review

Management of patients with hepatic metastases from neuroendocrine tumors

Ashley Kieran Clift,[a] Andrea Frilling[b]

From the [a]School of Medicine and the [b]Department of Surgery and Cancer Imperial College London, London, United Kingdom

Correspondence: Prof. Andrea Frilling · Department of Surgery and Cancer, Imperial College London, Hammersmith Campus, DuCane Road, London W12 0NN, United Kingdom · T: 00442083833210 F: 00442083833963 · a.frilling@imperial.ac.uk

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Neuroendocrine tumors have a disposition toward metastasis to the liver. A range of treatment modalities for neuroendocrine liver metastases is available in the clinical arena, the indications for which depend on tumor characteristics such as patterns of metastasis, tumor grade, and anatomical origin. The complete surgical resection of liver deposits represents the only option with the intent to cure and is the gold standard approach, whereas cytoreductive resection (debulking) presents another surgical option aiming to ameliorate the symptoms and prolong survival. Liver transplantation is generally an accepted option for highly selected patients. For patients ineligible for radical surgery, liver-directed therapies—transarterial embolization/chemoembolization, selective internal radiotherapy, and local tumor ablation—present alternative strategies. Systemic therapies include peptide receptor radiotherapy, somatostatin analogues, cytotoxic chemotherapeutics, and novel molecularly targeted drugs. However, despite the variety of treatments available, there exists little evidence to guide optimal clinical practice with currently available data predominantly retrospective in nature. In this review, we discuss the diagnostic procedures that influence the trajectory of treatment of patients with neuroendocrine liver metastases before critically appraising the evidence pertaining to these therapeutic strategies.

Neuroendocrine (NE) tumour disease comprises a spectrum of heterogeneous neoplasms originating from the neuroendocrine cell system. Most NE tumors (NETs) arise from the gastroenteropancreatic and bronchopulmonary systems. Originally described as "carcinoids," NETss have traditionally been regarded as rare clinical entities. However, recent epidemiological evidence demonstrates increases in incidence over the past 30 years. Indeed, in a UK population-based registry, the overall incidence of NET per 100 000 individuals increased from 0.27 and 0.35 to 1.32 and 1.33 for men and women, respectively.[1]

NE tumors exhibit a proclivity for liver metastasis (LM) although this is dependent on tumor localization and grade. For example, disseminated spread is rarely observed in the NET of gastric, rectal, or appendiceal origin. However, up to 85% of patients with pancreatic NET and up to 90% of individuals with small-bowel NET exhibit hepatic metastasis at initial presentation.[2] A wide variation is observed between estimates of NE LM prevalence; a prevalence of 27% is estimated[3] by the US Surveillance Epidemiology and End Results program, whereas between 40% to 95% prevalence is projected by specialist NET centers.[4]

Historically regarded as relatively indolent malignancies as compared to adenocarcinomas arising from the same organs, the presence of NE LM exerts stark detriment on patient prognosis. An overall 5-year survival of patients having colorectal NET with and without LM is 75% to 88% versus 30%, respectively.[5-7] While patients with non-metastatic gastrinoma may expect a 95% survival at 20 years, in the context of LM this is reduced to 15% at 10 years.[8] Together, tumor differentiation grade and presence of LM are major negative predictors of survival in patients with NET.[9-11] Clinical manifestations of NET are diverse, ranging

from asymptomatic to incapacitating endocrinopathy, and depend on their secretory activity and the extent of hepatic tumor load. Therefore, managing secondary hepatic lesions is a critical aspect of the treatment of patients with NET disease.

The morphologic distribution of LM dictates intervention strategies: three characterizations exist that both inform treatment decisions and function as prognosticators (**Figure 1**).[12] While the surgical resection of LM represents the mainstay of therapy by offering curative intent and immediate control of tumor-associated symptoms, only a minority of patients are eligible for radical procedures. Liver transplantation is indicated in highly selected patients. The introduction of an array of palliative nonsurgical therapies both liver-directed and systemic in nature has contributed favourably to the NET armamentarium. However, with the majority of available evidence in the format of institutional case series without controls, robust data from prospective randomized clinical trials comparing treatments are scarce and currently unable to optimally guide clinical decision making.[13,14]

In this review, we discuss the aspects of the diagnostic workup for patients with NE LM before turning to an analysis of the data regarding available therapeutic modalities (**Figure 2**). We additionally identify areas for future advances in the field and provide recommendations for clinical practice as the available evidence permits.

Diagnostic Workup

A range of morphological and functional imaging modalities may be utilized. Morphological imaging modalities employed in detecting hepatic neuroendocrine disease comprise contrast-enhanced ultrasound (CEUS), multiphase helical computed tomography (CT) with multirow detector scanners and diffusion-weighted magnetic resonance imaging (MRI). The latter represents a more sensitive modality as compared to CEUS, T2-weighted, and Gadolinium-enhanced MRI and is capable of detecting smaller (and more) foci of disease.[15] Characteristically, NE LMs are hypervascular

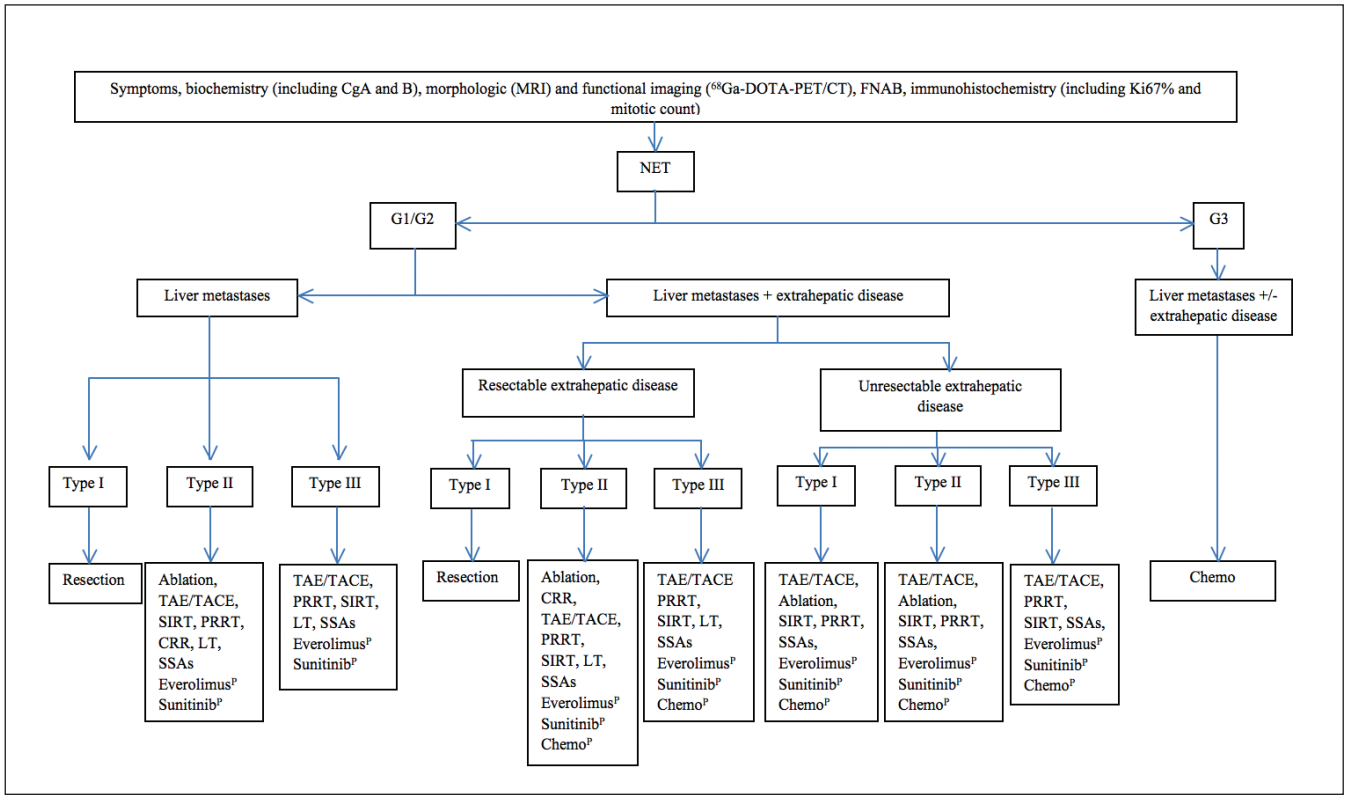

Figure 1. Management algorithm for neuroendocrine liver metastases. CgA and B=chromogranins A and B, MRI=magnetic resonance imaging, 68Ga-DOTA=68Ga-labelled tetraazacyclododecanetetraacetic acid, PET=positron emission tomography, CT=computed tomography, FNAB=fine needle aspiration biopsy, NET=neuroendocrine tumor, TAE/TACE=transarterial embolization/chemoembolization, CRR=cytoreductive resection, PRRT=peptide receptor radiotherapy, SIRT=selective internal radiotherapy, LT=liver transplantation, SSAs=somatostatin analogues, Chemo=cytotoxic chemotherapy, P=use in pancreatic NETs. Adapted from Frilling et al.[12]

lesions that exhibit a mixed hyper/hypoechoic pattern and a central cystic appearance on color Doppler ultrasonography.[16] Despite this diverse battery of morphological imaging tools, evidence suggests that compared to meticulous histopathogical examination, contemporary presurgical imaging may understage up to 50% of the true burden of NE LM.[17]

The tumor grading of specimens from CT- or ultrasound-guided biopsies informs treatment strategies and centers on the histopathological assessment of proliferation markers (Ki-67 and/or mitotic indices, **Table 1**) and also of vascular and neural invasion. NE LMs are staged as low grade (G1), intermediate grade (G2), or high grade (G3) by Ki67 scores of ≤2%, 3% to 20%, and >20%, respectively. Morphological imaging may stratify hepatic disease as type I (single metastasis of any size), type II (isolated bilobar metastatic bulk with smaller deposits), or type III (disseminated metastasis with little remaining unaffected hepatic parenchyma) (**Table 2**).[12]

Between 60% toand 100% of NET express somatostatin receptors (SSTRs), with 85% expressing SSTR-2.[18] Somatostatin receptor-based imaging exploits this target to concomitantly assess the burden of primary tumors and metastases, and the adequacy of somatostatin receptor-targeted treatments. Functional imaging may employ any of a range of radiolabeled tracers such as 111In-Octreotide, 68Ga-radiolabeled 'DOTA' peptides (DOTATOC, DOTATATE, and DOTANOC), 64Cu-DOTA, 18F-DOPA, and 11C-5-hydroxytryptophan HTP. Studies have demonstrated sensitivity and specificity of 68Ga-DOTATOC positron emission tomography (PET)/CT in G1/G2 LM of 82% to 100% and 67% to 100%, respectively,[19] and its ability to alter the initial management strategy of approximately one-third of patients.[20,21] 68Ga-radionuclide imaging is capable of detecting lesions escaping elucidation by CT and MRI in up to 67% of patients. In lieu of this, 68Ga-labeled SSTRs-based PET/CT has been proposed as the optimal modality to interrogate the amenability of a lower grade (G1/G2) NE LM to surgical resection.[18] The staging of a higher grade (G2/G3) neuroendocrine disease should utilize 18F-fluorodeoxyglucose PET/CT.

Although used in the diagnostic workup of all patients with NET, chromogranin (CgA) serum levels do not have specific utility in diagnosing hepatic deposits; however, they may be useful surrogates of body tumor burden and markers for follow-up and prognosis. Indeed, decreases of 80% or higher in CgA levels postresection may predict stabilization of disease and alleviation of symptoms.[22] Recent data has indicated potential

Table 1. Pathological grading of neuroendocrine liver metastases.

Grade	Mitotic Count (10 HPF)	Ki67 Index (%)
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

HPF: High-power fields. Source: Adapted from Rindi et al.[84]

Table 2. Morphological classifications of neuroendocrine liver metastases.

Morphological Classification	Description
Type I	Single metastatic lesion of any size
Type II	Isolated metastatic bulk and smaller deposits with bilobar involvement
Type III	Disseminated metastatic disease involving both lobes, a single lesion of varying size and little residual parenchyma

Source: Adapted from Frilling et al.[12]

for multiple novel biomarkers, such as transcriptome studies, circulating tumor cells for gastroenteropancreatic NET, metabolic spectra analysis, and paraneoplastic autoantibodies.[22-26] Thus, current biomarker panels for NE LM are scant, yet future studies may clinically validate the aforementioned novel prospects and steer management of patients with such neoplasms toward personalized approaches.

Surgical Treatments

Resection

Surgical resection represents the gold standard treatment for patients with NE LM, offering intent to cure and immediately ameliorate tumor-associated symptoms. Unfortunately, only a minority of patients (approx. 20%-30%) are suitable for radical surgery, with many exhibiting type III metastases at initial diagnosis. Individuals with disease initially deemed unresectable may be candidates for a 2-step resection or other advanced surgical procedures.[27,28] Resection with microscopically (R0) or macroscopically (R1) clear margins may be attained. Cytoreductive surgery or "debulking" (R2) results in disease being left in situ and may be indicated in patients in which at least 70% to 90% of disease can be excised. Surgical resection is associated with an overall survival of 46% to 100% at 5 years, and 35% to 79% at 10 years (**Table 3**).

A systematic review by Saxena et al identified 29

case series reporting results of surgical resection for NE LM.[29] Median 1-, 3-, 5-, and 10-year survivals were 94% (range 79%-100%), 83% (range 63%-100%), 70.5% (range 31%-100%), and 42% (range 0%-100%), respectively, with 71% (range 6%-100%) and 18% (range 0%-36%) median rates of R0/R1 and R2 resection, respectively. Despite promising overall survival data, this analysis demonstrated the major hindrance of disease recurrence. Indeed, 1-, 3-, 5-, and 10-year recurrence-free survivals were 63% (range 50%-80%), 32% (range 24%-69%), 29% (range 6%-66%), and 1% (0%-11%), respectively. Such disconnect between survival parameters was echoed in the international multicentric 339-patient series of Mayo and colleagues, which demonstrated overall survival and disease/progression-free survival at 1, 5, and 10 years of 92% versus 56.9%, 74% versus 24.2%, and 51% versus 5.9%, respectively.[30] Furthermore, 99% of all patients exhibited recurrence at 10 years.

Surgical resections of both curative and palliative intents are hampered by the issue of disease recurrence. However, cytoreductive surgery is associated with a poorer overall survival generally. In the aforementioned study of Mayo et al, R2 resection status was not identified as a significant prognosticator of recurrence, but was associated with poorer overall survival. Macroscopically complete (R0/R1) resection correlated with favorable survival with LM from secretory NET compared to R2 resection, yet this was not the case in metastases from nonfunctioning primaries.[30] Results from the 172 patient series of Glazer et al were similar, with positive resection margins failing to significantly associate with overall survival or recurrence/progression-free survival.[31] Thus, it has been posited that rather than resections being strictly curative or palliative in nature, all manifest as reductions in disease burden of varying ardour.

Nevertheless, surgical resection epitomizes the treatment of patients with NE LM, and should be offered as a first-line strategy in patients with G1/G2 disease fit enough to undergo hepatectomy. Cytoreductive resection may be useful in patients with treatment-refractory tumors, or those with symptoms of endocrinopathy or local tumor-mass effects. With the recent introduction of novel and promising palliative treatment options, the place for debulking requires consideration. Indeed, the role of debulking surgery has been retrospectively compared with transarterial embolization procedures in a cohort of 120 patients,[32] showing significantly favorable results with the former. However, the analysis requires evaluation from prospective comparative clinical trials.

Transplantation Procedures

Highly selected patients with nonresectable, G1/G2

Table 3. Results from hepatic resection in patients with NE LM – selected studies published since 2000.

First Author	Year	Total Patients	R0/R1 resection			R2 resection		
			Patients (n)	OS	PFS	Patients (n)	OS	PFS
Saxena et al[85]	2011	74	48	Median 98 mo	Median 48 mo	26	Median 27 mo	Median 24 mo
Scigliano et al[86]	2009	41	37	88% R0 82% R1	31% R0 9% R1	4	50%	0%
Frilling et al[12]	2009	119	23	100%	96%	4		
Gomez et al[87]	2007	18	15	86%	90%	3		25%
Elias et al[88]	2003	47	37	74% R0 70% R1	66% R0 46% R1	10	47%	30%
Sarmiento et al[89]	2003	170	75		24%	95		9%
Norton et al[90]	2003	16	16	82%		0		
Nave et al[91]	2001	31	10	86%		21	26%	
Coppa et al[92]	2001	29	20	67%	29%	0		
Yao et al[93]	2001	36	16	70%		0		
Chamberlain[94]	2000	85	15	85%		19	63%	
Pascher et al[95]	2000	41	16	Median 70 mo		10	Median 50 mo	

OS=5-year overall survival; PFS=5-year progression-free survival; mo=months; NELM: neuroendocrine liver metastases; OS: overall survival; PFS: progression-free survival.

NE LM may be considered as candidates for orthotopic liver transplantation (OLT). The indolent nature of metastasized NET as relative to metastatic adenocarcinomas derived from the same organs justifies this example in which visceral transplantation is generally accepted. Data from single-center case series published post-2000 demonstrate 5-year overall and disease-free survivals of 33% to 80% and 9.1% to 53%, respectively (**Table 4**). Overall, published data on approximately 700 patients transplanted for NE LM exist. Although some selection criteria differ between specialist centers, there is general consensus regarding higher tumor grade, nonportal tumor drainage, extrahepatic disease (excepting resectable perihilar lymph node metastases),

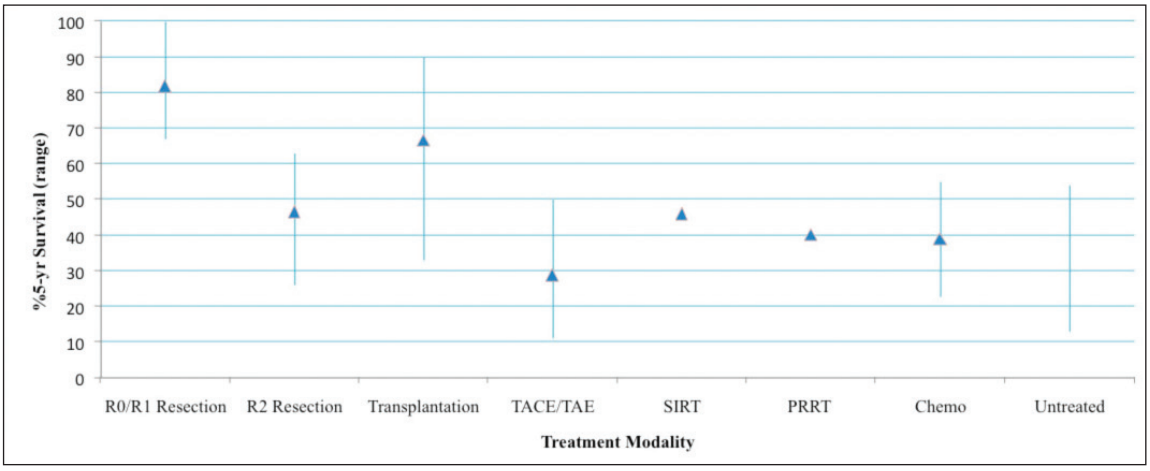

Figure 2. Overall survival outcomes at 5 years for various treatment modalities–data from selected studies published since 2000.

Table 4. Selected studies reporting survival outcomes from liver transplantation for neuroendocrine liver metastases (published since 2000).

First Author	Year	Patients (n)	Overall survival					Disease-free survival			
			1-year (%)	2-year (%)	3-year (%)	5-year (%)	10-year (%)	1-year (%)	3-year (%)	5-year (%)	10-year (%)
Single Centre											
Bonaccorsi-Riani et al[96]	2010	9	88		77	33[c]		67	33	11	
Olausson et al[34]	2007	15[a]				90			70	20	
Marin et al[97]	2007	10	86		57				38		
Mazzaferro et al[33]	2007	24				90				77	
van Vilsteren et al[98]	2006	19	88					80			
Frilling et al[99]	2006	15[b]	78.3			67.2		69.4		48.3	
Florman et al[100]	2004	11	73			36					
Cahlin et al[101]	2003	7		80							
Rosenau et al[102]	2002	19	89			80	50	56		21	21
Coppa et al[92]	2001	9				70				53	
Multi-centre											
Le Treut et al[35]	2013	213[a]	81	73	65	52		65	40	30	
Gedaly et al[36]	2011	150[b]	80		64	48		77	50	32	
Le Treut et al[103]	2008	85	72	67	59	47		56	37	20	

[a]Includes 5 patients undergoing multivisceral transplantation; [b]Includes 1 patient undergoing multivisceral transplantation; [c]Includes 4 patients transplanted prior to 1990. aincludes 6 patients undergoing multivisceral transplantation; b17 patients had additional organs transplanted.

and advanced carcinoid heart disease as exclusion criteria.

The Milan criteria, originally formulated to aid the selection of patients with hepatocellular carcinoma, were adapted for NE LM by Mazzaferro et al and stipulate low-grade NET (with/without clinically evident endocrinopathy), portal venous drainage of the primary tumor, complete resection of primary and extrahepatic lesions prior to OLT, ≤50% hepatic involvement, age ≤55 years, and at least stable disease for 6 months prior to the procedure. These have been associated with 90% 5-year overall survival and 77% 5-year disease-free survival.[33]

Contrastingly, in their series of 15 patients undergoing OLT (n=10) or multivisceral transplantation (MVT, n=5), Olausson et al have reported similarly favorable outcomes while allowing less stringency.[34] Although they allowed increased age (up to 64 years), >50% hepatic tumor involvement (in 12/15 patients), and higher tumor grade (Ki67 up to10%), 5-year overall survival was 90% for OLT and 70% for all patients. None of the aforementioned divergences was significantly associated with predicting recurrence, and 1-year recurrence-free survival was 70% for the cohort. Notably, the Göteborg group employed a more aggressive surgical procedure in patients with primary tumors at the head of the pancreas. In these individuals, the resection of primary tumor, locoregional lymph nodes, and LM accompanied multivisceral transplantation including stomach, liver, duodenum, and pancreas.

The recent retrospective analysis of 213 patients undergoing liver transplantation for NET in European centers between 1982 and 2009 demonstrated 1-, 2-, 3-, and 5-year overall survival of 81%, 73%, 65%. and 52%, respectively.[35] Disease-free survival at 5 years was 30%, with hepatomegaly, age>45 years, poor tumor differentiation, and concomitant surgical procedures shown to be unfavorable prognosticators. A sizable proportion of patient deaths within the first year post-transplant was attributable to early or late complications of transplantation, with 37 patients (17%) dying without evidence of recurrence with a median survival of 8 months (range 4-165). Combined with a 3-month postoperative mortality of 10%, these suggest that the majority of patients dying within the first year did so as a result of the procedure as opposed to their malignancy. A similar analysis of the United Network for Organ Sharing database reported the outcomes of 150 patients receiving liver allografts as OLT (n=137) or MVT (n=13) in US centers.[36] Comparable outcomes were demonstrated as follows: overall survivals at 1, 3, and 5 years were 81%, 65%, and 49% versus 80%, 65%, and 48% for OLT and MVT, respectively. Data regarding disease-free survival was calculable from 83 patients, and the results were 77%, 50%, and 32% at 1, 3, and 5 years, respectively. Transplants were carried out between 1988 and 2008, and outcomes were comparable for patients with NE LM and hepatocellular carcinoma in this era.

As opposed to a treatment of last resort, liver transplantation should be considered in patients whose tumors are still controllable. A 6-month waiting list policy is advocated by some centers to enable identification of patients with stable disease. However, the presently available evidence does not permit to consider this as a selection criterion. Tumor recurrence is a major problem in liver transplantation. Although encouraging outcomes have been reported with advances in surgical technique, patient selection, and immunosuppressive strategies, there is a major disconnect between overall survival and disease-free survival. Novel adjuvant and neoadjuvant strategies should be developed to target this issue of recurrence, as should biomarkers that can predict patient outcomes. The data pertaining to MVT for NE LM is scarce and contradictory.[37,38]

Liver-Directed Treatments

Percutaneous angiographic modalities

NE LMs are classically hypervascular lesions. Furthermore, hepatic metastases derive the majority of their blood supply from the hepatic artery in contrast to the normal parenchyma that obtains the majority of its oxygenation via the portal venous tract. The "transarterial" liver-directed therapies of transarterial embolization/transarterial chemoembolization (TAE and TACE, respectively) and selective internal radiotherapy (SIRT) exploit these observations. Contrastingly to hepatic resection and ablation, these methods are not limited by the number or distribution of LM.

TAE and TACE seek to establish ischaemic necrosis of hepatic tumors via embolization of the hepatic artery. Despite wide implementation, divergences exist in treatment protocols and treatment response criteria that hamper the comparative analysis of outcomes with these modalities from the reported series. Nonetheless, 5-year survivals of 11.1% to 71.5% have been demonstrated.[39-43] In their retrospective multicentric analysis of 100 patients, Pitt et al demonstrated no significant differences between TAE and TACE in terms of overall survival, symptom improvement, morbidity, and mortality.[42] TACE may be coadministered with drug-eluting beads. Of the few available reports, comparable efficacy has been suggested,[44,45] although a notably high rate of biliary injury was reported by Bhagat et al in 7 of their 13 patients.[46]

SIRT (also termed radioembolization) involves the infusion of resin or glass microspheres radiolabeled with the pure β-emitter Yttrium-90 (90Y) into the hepatic artery via transfemoral catheterization. Microspheres preferentially lodge in tumor microvasculature. This allows targeting of multiple sites of disease, there combining embolization with deliverance of high localized doses of cytotoxic radiation, although it has been suggested that anti-tumor activity is mostly attributable to the latter.[47] Long-term data pertaining to SIRT in NE LM is sparse. Existing single-center reports document 3- and 5-year survivals of 45% to 57%, and 45%, respectively. In the series of Kennedy et al, 148 patients underwent SIRT for unresectable NE LM; complete response, partial response, stable disease and progressive disease were observed in 2.7%, 60.5%, 22.7%, and 4.9% of patients, respectively. Median survival was 70 months.

A recent systematic review[49] reported for TACE and SIRT median overall survivals of 34.9 months (range 15-69 months) versus 28 months (range 14-70 months), and median progression-free survivals of 16.1 months (range12-22.7 months) versus 4 to 14 months, respectively. For TACE, median clinical and biochemical responses of patients were 88.5% and 73%, respectively, whereas for SIRT, median clinical and biochemical responses of patients were71% to 95% and 55% to 89%, respectively. A pooled-data analysis yielded comparable disease response rates of 63.1% (range 12.5-100%) and 58.4% (range 11.1%-89%) for TACE and SIRT, respectively. Patients undergoing transarterial procedures frequently experience "post-embolization syndrome," manifesting as fatigue, fever, abdominal discomfort, and slightly deranged liver function tests. Toxicities of grade 3 or higher have been observed with TACE and SIRT in 0% to 25% and 0% to 12.9% of patients, respectively.

Percutaneous liver-directed therapies present attractive palliative options in managing patients with G1/G2 NE LM with disease predominantly confined to the liver. Low hepatic involvement (<50%), low-grade tumor differentiation, and lack of extrahepatic deposits have been shown to function as a favorable prognosticator for these techniques.[50-52] While portal venous thrombosis and impaired hepatic function act as contraindications for TAE and TACE, this is not the case for SIRT. The pre-treatment workup of patients undergoing SIRT must involve the assessment of the degree of hepatopulmonary shunting with hepatic angiography using 99technetium- labeled macroaggregated albumin with gamma scintigraphy. Embolization of other upper abdominal arterial shunts may be required to minimize the risk of microsphere impaction elsewhere with resulting iatrogenic radiation damage.

Locally ablative modalities

Ablative techniques can be used in the management of nonresectable LM either alone via percutaneous, laparoscopic,[53] or open approaches, or as an adjunct to surgical procedures.[54] Furthermore, they may be used repeatedly in attempts at tumor and symptom control. Radiofrequency ablation (RFA) has the most widespread use, although microwave ablation (MWA), laser ablation, cryoablation, and US-guided ethanol injection represent alternative forms of this modality. Best treatment outcomes have been attained with RFA and MWA, the benefits of which are comparable, but the latter is less time-consuming and may be preferential in the ablation of larger, multifocal tumors.[55] Case series demonstrate 5-year overall survivals of 37% to 57%, with optimal results obtained in patients with lower hepatic neoplastic involvement, >1 cm postprocedural ablation margins, and those with dominant foci of disease <5 cm in diameter.[56-58] The largest series reported involved 89 patients receiving a total of 119 RFA treatments administered via a laparoscopic approach.[58] In this cohort, the median overall and disease-free survivals following the first treatment were 6 years and 1.3 years, respectively, with symptom control attained in 97% of individuals. Local hepatic recurrence, new hepatic lesions, and extrahepatic deposits were observed in 23%, 63%, and 53% of patients, respectively, within a median follow-up of 30 (3) months.

Ablative modalities present a palliative strategy for patients with a small number of unresectable hepatic lesions which may be repeatedly used. Offering rapid amelioration of symptoms of hormone excess and/or tumor bulk, optimal results are achieved with foci of disease <5 cm in size. These treatments present a useful option in patients harboring LM refractory to medical management strategies.

Systemic Therapies

Somatostatin analogues

Capable of exerting both antisecretory and antiproliferative effects, somatostatin analogues (SSAs) are utilized in hormonally active and, more recently, also in nonsecreting NET. Secretory tumors may be treated with octreotide or lanreotide, both of which are available in immediate-release and long-acting repeatable (LAR) formulations. These have comparable efficacy in symptom control, with flushes and diarrhea controlled in 50% to 68% and 45.4% to 53.8% of patients, respectively.[59] The novel, multiligand SSA pasireotide (SOM 230) may be

implemented for managing SSA-refractory symptoms.

The antiproliferative effects of SSA therapy were first realized in a randomized, placebo-controlled context in the PROMID trial with patients with NET of midgut or unknown origin.[60] The median time to progression was 14.3 months versus 6 months in the cohorts treated with 30 mg octreotide LAR and placebo, respectively, with multivariate analyses elucidating primary tumor resection and <10% hepatic involvement as positive predictors for response. The randomized, placebo-controlled CLARINET trial demonstrated significantly prolonged progression-free survival in patients with G1/2 midgut NET treated with lanreotide 120 mg. Treatment benefit was not dependent on the degree of hepatic involvement. Antiproliferative effects were demonstrated in patients with pancreatic NET, with 62% of patients treated with SSA neither dying nor progressing at 2 years versus 22% of those in the placebo cohort.

Peptide receptor radiotherapy

Patients harboring unresectable metastatic NET disease of low or intermediate grade expressing SSTRs may be suitable for treatment with peptide receptor radiotherapy (PRRT). PRRT involves the administration of SSAs conjugated to the radionuclides 90Y or lutetium-177 (117Lu). The binding of radiopharmaceuticals to SSTRs leads to the internalization of the agent, with resulting targeted delivery of radiation to tumor cells. A range of radiopharmaceuticals may be used, including [DOTA0, Tyr3]octreotide (DOTATOC), [DOTA0, Tyr3octreotate (DOTATATE), and [DOTA0-1-Nal3] octreotide (DOTANOC). 90Y- and 177Lu-based agents exhibit favorable tissue penetration ranges compared to previously used 111In-based conjugates.

Generally treatment involves 4 treatment cycles, which may be extended in patients showing disease response. A number of mild, but normally reversible, side effects include nausea, headache, myelosuppression,[61] and hypocalcemia.[62] Adverse renal effects may be circumvented with the use of renal protective agents (amino acids) and precise dosimetry calculations. Approximately, one-third of patients undergoing PRRT can expect disease response.[20,63-67]

Complete and partial tumor regressions were observed in 2% and 28% of patients, respectively, in the series of 310 patients with metastatic NET undergoing treatment with 177Lu-DOTATATE reported by Kwekkeboom et al.[66] LMs were present in 89%, with all demonstrating moderate or extensive hepatic involvement. Treatment was associated with a median time to progression and a median overall survival from initial course of 40 months and 46 months, respectively, with a few adverse effects reported. Larger series have confirmed the efficacy of PRRT as a promising palliative modality. In a series of 1109 patients (82.2% of which had LM), treatment with 90Y-DOTATOC was associated with morphologic, biochemical, and clinical response rates of 34.1%, 15.5%, and 29.7%, respectively, and median TTP of 12.7 months. Favorable mean survival outcomes were 73 months and 43.2 months, respectively, in patients attaining complete disease remission and in those whose disease progressed.[68]

A combinatorial approach utilizing sequentially administered radionuclides has been demonstrated to achieve outcomes superior to the use of a single agent. In the study by Villard et al., patients were treated with either 90Y-DOTATOC (n=237) or a regimen alternating 90Y-DOTATOC and 177Lu-DOTATOC (n=249).[63] Although side effect rates were comparable between arms, the combination therapy was associated with favorable overall survival of 5.51 years versus 3.96 years. For combination and single therapy, complete and partial responses were observed in 2.2% versus 3.4%, and 20.9% versus 16%, respectively, with disease stabilization in 23.9% versus 15.1%. It was postulated that alternation between the use of high- (90Y) and low-energy (177Lu) β-emitters predicates the sequential targeting of large and small metastatic deposits.

PRRT can be used in individuals with G1/2 tumors with hepatic and extrahepatic metastases, as visualized with SSTR-based imaging modalities. A small number of reports have shown PRRT as an effective neoadjuvant treatment to downstage primary[69,70] and liver[71] lesions initially deemed unresectable. Poorer treatment outcomes have been observed in those with >50% hepatic involvement, low SSTR expression, and those who have undergone previous chemoembolization.[64,72] Serious adverse effects include renal and bone marrow toxicity, but are infrequent and can be avoided in the most part with effective prophylaxis.

Chemotherapy

With chemotherapy typically targeting the rapid proliferation of neoplastic cells, the relatively protracted natural history and indolent behaviour of NET does not appear tractable to such approaches in the most part. Chemotherapy does however represent an option for managing NET, albeit reserved primarily for pancreatic-derived NET and also for those of high grade irrespective of their origin. Traditionally centered around cytotoxic agents including streptozocin, 5-fluorouracil (5-FU), and doxorubicin, chemotherapy regi-

mens for NETs may now incorporate temozolomide and capecitabine. The efficacy of chemotherapeutic approaches is typically low in well-differentiated midgut NET. Indeed, no chemotherapeutic regimen has been demonstrated to be effective in gastrointestinal NET. However, systemic chemotherapy represents the modality of choice in metastatic, nonresectable G1/2 pancreatic NET.[73] A higher grade NET may be treated with a combined etoposide and cisplatin therapy. Welin et al[74] also recently reported a 71% rate of objective response or disease stabilization in patients with G3 gastrointestinal NETs unresponsive to initial therapy transferred onto treatment with temozolomide either as a single agent or combined with bevacizumab and capecitabine.

Kouvaraki et al[75] reported a 2-year PFS of 41%, a median response duration of 9.3 months, and a median OS of 37 months in 84 patients with NET (73 had LM) treated with 5-FU, doxorubicin and streptozocin. The overall survival of the cohort was 74%, with a favorable prognosis associated with a lower hepatic (<75%) tumor burden. A combined therapy with temozolomide and thalidomide for metastatic pancreatic NEThas been reported to attain biochemical and radiological responses in 40% and 45% of patients, respectively.[76] The response rate was only 7% for the mid-gut NET.

Immune Modulatory Agents

Symptomatic and biochemical responses in patients with metastatic NET have been demonstrated with the administration of interferon-α, alongside appreciable intratumor fibrosis.[77,78] One randomized trial of 80 patients with NET examined efficacies of single interferon-α, lanreotide, or combination therapy.[79] All patients were treatment naive, and 72 harbored LM. Stable disease, partial response, complete response, and progressive disease were observed in 23.9%, 5%, 0%, and 53.7% of patients, respectively, over a treatment period of 12 months, with results comparable between therapy subsets. Interferons are used in managing slow-growing NET, yet the data pertaining to the use of immune-modulating therapies in this context use is sparse.

Novel Molecularly Targeted Drugs

Targeted therapies including the PI3K-Akt-mammalian target of rapamycin inhibitor (i.e., everolimus) and the tyrosine kinase inhibitor (i.e., sunitinib) may be useful in managing advanced, slow-growing tumors of a lower grade (G1/2). No evidence exists regarding the use of these novel therapies for the advanced gastrointestinal NET. A phase II trial demonstrated the efficacy of everolimus as a single agent or combined with octreotide LAR (up to 30 mg) in patients with G1/2 metastatic pancreatic NET refractory to cytotoxic chemotherapy.[80] The placebo-controlled RADIANT-3 trial accrued in 410 patients also with progressive G1/2 pancreatic NET, reporting favorable PFS as compared to the placebo arm: 11 months versus 4.6 months, respectively.[81] Patients treated with everolimus showed 34% PFS at 18 months, versus 9% of those treated with placebo. The superior efficacy of everolimus in conjunction with SSAs (octreotide LAR 30 mg) compared to single-agent everolimus was demonstrated in the RADIANT-2 phase III trial of patients with progressive G1/G2 tumors. PFS with everolimus and octreotide versus placebo with the same dose of octreotide were 16.4 months and 11.3 months, respectively.[82] RADIANT-4 is another phase III trial examining everolimus at 10 mg per day in nonsecretory midgut pulmonary NET, the results of which are awaited.

Raymond et al[83] reported the results of a multicenter randomized double-blind placebo-controlled phase III trial of sunitinib (37.5 mg per day) in 171 patients with advanced, well-differentiated pancreatic NET. Median PFS and objective response rates were 11.4 months and 9.3% in the sunitinib groups versus 5.5 months and 0% with placebo, respectively. The hazard ratio for death was 0.41 (95% CI 0.19-0.89, P=.02).

In conclusion, with their impact on prognosis and their regularity, the management of hepatic metastases is an essential component of the management of patients with NET. Although the armamentarium for metastatic NET is diverse, incorporating surgical, radiological, nuclear medicine-based and chemotherapeutic modalities, a pertinent hindrance in the field is the paucity of evidence gained from prospective randomized clinical trials to inform the optimal clinical management strategies. Indeed, much of current practice is dictated by either center-specific preferences and/or consensus guidelines based on imperfect evidence. Continued advances in the study of patient and disease-specific biomarkers capable of stratifying patients for optimal therapeutic strategies and the execution of large-scale comparative trials will facilitate progress in this clinical arena.

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