Practical Guide to Supportive Care of Patients With Functional Neuroendocrine Tumors

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Supportive care of patients with functional neuroendocrine tumors (NETs) has evolved to include the use of multiple targeted agents to control paraneoplastic states and newer surgical and interventional radiologic techniques to reduce tumor bulk. Challenges encountered by the clinician are the recognition of specific symptom complexes, selecting the relevant laboratory tests and radiologic/scintigraphic scans, and the timing of intervention(s). Individual variables such as the severity of symptoms in the context of primary and metastatic disease sites, tumor bulk, comorbidities, and previous treatment are factors determining the prioritization of specific treatment regimens for patients with functional NETs. Symptoms such as flushing, secretory diarrhea, hypercalcemia, hyper /hypoglycemia, hypercortisolism, and peptic ulcers should improve with decreasing the elevated amino acid and/or peptide levels produced by NETs. These paraneoplastic symptoms may be accompanied by complaints related to tumor burden such as fatigue, pain, early satiety, anorexia, weight loss, night sweats, and/or symptoms secondary to adverse drug effects such as mucositis, dysgeusia, diarrhea, rash, hypertension, and myelosuppression. Developing a comprehensive continuum of care plan early in disease management assists in controlling the presenting signs and symptoms, and in minimizing disease- and/or treatment-related side effects. This guide serves as a framework to manage the signs and symptoms of metastatic functional neuroendocrine tumors.
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Significant advances in supportive care occurred over three decades ago with the development of the somatostatin congeners resistant to degradative enzymes.[1] The recognition that specific life-threatening conditions such as carcinoid syndrome, carcinoid crisis, and WDHA (watery diarrhea, hypokalemia, achlorhydria syndrome or Verner-Morrison syndrome, vasoactive intestinal peptidoma [VIPoma], or pancreatic cholera) could be medically controlled by octreotide acetate when surgical extirpation was not an option dramatically changed clinical management.[2-4] The hormonal-suppressive effects of somatostatin congeners extended to other functional NETs such as gastrinomas, glucagonomas, insulinomas, acromegaly, Cushing's disease, and syndrome.[5-8] These observations ushered in a new era in the medical management of functional NETs by targeting specific receptors and cell signaling pathways affecting hormonal synthesis and/or secretion.[9] Applying somatostatin receptor autoradiographic imaging technology to the in vivo setting resulted initially in the development of indium-111 pentetreotide scintigraphy and more recently, gallium-68 DOTA octreotide for the detection and localization of somatostatin subtype receptors 2 and 5 (sst2, stt5)-expressing tumors.[10,11]

Advances in somatostatin formulations occurred when depot injections became the preferred route of administration.[12] Within the last 5 years, the introduction of temozolomide-based therapy, oral vascular endothelial growth factor (VEGF) tyrosine kinase and mammalian target of rapamycin (mTOR) inhibitors as therapeutic options in the pancreatic subtype of NETs has led to improved control of symptoms as well as the underlying disease.[13-15] This guide to the supportive care of functional NETs focuses on the management of those signs and symptoms encountered in clinical practice.

Medical advances coupled with newer operative techniques and interventional radiology procedures provide for improved symptom control in patients with

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metastatic functional NETs. The challenge is to recognize which symptom or symptom complex is attributable to the disease or disease progression versus other etiologies such as adverse drug effects, surgical anatomical changes, or other superimposed condition(s). Worsening of either symptoms or signs of the disease may simply reflect "tachyphylaxis" or may have more serious implications such as anatomical progression.[16] Despite symptom progression, it is common for patients to continue somatostatin analog therapy at the same or an alternative dose and schedule as symptoms remain suppressible, at least in part. With definitive evidence of hepatic disease progression, local regional treatments such as bland embolization, chemoembolization, or radioembolization may be options. Alternatively, enrollment in a clinical trial of agents in development such as bevacizumab, pasireotide in combination with cixutumumab (IMC A-12, an insulin-like growth factor-1 inhibitor), everolimus in combination with bevacizumab, and peptide receptor radiotherapy (PRRT) using lutetium-177 DOTATOC would be recommended (http://clinicaltrials.gov/ct2/results?term=neuroendocrine+cancer).

Various well-defined clinical syndromes and their presenting symptoms related to hormonal secretion(s) from either a primary mass and/or metastases from a well-differentiated or intermediate-grade NET category with management options are discussed below. Even though the pancreas and small and large intestines comprise the majority of tumors addressed, functional syndromes may also arise from the lung, thymus, or an unknown primary tumor.

CARCINOID SYNDROME

Presenting symptoms are generally attributable to a well-differentiated (low- or intermediate-grade) NET metastatic to the liver, often present for years prior to diagnosis and typically with an insidious onset. Symptoms may be isolated flushing or diarrhea or the combination of flushing and diarrhea.[17] As early symptoms are vague and nonspecific, misdiagnosis or a delay in diagnosis may occur even in patients presenting with advanced disease.[18] Provocative factors for flushing include ethanol, emotional upsets, exercise, eating, epinephrine, and pentagastrin.[19,20] The Valsalva maneuver, hepatic palpation during the physical exam, breast compression during mammography, hepatic embolization, or resection also may provoke symptoms and even crises in some circumstances.[21–23]

Should flushing be an early symptom in a perimenopausal female, confusion with physiologic flushing is common despite distinct differences between the two mechanisms. Menopausal flushing typically encompasses the whole body and is diaphoretic. Sensitivity to estrogen therapy assists in establishing the correct diagnosis but it is possible for these patients to have multiple causes of flushing. A detailed clinical history is necessary to establish the presence of two distinctly different flushing patterns in the perimenopausal female with carcinoid. Carcinoid syndrome flushing usually is facial, neck and upper chest and sometimes accompanied by palmar and plantar erythema. Carcinoid syndrome flushing is usually a dry flush and may last from a few seconds to a few minutes for those primaries arising in the luminal intestinal tract versus 30 minutes to hours for foregut primaries such as those arising in the lung.

Carcinoid diarrhea is typically secretory in nature, may be nocturnal, and is not responsive to fasting. Weight loss, dehydration, malaise, electrolyte disturbances, and cramping can occur, with their severity correlated with tumor bulk. Other manifestations of carcinoid syndrome may be a facial rash mimicking rosacea, cardiac valvular disease (tricuspid insufficiency, pulmonic stenosis), wheezing, and malaise.

Flushing, asthma, and secretory diarrheal symptoms require immediate control by subcutaneously administered octreotide as the majority of patients respond within a few days to 1–2 weeks (see Figure 1).[3] The severity of symptoms will determine which octreotide formulation and route of administration is optimal. The subcutaneous route is satisfactory for most patients to control symptoms quickly with eventual conversion, usually within 2–4 weeks, to the intramuscular or depot monthly formulation, octreotide long-acting repeatable (LAR).[12] Subcutaneous octreotide should be continued for 2 weeks after the initial intramuscular LAR injection until therapeutic levels are achieved. Breakthrough symptoms that occur after conversion to LAR are more common during the week prior to the monthly intramuscular injection and may require subcutaneous dosing depending on their severity and duration.

Following octreotide initiation, the clinician can focus on other individual factors that may contribute to symptomatology and disease morbidity such as bowel obstruction, high tumor bulk, or concomitant illnesses such as irritable or inflammatory bowel disease, hypertension, dumping symptoms from bowel surgery, bile acid colitis, and malabsorptive syndromes. As a mesenteric desmoplastic process is common with intestinal NETs, chronic abdominal pain and recurrent bowel obstructions may limit quality of life.

While octreotide controls secretory diarrhea, it induces steatorrhea. With diet adjustment and loperamide, this steatorrhea is controllable in most patients. For those few patients who experience significant weight loss, a trial of pancreatic enzyme(s) may be warranted. Octreotide dose escalation is recommended with worsening of secretory diarrhea. In depot octreotide patients whose diarrhea responds to "rescue" octreotide, escalating the monthly dose may result in improved diarrhea control.

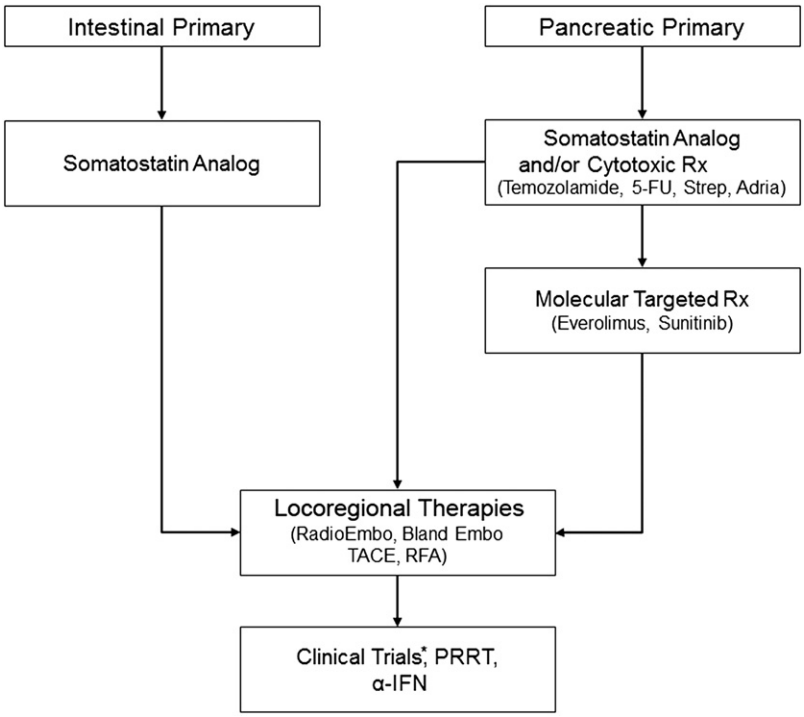

Figure 1. Functional metastatic well-differentiated (grades 1 and 2) neuroendocrine tumors: potential algorithm for symptom control and disease management. *Clinical trials could be initiated earlier in disease management.

As NET patients have multiple etiologies contributing to their diarrheal symptoms, a careful history assists in developing a differential diagnosis. After excluding dietary and medication factors (excessive fat, fruits, cathartics), less common possibilities such as infection with *Clostridium difficile or Helicobacter pylori*, intestinal bacterial overgrowth, and intestinal ischemia should be considered. A gastrointestinal workup inclusive of upper and lower endoscopy may assist in identifying or excluding an etiology. Postprandial diarrhea suggests either dumping syndrome or intestinal ischemia. The former may respond to a dumping diet and shifting liquid ingestion to 30 minutes after a meal. Intestinal ischemia is definitively diagnosed with angiography, but the patient's history is one typically of a gradual worsening of symptoms and may result in food phobia and profound cachexia.

CARCINOID CRISIS

Carcinoid syndrome symptoms that are unremitting can be life-threatening and should be considered an oncologic emergency. Volume electrolyte replacement, octreotide, and correcting the metabolic acidosis while improving any diarrheal symptoms are required to reverse clinical deterioration.[2,24] Identifying and treating the precipitating event such as sepsis, bleeding, or a viral illness is critical in controlling the crisis. Corticosteroids, antibiotics, and infusional octreotide are additional options to consider in the acute care setting.[25,26]

Carcinoid Crisis Prophylaxis

For carcinoid syndrome patients undergoing general anesthesia or an invasive procedure such as embolization, decreasing the risk of carcinoid crises with supplemental octreotide is recommended.[27,28] The risk for crisis is greater in the more symptomatic patient with greater disease bulk. Resuscitative intraoperative techniques for treating hypotension are unique in that symptoms are generally refractory to fluid resuscitation alone. Adding calcium and/or catecholamines, including low-dose dopamine, may only worsen the deterioration by provoking the additional release of tumor mediators (tachykinins). The blood pressure should be supported by infusion of colloid and octreotide (300–500 micrograms intravenously [IV]) given immediately.[24,27] A continuous IV drip of octreotide may be necessary for an indefinite postoperative period (eg, 50–150 μg/h). For patients at high risk of carcinoid crisis (significant hepatic tumor involvement and/or history of difficult to control syndrome symptoms), IV octreotide may be initiated prophylactically preoperatively (eg, 50–150 μg/h).

There are no guidelines for supplementing patients receiving monthly octreotide LAR. One approach is to schedule an elective procedure within 1–2 weeks after an intramuscular (IM) injection and to provide supple-

mental continuous infusion of octreotide for the high-risk patient undergoing general anesthesia or any stressful procedure. As octreotide's therapeutic index is wide, the risks are minimal with higher blood levels associated with greater somatostatin receptor occupancy.[29]

CARCINOID HEART DISEASE

Carcinoid heart disease is characterized by a fibrous, plaque-like endocardial thickening with shortening of the chordae tendineae, immobility of the tricuspid/pulmonic valve cusps producing regurgitation, and stenosis of varying degrees. Tricuspid insufficiency is the predominant finding with tricuspid stenosis, pulmonary insufficiency, and stenosis being less common. Minimizing cardiac hepatopathy while maximizing cardiopulmonary function and quality of life are the major goals in diagnosing and controlling carcinoid heart disease.[30]

In the pre-somatostatin era, echocardiographic evidence of carcinoid heart disease occurred in approximately two thirds of patients with histologically proven midgut tumors.[31] As supportive care evolved in the post-somatostatin era, the occurrence of carcinoid heart disease decreased markedly.[32] This may be related to achieving better control of serotonin levels through a variety of mechanisms. Following patients at risk for carcinoid heart disease (high 24-hour urinary 5-hydroxyindolacetic acid [5-HIAA] levels) or those with symptoms of right-sided heart failure (dyspnea, lower extremity edema) with careful serial history and physical exams, echocardiograms, and selective exercise testing every 6–12 months may assist in optimally timing valve replacement.

General measures for treating heart failure include salt and water restriction while monitoring electrolytes, fluid balance, and weight. Initiating diuretics is a double-edged sword as improving the lower extremity edema decreases left-sided cardiac output and increases fatigue and dyspnea. A combination of loop diuretics and digoxin may be the initial intervention in treating right-sided heart failure. Judiciously adding a thiazide diuretic may be necessary when the loop diuretics reach their maximal effect. Even though data are lacking, it is generally accepted that digoxin improves right heart function.

CUSHING'S SYNDROME

Recognizing and correctly identifying the cause of hypercortisolism are important in potentially curing the underlying disorder and alleviating long-term complications while decreasing the risks for opportunistic infections.[33–36]As Cushing's syndrome signifies more of a symptom complex rather than a single complaint, it is not only the symptoms of central obesity, moon facies, hypertension, diabetes, acne, hirsutism, striae, buffalo hump, and menstrual irregularity being present but also the rapidity of onset that assists in making the correct diagnosis.[37,38] After excluding exogenous sources, possible etiologies for hypercortisolism include primary pituitary or hypothalamic tumors, the ectopic production of adrenocorticotropic hormone (ACTH), or corticotrophin-releasing hormone (CRH)-releasing tumor or autonomous adrenal production.[39,40] Guidelines for making the diagnosis and treatment are well-defined.[41,42]

The initial therapeutic challenge is to immediately decrease the harmful effects of hypercortisolism by removing the source of ACTH and/or by inhibiting adrenal enzymes. Prescribing fast-acting steroidogenesis inhibitors such as ketoconazole and metyrapone, and those with a slower onset of action such as mitotane, singly or in combination would be options depending on the severity of the hypercortisolism.[43,44] Mifepristone (RU-486) was recently approved for endogenous Cushing's syndrome patients with glucose intolerance secondary to hypercortisolemia and who have failed surgery or are not surgical candidates.[45–47] Somatostatin congeners such as octreotide or lanreotide, used alone or in combination with the dopamine receptor agonist, cabergoline, respectively, may be additional therapeutic options.[37,48,49] The expression of the somatostatin receptors may assist in predicting response and may be downregulated in the setting of hypercortisolemia.[46,50]

Cushing's syndrome induces a hypercoagulable state and patients are at significantly higher risk for a thromboembolic event during a procedure.[51,52] Anticoagulation guidelines are lacking. There also can be a compensatory increase in the thymus gland or the presence of a mediastinal "pseudo" tumor following cortisol normalization.[53] Such masses do not require further evaluation and routine surveillance usually suffices. Bone mass and bone turnover remain impaired for at least 2 or more years following cortisol normalization.[54]

GASTRINOMAS

Presenting symptoms of abdominal pain, dyspepsia, diarrhea, and gastrointestinal bleeding can be insidious in onset and present for years.[55,56] Gastrin oversecretion or Zollinger-Ellison syndrome (ZES), may arise from a tumor that is either sporadic in its occurrence or hereditary as in patients with multiple endocrine neoplasms 1 (MEN 1). Effective acid suppressive therapy, such as the H_2 antagonists and proton pump inhibitors (PPIs), reduces the need for and complications of total gastrectomy.[57,58] The goal of medical management of gastrinomas is to control symptoms while minimizing any treatment-related side effects.

Dose titration of acid-suppressive agents is more of an art than the science of medicine as peptic symptoms

are poor markers of acid secretion and quantitative acid studies are impractical. High initial doses of PPIs (such as 60 mg/d of omeprazole) are frequently prescribed, with dose adjustment as necessary based on symptom response.[59] PPIs (omeprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole, and pantoprazole) irreversibly bind to and inhibit the parietal cell enzyme, hydrogen/potassium adenosine triphosphatase (ATPase). In the acute setting where oral medications may be contraindicated, IV formulations are effective.[60] Forty ZES patients participated in a 4-year study which concluded that omeprazole effectively controls acid secretion in all patients. Once-daily omeprazole administration was effective in approximately 60% (31/50) of patients, while complete peptic symptom resolution occurred in 23 or 29 subjects who failed H_2 antagonist therapy. The absence of gastric NET on endoscopies and gastric biopsies after long-term omeprazole therapy is encouraging.[61] Dose de-escalation to 20 mg/d is feasible after several years of high-dose omeprazole therapy.[62]

Complications of the chronic pharmacologic maintenance of the achlorhydric state include vitamin B_{12} deficiency. A 29% frequency was reported in patients on long-term PPI therapy with blood B_{12} levels underestimating the true occurrence.[63] Iron absorption is not altered by chronic PPI treatment.[64] Chronic PPI therapy induces enterochromaffin-like (ECL) cell hyperplasia by increasing gastrin release from gastric cells. ECL hyperplasia may be a precursor to type I gastric NET.[65] Chromogranin A (CGA) levels are elevated by chronic PPI therapy. Early observations suggest that pancreastatin, a subunit of CGA, may distinguish between a benign condition and a malignant one, as the enzyme convertase-1, expressed in the latter, results in elevated pancreastatin levels.[66]

Somatostatin analogs lower gastrin levels and can control symptoms and disease in some patients. Their use as single agents or in combination with chemotherapy in the second-line setting may improve symptom control and result in disease regression.[6,67,68]

Radiation therapy from either open or closed sources is an option for selected patients. For symptom palliation in metastatic disease and/or disease control for locally advanced pancreatic NET patients, external-beam radiotherapy with or without chemotherapy is effective.[69-71] PRRT (yttrium 90, lutetium 177, rhodium 188, indium 111), while available in multiple European centers, is investigational in the United States.[72-76]

INSULINOMAS

Presenting symptoms of an insulinoma patient are often confusing and constitute an unusual spectrum, including hypoglycemia, syncope, involuntary weight gain, and unexplained seizure disorder. Symptoms can occur both fasting and postprandial and in a smaller group of patients, only postprandial.[77,78] Confusion, changes in vision, and strange behavior including amnesia reinforce the perception of a psychiatric illness in some cases. Signs of hypoglycemia include tachycardia, diaphoresis, and tremulousness. The median duration of symptoms before the correct diagnosis is typically less than 1.5 years, with the upper range being decades.[79]

Screening the patient for multiple endocrine neoplasia type 1 (MEN 1) includes taking a family history, inquiring about disorders of calcium homeostasis and prior neck surgery. Insulinomas are the second (following gastrinomas) most frequent pancreatic neuroendocrine tumor (pNET) occurring in MEN 1.[80]

Following tissue diagnosis and standard staging procedures, treatment options include complete tumor removal for localized disease or debulking metastatic disease to improve symptoms. The metastatic disease patient requires ongoing medical management for symptom and tumor control.

At times of hypoglycemia, dextrose administration, intramuscular glucagon, and potassium replacement may be required emergently. For more chronic control, diazoxide (3–8 mg/kg/d orally every 8–12 hours with total daily doses up to 1,200 mg), limiting energy expenditure, and small frequent feedings are options. The adverse effects of diazoxide include fluid retention requiring diuretics and nausea at higher doses.[81,82]

The somatostatin analogs (octreotide, lanreotide) can control symptoms in approximately 50% of patients and, in a small percent, decrease tumor burden, with at least one report of a complete tumor response.[83,84] As hypoglycemic symptoms may worsen (paradoxical response) with somatostatin analog therapy, inpatient management should be considered when initiating octreotide in patients with tumors that are negative on ^{111}In-pentetreotide scintigraphy (OctreoScan, Mallinckrodt, Maryland Heights, MO) Additional treatment options include chemotherapy, sunitinib, everolimus, ^{90}Y radioembolization, bland or chemoembolization, and radiofrequency ablation (RFA) or peptide receptor radiotherapy (PRRT) (see Figure 1).[85,86,87,88]

VIPomas

High-volume (0.7–3 L/d) secretory diarrhea that persists during fasting and is accompanied by electrolyte imbalance (hypokalemia, hypomagnesemia, and hypocalcemia), dehydration, nausea, emesis, muscle weakness, cramps, and sometimes flushing are classic VIPoma symptoms. Usually occurring as solitary masses in the tail of the pancreas and metastatic at the time of diagnosis, VIPomas comprise one of the more rare pNETs.[89-92]

Reversing dehydration and correcting electrolyte abnormalities and acid-base balance constitutes the immediate medical need while initiating octreotide (50–100

μg subcutaneously every 8 hours) for chronic control. Converting to the intramuscular octreotide formulation (20–30 mg of octreotide LAR) allows for better quality of life. Although not anticipated, tumor shrinkage can occur with long-term octreotide.[93] Regional therapy and debulking techniques are other effective methods to improve symptom control.[94,95]

GLUCAGONOMAS

Diabetes accompanied by the "4Ds"—dermatosis (necrolytic migratory erythema), depression, diarrhea, and deep venous thrombosis—is diagnostic for glucagonomas that should be considered malignant despite a benign histologic appearance.[96–98] Diarrheal symptoms may be indicative of co-secreted amines/peptides, thus measuring gastrin, VIP, 5-HIAA, and calcitonin concentrations may have value. Among endocrine tumors, venous thrombosis is unique to glucagonomas and occurs in approximately one third of subjects.[99] The glucagonoma syndrome can be present without hepatic metastases and is rarely associated with MEN 1.

As glucagon is a catabolic hormone, weight loss is an expected symptom either at the time of diagnosis or during management. Weight loss and the dermatosis are the most common symptoms and are present in approximately two thirds of patients at diagnosis.[98] The hyperglycemia induced by glucagon ranges from mild to moderate, though ketoacidosis has been documented.[100] In most cases, blood sugar levels are easily controlled by diet, oral agents, and insulin, as beta-cell function remains intact in most patients.

Hyperglycemia, anemia of chronic disease, and nutritional deficiencies require immediate management. Somatostatin analogs are effective for long-term management with improvement in the dermatosis, diarrhea, and neurologic symptoms such as ataxia, optic atrophy, dementia, and proximal muscle weakness.[98,101,102] Titrating octreotide from 50 μg subcutaneously three times daily to the depot formulation effectively controls symptoms for 2 months to 3.5 years.[98] As amino acid levels are decreased secondary to oxidation and gluconeogenesis, amino acid infusions may improve the rash characteristics.[103] Rash prevention in glucagonomas has been documented with zinc therapy[101,102]

Alpha-interferon is another option to improve hormonal hypersecretion symptoms. In general, it causes tumor shrinkage in up to 15% of patients and stabilizes tumor growth in 20%–40% of NET patients; however, data specifically in glucagonomas are lacking.[104]

SOMATOSTATINOMAS

The triad of cholelithiasis, hyperglycemia, and steatorrhea triggers the suspicion for a somatostatinoma, a neuroendocrine tumor of the pancreatic D cell.[105,106] Abdominal pain and weight loss frequently accompany this classic triad when the primary tumor is in the pancreas. Jaundice with abdominal pain and weight loss, signals that the primary tumor may be in the pancreas or duodenum. Measuring relevant hormonal biomarkers that may be elevated, such as fasting levels of somatostatin, pancreatic polypeptide, and chromogranin A confirms any clinical suspicion. Therapy with octreotide may improve the diarrhea, diabetes, and weight loss.[107] Patients presenting with hepatic disease have a worse prognosis, although their 5-year survival approaches 56%.[108]

TUMOR DEBULKING OPTIONS FOR IMPROVED SYMPTOM CONTROL

An increase in disease-related symptoms from local tumor progression in the liver, eventually with liver failure due to hepatic replacement by tumor, is a common cause of death.[109] For patients with either well-differentiated or intermediate-grade neoplasms, debulking with either cytoreductive surgery, hepatic embolization, or RFA offers the potential for meaningful improvement in symptom palliation by reducing hormonal levels and overall tumor burden (Figure 2).

For patients who are not surgical candidates, liver regional therapy options include hepatic embolization, chemoembolization, hepatic perfusion, and brachytherapy.[110] These regional arterial therapies are administered through angiographic catheters and delivered into a segmental, lobar, or whole liver distribution. Particle embolization with or without chemotherapy has become standard therapy for patients with extensive liver involvement. While data suggest that the addition of intra-arterial cytotoxic chemotherapy improves outcome for patients with pancreatic NETs, there are conflicting data for patients with midgut NETs as the target populations and techniques are too heterogeneous and inconsistent, respectively.[111] The post-embolization syndrome (malaise, fever, pain, and nausea) that predictably occurs following a bland or chemoembolization requires a short hospitalization stay for support (IV fluids, antibiotics, antiemetics, and analgesics).

Radioembolization is a form of brachytherapy that uses the hepatic artery as a conduit to selectively deliver the β-emitter ^{90}Y. This type of radiation is effective and well-tolerated in cancer patients with hepatic metastases.[112,113] Since stasis of blood flow is not a goal of radioembolization, patients do not generally require hospitalization for management of symptoms and complications. In the absence of prospective multicenter head-to-head comparator trials assessing the efficacy and safety of embolization procedures versus regional brachytherapy, deciding between the two procedures is determined more by individual patient characteris-

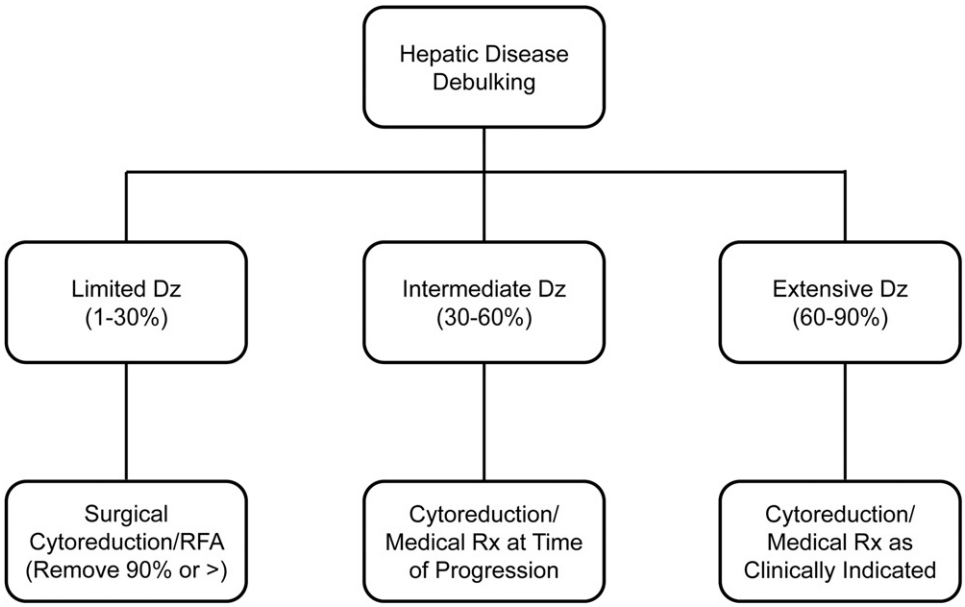

Figure 2. Locoregional debulking algorithm for functional well-differentiated neuroendocrine tumors. Patients with "low bulk" disease or <30% hepatic involvement, if not surgical candidates, could be treated systemically with locoregional therapies considered at the time of progression. For patients with "moderate bulk" disease or between 30%–60% of hepatic involvement, locoregional therapy should be considered prior to progression. Locoregional therapy for the "high bulk" disease patient with >60% of liver involvement, is dependent upon patient factors with regards to hepatic function and comorbidities.

tics and/or the experience of the managing physician/team.

Therapies that anatomically or physiologically disrupt blood vessels such as embolization/chemoembolization or VEGF inhibitors may affect the efficacy of subsequent agents intra-arterially delivered. Sequencing bland or chemoembolization with radioembolization has been reported.[114] As one intrahepatic therapy may influence another, there are no studies to guide the optimal sequencing of these treatments. The success of intrahepatic brachytherapy depends upon, at least in part, the anatomy and integrity of the hepatic vasculature.

CONCLUSION

Controlling the symptoms of functional NETs includes medical, surgical, and interventional radiologic procedures. As the options in controlling symptoms have increased dramatically over the last three decades, NET patients have experienced not only improved survival but also a better quality of life. The challenge becomes the early recognition and diagnosis of a functional hormonal condition followed by the timely sequencing of medical, surgical, and radiologic therapies.

As not all NETs have the same prognosis and manifestations, the symptoms (and the methods needed to control them) differ according to primary site. The personalization of therapy for symptom control mimics that of tumor control. As signaling pathways are better understood, symptom control in the future will be based more on molecular physiology than empiricism.

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