care in the treatment of NLMs. These systemic therapies are not first line, but can still achieve longer lifespans as a salvage therapy. Newer technologies, including genetic targets such as microRNA subtypes, are fast evolving and will continue to allow patients with NLMs several options. Even though NETs are rare tumors, NLMs are even more rare, and this characteristic prevents large, randomized-controlled trials and modalities of treatment for these tumors continue to improve as there is an obvious need. These treatments are expected to maintain this progression well into the future, especially as knowledge of NLMs increases with additional studies, so that we may provide patients diagnosed with NLMs with every possible chance towards increased survival.

Conflict of Interest Statement

The authors declared that there is no conflict of interest.

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