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Treatment of Symptomatic Neuroendocrine Tumor Syndromes: Recent Advances and Controversies

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Abstract

Introduction—Neuroendocrine tumors (NETs), once thought rare, are increasing in frequency in most countries and receiving increasing attention. NETs present two treatment problems. A proportion is functional, hormone-excess-state (F-NET), each of which must be treated. Recently, there are many advances, well-covered in reviews/consensus papers on imaging-NETs; new, novel anti-tumor treatments and understanding their pathogenesis. However, little attention has been paid to advances in the treatment of the hormone-excess-state. These advances are usually reported in case-series, and case-reports with few large studies. In this paper these advances are reviewed.

Areas covered—Advances in the last 5-years are concentrated on, but a review up to 10-years was performed. PubMed and other databases (Cochrane, etc) were searched for F-NET-syndromes including carcinoid-syndrome, as well as meeting-abstracts on NETs. All advances that controlled hormone-excess-states or facilitated control were covered. These include new medical-therapies [serotonin-synthesis inhibitors (telotristat), Pasireotide, new agents for treating ACTHomas], increased dosing with conventional therapies (octreotide-LAR, Lanreotide-Autogel), mTOR inhibitors (everolimus), Tyrosine-kinase inhibitors (sunitinib), cytoreductive surgery, liver-directed therapies (embolization, chemoembolization, radioembolization, RFA), peptide radio-receptor-therapy (PRRT) and ¹³¹I-MIBG, ablation of primary F-NETs.

Expert Opinion—Although many of the newer therapies controlling the hormone-excess-states in F-NETs are reported in relatively few patients, all the approaches show promise. Their description also generates some controversies/unresolved areas, such as the order of these new treatments, their long-term efficacy, and effectiveness of combinations which may require large, controlled studies.

Keywords

Acid hypersecretion; carcinoid syndrome; chemoembolization; chemotherapy; cytoreductive surgery; embolization; gastrinoma; insulinoma; Lanreotide; multiple endocrine Neoplasia type 1; neuroendocrine tumor; pancreatic endocrine tumor; peptide radio-receptor therapy; octreotide;

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radioembolization; radio-frequency ablation; SIRT; somatostatin analogues; telotristat; Zollinger-Ellison syndrome

1. Introduction

Almost 70% of neuroendocrine tumors (NETs) occur in the gastrointestinal tract (GI) and they have long fascinated clinicians, because they can produce florid, specific clinical syndromes, secondary to their unique secretory products [1, 2]. All gastrointestinal tract NETs have many similarities in both their cytochemical properties, with characteristic expression of specific proteins (neuron specific enolase, syntrophophysin, chromogranin A [CgA]), ultrastructural features with electron dense granules, their ability to produce multiple amine/peptides and their characteristic histological appearance with generally uniform nuclei and cytoplasm [2]. The gastrointestinal NETs include both pancreatic neuroendocrine tumors (pNETs) as well as NETs from other gastrointestinal sites (GI-NETs) (carcinoids) [2].

Recent studies demonstrate gastrointestinal NETs are not as infrequency as is commonly believed and in fact, both pNETs and GI-NETs (carcinoids) are increasing in frequency [3–5]. Although this very well many represent increased detection, nevertheless, clinicians will be seeing an increasing number of these patients. Patients with NETs can have two distinct therapeutic problems that both need to be dealt with. Numerous studies demonstrate that a significant proportion of NETs can have aggressive growth with the development of metastatic disease and in addition, up to 30% of patients with pNETs and 3–13% with GI-NETs (carcinoids) of the small intestine, a specific hormone-excess state is present [2]. Although curative resection would cure both problems, in many cases, because of the extent of disease, this is not possible and therefore treatment must be directed at each of these two problems [2, 6, ••8]. Historically, primarily for control of aggressive growth, both chemotherapy and interferon treatment has been used, however, particularly with chemotherapy, it generally has a slow duration of action (weeks) and thus has not been generally useful for control of the hormone excess state, especially acutely. Recently, much attention has been directed at establishing newer treatment approaches directed at the growth of the NETs with a number of studies involving large groups of patients as well as placebo controlled, randomized, double-blind studies demonstrating the ability to extent progression-free survival with the use of somatostatin analogue [9, 10], the mTor inhibitor-everolimus [11, 12], and tyrosine kinase inhibitor, sunitinib [13], as well as the usefulness of peptide-directed radiotherapy (PRRT) with ¹⁷⁷Lu-labeled somatostatin analogues [••14, 15, 16]. Each of these antitumor treatments, as well as other antitumor treatment approaches directed at the growth and malignant nature of the NET such as the role of aggressive surgery [17, 18, •19] or liver-directed therapies (embolization, chemoembolization, radiofrequency ablation, radioembolization) [17, 20, 21, •22] have been well covered in recent reviews. Furthermore, recent overall guidelines for emphasizing the management NET per se of various gastrointestinal NETs including GI-NETs (carcinoids) in different GI locations [1, ••8, 23, •24, 25, 26] as well as pNETs [1, ••8, 23, 25, 27, 28] have been published.

In these recent reviews and consensus statements, what has not been specifically covered, is the recent changes including advances and controversies, in the management of the hormone hypersecretory states. These are not specifically covered because in many cases the antitumor management of the NET itself may not specifically control the hormone-excess state, for example, in the patient who is not surgically cured or in a patient with an advanced disease present from the beginning, which occurs in 30–50% of most functional pNET(F-pNETs)(except insulinomas) and in up to 50–70% of patients with GI-NETs in some locations[2].

This article will concentrate on recent advances as well as controversies in the management of the functional hormone-excess states and will only deal with advances in the management of the NET per se(antitumor treatment, etc) when it impacts on the management of the hormone-excess state. It will concentrate primarily on changes within the last 5 years. Unfortunately, for a number of reasons a systematic analysis or critical analysis of the data available on controlling the hormone excess states is limited. Most of the reports on efficacy of the advances in control of the hormone excess state are reported in case-series, case-reports, or retrospective studies. In addition, symptom control is frequently not the primary endpoint, and the studies are usually single centered. Nevertheless, the review of this data provides some important insights in promising therapeutic approaches, which should be examined in the future by larger, controlled studies.

Before the specific advances/controversies are considered it is important to understand a number of background issues involved in the management of these syndromes

2. Functional neuroendocrine tumor syndromes(F-NETS)

2.1. F-NETS: General

F-NET syndromes can be classified into those generally associated with pNETs and those generally associated with GI-NETs(carcinoids)[29]. Whereas, a number of the pNET syndromes are caused almost entirely by NETs in the pancreas(insulinoma, glucagonoma), other syndromes that are classified as pNET syndromes, in fact, can occur in NETs in extrapancreatic sites. Examples of this include duodenal gastrinomas causing Zollinger-Ellison syndrome(ZES), duodenal somatostatinomas(SSomas) associated rarely with the somatostatinoma syndrome, VIPomas occurring in neural tissues(especially in children), and GRFomas occurring in the small intestine[1, 28, 29]. Similarly, while carcinoid syndrome is characteristically usually seen in patients with liver metastases from GI-NETs from the jejunum/ileum, it can also occur with GI-NETs(carcinoids) from other GI locations, as well as rarely due to pNETs secreting serotonin[1, 29].

There are ten well-established pNET syndromes of which 9 are associated with a functional syndrome(F-pNETs) and one is not associated with a specific clinical syndrome(nonfunctional-pNET, NF-pNET). NF-pNETs, in the strict sense are not nonfunctional, in that they usually secrete a number of different products (CgA, neuron specific enolase, pancreatic polypeptide, ghrelin, neurotensin, etc.), however, these do not result in a specific clinical syndrome [1, 2, 30]. The nine F-pNETs include gastrinomas releasing gastrin to cause ZES; insulinomas; VIPomas secreting vasoactive intestine peptide;

glucagonomas; SSomas; GRFomas secreting growth hormone-releasing factor; ACTHomas; pNETs secreting serotonin causing carcinoid syndrome and pNETs causing hypercalcemia by secreting PTH-RP[1, 2]. In addition to these well-established pNET syndromes, there are number of other very rare pNETs with functional syndromes(1–5 cases) which include pNETs secreting luteinizing hormone, renin, GLP-1, IGF-2, erythropoietin, enteroglucagon and cholecystokinin[1, 31], which will not be further discussed because there are too few cases studied.

2.2. F-NETS: Why treatment of hormone-excess state needed throughout care of many F-Net patients

Numerous older studies demonstrate the functional hormone-excess state needs to be controlled at all times in these patients or there is a marked increase in both morbidity and mortality[2, 27, 32–34]. This includes both acutely when the patient is initially seen as in the pre-operative period, immediate postoperative period and during long-term follow-up[2, 32, •33].

Almost all of the patients with F-pNETs, and the majority of patients with carcinoid syndrome due to a GI-NET(carcinoid), present with symptoms due to the hormone-excess state[1, 2, 35]. Therefore, in addition to suspecting the diagnosis and establishing the diagnosis, one of earliest steps in the management of these patients is to control the hormone-excess state. This need exists throughout the management of most F-NET patients because it also has to be done during any surgical operation, as well as during the follow-up if they are not cured. The need to treat the hormone-excess state is a life-long problem in >60% of all F-NET patients because cure is possible in only the minority of patients. Cure is possible in 60% of patients with gastrinomas, less than 50% of patients with all the other F-pNETS(except insulinomas which can be surgical cured in >90%), and in <5% of patients with carcinoid syndrome due to its most frequent cause(i.e. a jejunal-ileal GI-NET(carcinoid))[6, ••8, 27, 36, 37].

In the following sections the newer modalities for treating the hormone-excess state will be briefly discussed followed in a separate section by their specific use in the various F-NET syndromes. In this latter part existing therapies of the hormone-excess state will be briefly covered also. This will be followed by a discussion of the controversies/unresolved issues.

3. Summary of recent advances/controversies in management of hormone-excess states of functional NETs(Tables 1 and 2)

3.1. Use of mTor inhibitors to control symptoms of F-NETS hormone-excess states in refractory patients

The mTor inhibitor, everolimus is now approved in the United States for its antigrowth effects on both pNETs and GI-NETs(carcinoids), as well as for pulmonary NETs, in patients with advanced progressive disease. Two placebo-controlled, prospective, randomized phase 3 studies supported this result with everolimus significantly prolonging progression-free survival in each of these patient groups[11, 12].

While its principal use in patients with NETs is for its antigrowth effects, recent studies involving small series[•38, •39, 40, 41] as well as case reports[42–46] provide support for the conclusion that everolimus also is effective at controlling the hormone-excess state in patients with refractory F-NET syndromes, including both F-pNETs and with carcinoid syndrome due to GI-NETs(carcinoids). One study shows a similar benefit with the mTor inhibitor, rapamycin[47]. [This will be discussed in more detail on the specific syndromes in the following section.

3.2. Use of the tyrosine kinase inhibitor, sunitinib, to control symptoms of F-NETs hormones-excess states in refractory patients

The tyrosine kinase inhibitor, sunitinib, inhibits the tyrosine kinase activity of PDGFRs, VEGFR-1, VEGFR-2, c-KIT and FLT3[48]. Sunitinib is approved in the United States for its antigrowth effects of pNETs in patients with progressive advanced disease. This approval was based on the results of a double-blind, prospective, placebo controlled phase 3 study which demonstrated sunitinib significantly extended progression-free survival in these patients as well and increased overall survival[13].

Sunitinib's principal use is in patients with pNETs for its antigrowth effect in patients with advanced disease, however small series[49] and case reports[•50, 51], support the conclusion that it is effective at controlling hormone-excess states in patients with refractory, symptomatic pNET syndromes.

3.3. Use of Peptide radio-receptor therapy(PRRT) with ¹⁷⁷Lu-labeled somatostatin analogues, to control symptoms of F-NETs hormone-excess states in refractory patients

Gastrointestinal NETs including both pNETs and GI-NETs(carcinoids) resemble each other and NETs in other locations, by overexpressing somatostatin receptors(sst2, 5) in 80–100% of well-differentiated tumors[17, 52, 53]. This overexpression of somatostatin receptors has been successfully used to image both the primary tumor and the tumor extent, using primarily ¹¹¹In-labeled-somatostatin analogues or ⁶⁸Ga labeled somatostatin analogues[••8, 17, 52, 53]. At present, the use of ⁶⁸Ga-labeled somatostatin analogues with positron emission tomography and computed tomographic scanning(PET/CT) is the most sensitive imaging modality available for these tumors and is approved for this use both in the United States and Europe[••8, 52, 53].

Numerous studies have extended the observation of overexpression of somatostatin receptors by NETs to develop radiolabeled (¹¹¹In, ¹⁷⁷Lu, ⁹⁰Y) somatostatin analogues to deliver cytotoxic doses to malignant NETs[15, 16, 52]. These studies provided strong support that peptide radioreceptor therapy [PRRT] using radiolabeled somatostatin analogues had promise as an effective cytotoxic therapy for patients with advance unresectable NETs[15, 16, 52]. Recently, a double-blind, prospective, randomized trial has supported the efficacy and safety of this approach in patients with advanced inoperable, progressive midgut GI-NETs(carcinoids)[••14]. In this trial of 230 patients with grade ½ midgut carcinoids, a marked increased in progressive-free survival (p<0.0001) was seen with PRRT treatment with a ¹⁷⁷Lu-labeled-somatostatin-analog, with an acceptable safety profile(low rate of

grade 3/4 toxicity) and with a suggestion of an improved survival, although the analysis is not yet complete[•14,].

At present PRRT with ^{177}Lu labeled somatostatin analogues is not approved by the FDA in the United States for its antitumor treatment in patients with advanced unresectable NETs, but it is widely used on a compassionate basis, especially in Europe[15, 16, 55]. Recent studies involving small series[•56, 57] as well as case reports[58–60, •61, 62, •63, 64–66] provide support for the conclusion that PRRT with radiolabeled somatostatin analogues also is effective at controlling hormone-excess states in patients with refractory F-NET syndromes, including both F-pNETs and with carcinoid syndrome due to GI-NETs(carcinoids).

3.4. Use of liver-directed therapies[TACE, TAE, Radioembolization (SIRTs), RFA] to reduce tumor mass/hormone release and increase response to medical therapy to control symptoms of F-NETs hormone-excess states in refractory patients

Approximately 30–50% of patients with different F-PNETs syndromes (except insulinoma=where 90% benign) and 98–100% of patients with carcinoid syndrome due to a malignant GI-NET(carcinoid), have liver metastases at presentation[2, ••8, ••24, 27, 28, 67]. These patients are rarely cured surgically and thus are candidates for various forms of liver-directed therapies, particularly when the primary tumor is resected[1, 20, 21, •22, 68, •69, 70]. Liver-directed therapies include trans-arterial embolization (TAE), trans-arterial chemoembolization(TACE), radioembolization or selective internal radiation therapy(SIRT), as well as radio-frequency ablation(RFA) and cytoreductive surgery. The later two will be considered in separate sections below.

TAE and TACE can be safely performed because NET metastases in the liver are highly vascular and derive their blood supply primarily from tributaries of the hepatic artery, whereas normal liver parenchyma is supplied primarily by the portal vein[17, 20, 21, 22, 68, 71]. Consequently, interruption of the tributaries of the hepatic artery affects the tumor deposits much more than the normal liver. This interruption can be performed at surgery, but is usually performed percutaneously and can be either occlusion only (TAE) or with the co-administration of chemotherapeutic agents(TACE) (usually doxorubicin, mitomycin C, streptozotocin, fluorouracil, cisplatin)[17, 20, 21, •22, 68, 71].

TAE or TACE are usually performed for palliative treatment of liver-predominant disease which is not surgically resectable to reduce the hepatic tumor mass and 25–85% of patients have an objective tumor response, with a mean duration of response of 6–45 months[17, 20, 21, •22, 68, 71]. This approach has been particularly considered in patients with hepatic symptoms or refractory malignant F-NET syndromes[17, 20, 21, •22, 68, 71]. In general TACE/TAE result in a symptomatic response in 50–100% of patients and numerous series as well as case reports have documented their control of symptoms in patients with both carcinoid syndrome and F-pNET syndromes[17, 20, 21, •22, 68, 71, 72, •73, 74, 75, •76, 77, •78].

Radio-frequency ablation or other forms of ablation of metastatic NETs can also be performed at the time of surgery or percutaneously[17]. Of these different ablative surgeries,

RFA is the most frequently performed, often in combination with surgery, especially to remove isolated metastases in other hepatic locations[17, 20, 21, •22, •24, •69, 79–81]. Numerous criteria for when this should be considered have been proposed depending on the number of lesions, size, and proximity to vital structures[17, 20, 21, •22, •24, •69, 79–82]. Besides the use of RFA as an anti-tumor treatment, a number of studies have reported enhanced symptomatic control of functional NETs after its use[17, 20, 21, •22-, •24, •69, 79–83].

Radioembolization or SIRTs primarily involves primarily the use of ^{90}Y trium(^{90}Y) microspheres (either ^{90}Y resin microspheres[SIR-spheres) or ^{90}Y glass microspheres(Therespheres))(17, 20, 21, •22, •69, 70). These are administered intra-arterially primarily as an anti-tumor treatment, however a number of studies have reported enhanced symptomatic control of F-NETs after their use[17, 20, 21, •22, •69, 70].

These approaches will be discussed in more detail on the specific syndromes in a latter section.

3.5. Use of percutaneous/endoscopic ablative therapies(ethanol, etc.) for primary or metastases(F-pNETs) to reduce tumor mass/hormone release and increase response to medical therapy or to control symptoms of F-NETs hormone-excess states in refractory patients

As pointed out in #3.4. above a proportion of patients with F-NET syndromes have extensive disease and are not surgical candidates. In addition a portion of patients, primarily with F-pNETS have increasingly refractory symptomatic disease with only a primary or adjacent localized disease, who are not candidates for surgery, because of accompanying medical problems, risks from age, etc. Recent studies, including small series as well as case reports, demonstrate, particularly the use of ethanol injections, administered percutaneously or by endoscopic ultrasound guidance, can be highly successful in this situation in controlling the hormone-excess-state in these patients and greatly enhancing the ability to control the hormonal symptoms[84–88, •89, 90–92, •93]. This approach will be discussed in more detail on the specific syndromes in a latter section.

3.6. Use of a supra-maximal doses of conventional therapies(carcinoid syndrome, F-pNETs) to increase response to medical therapy and to control symptoms of F-NETs hormone-excess states in refractory patients

Somatostatin analogues are the initial treatment to control the hormone-excess state in most F-NET syndromes, including the carcinoid syndrome, as well as number of F-pNET syndromes(GRFomas, VIPomas, SSomas, glucagonomas, and the very rare F-pNET syndromes)[1, 2, ••8]. However, in insulinomas, gastrinomas and ACTHomas, other drugs are usually initially used, as will be discussed in the separate sections on these syndromes below.

A proportions of patients with these F-NET syndromes do not have successfully control of the hormone-excess state with conventional doses of these drugs initially (20–30% with carcinoid syndrome). Furthermore, a proportion of patients with time, especially patients with F-NETs with nongastrinoma, insulinoma syndromes, treated with somatostatin

analogues, develop increasing resistance with time, when used at conventional doses[94–98]. Numerous studies, especially in patients with the carcinoid syndrome or VIPomas, have reported that increasing the doses of the somatostatin analogues by either using a higher dose, or using a conventional dose, at increased frequency than is conventionally used (more frequent than 1x/month) can help control the hormone-excess symptoms[94, 95, •96, 97–102].

3.7. Use of cytoreductives surgery to reduce tumor mass/hormone release and increase response to medical therapy or to control symptoms of F-NETs hormone-excess states in refractory patients

Unfortunately, only 5–15% of patients with F-NET syndromes with metastatic disease to the liver have potentially, completely resectable disease with the possibility of surgical cure, because of the presence of diffuse, bilobar hepatic metastases[••8, 17, •19, ••24, 28].

However, a number of authorizes recommend that cytoreductive surgery or debunking surgery be considered in patients in which 70–90% of the visible disease is resectable[••8, 17, •19, ••24, 28, 80]. This is recommended is to primarily control refractory hormone-excess symptoms, to possibly facilitate medical control of the hormone-excess state, or to control local symptoms due to the tumor bulk, such as pain[••8, 17, •19, ••24, 28, 80, 100, 103]. Even though numerous studies report this also contributes to increased survival, there are no controlled studies, which establish this[17, •19, ••24, 28, •104]. Despite lack of controlled studies, the ENETs guidelines recommend surgery for curative intent whenever possible [9].

Numerous studies, as well as case reports, have demonstrated that cytoreductive surgery can facilitate the management of the hormone-excess state symptoms and therefore should be considered in any patients with increasing refractory symptoms[••8, 17, •19, ••24, 28, 103]. However, it is becoming increasingly confusing for many practitioners the exact role of cytoreductive surgery, with the increasingly effective numbers of medical therapies available, as well as PRRT, and increased numbers of liver directed therapies.

Liver transplantation is the ultimate hepatic debulking procedure and is occasionally used in patients with refractory hormone excess states with F-NETs confined to the liver[17, 18, 19, 24, 103].

3.8. Increased use of ¹³¹I-MIBG to reduce tumor mass/hormone release and increase response to medical therapy or to control symptoms of F-NETs hormone-excess states in refractory patients

Meta-iodobenzylguanidine(MIBG) is a biogenic amine precursor analogue, which is taken up by the norepinephrine transporter and stored in primarily the cytoplasm of number of neurosecretory cells[105, 105, 106].

MIBG radiolabeled with ¹³¹I(¹³¹I-MIBG) has been used for more than 20 years in the management of chromaffin tumors(neuroblastomas, pheochromocytomas, paragangliomas), but less frequently in NET tumors[105–110]. Up to 70% of GI-NETs(carcinoids) and 9–25% of pNETs demonstrate positive uptake with ¹³¹I-MIBG and a number of studies have

reported palliative effects with treatment of palliative with advanced carcinoid tumors[105–110]. These palliative effects included not only effects on tumor growth/size but also symptomatic improvement in patients with carcinoid syndrome[105–109]. ^{131}I -MIBG treatments have also been used in occasional patients with refractory F-pNET syndromes[•73, 110–112]. Therapy with ^{131}I -MIBG is generally well tolerated but can include pancytopenia, thrombocytopenia, nausea and emesis.

3.9. Use of a new specific syndrome therapies to reduce tumor mass/hormone release and/or increase response to medical therapy or to control symptoms of F-NETs hormone-excess states in refractory patients

3.9.1 Use of Telotristat, a tryptophan hydroxylase inhibitor, to inhibit serotonin synthesis and control symptoms of the carcinoid syndrome—The carcinoid syndrome is characterized by the presence of diarrhea, bronchospasm, episodic flushing of the skin and in its later stages, by the development of valvular heart disease[2]. It has long been known that serotonin is one of the key mediators of the carcinoid syndrome, and is especially involved in the development of carcinoid heart disease, as well as the diarrhea, which is seen in 60–100% of patients with the carcinoid syndrome[2]. Another important feature is the requirement that the serotonin enters the general circulation and not be inactivated by the liver, which occurs in most cases(>95%) by the presence of liver metastases[2].

Recently a tryptophan hydroxylase inhibitor, telotristat etiprate, has been developed, which, by inhibiting this enzyme, blocks the conversion of tryptophan to serotonin[2, 113, 114, •115]. Telotristat is an orally active, small molecule which was designed not to cross the blood brain barrier and only act peripherally, thus avoiding the CNS side-effects that were seen with older serotonin inhibitors such as parachlorophenylalanine, which limited their use[2, 113, 114, •115].

In a number of recent studies[1•14, •116, •117] including a Phase 3 prospective randomized trial(TELESTAR)[•115, •116], telotristat has been shown to decrease the occurrence of diarrhea, as well as markedly decrease or normalize urinary serotonin/5-HIAA levels in patients with the carcinoid syndrome. The telotristat decrease in the diarrhea had a large impact on the emotional, social and physical aspects of the patient's lives[113, •117, 118]. In these studies telotristat was well tolerated and adverse side effects were mild and generally of a GI nature[1•14, •115, •117]. One of the key questions is whether the use of telotristat will alter the course of the valvular heart disease. The only information available so far is a recent abstract based on two patients in the TELESTAR study with carcinoid heart disease reported who demonstrated no further progression in the valvular disease occurred while taking telotristat and the authors proposed the use of the drug may prevent the need for valve surgery in some patients[119].

3.9.2. Use of Pasireotide, a broad spectrum sst receptor agonist, to reduce tumor mass/hormone release and/or increase response to medical therapy, to control symptoms of F-NETs hormone-excess states in refractory patients—Well-differentiated gastrointestinal NETs overexpress at least one of the 5 subclasses of

somatostatin receptors(sst₁₋₅) in almost all cases, with the most frequent being sst₂(80–100%) and sst₅(50–60%)[2]. Somatostatin has high affinity for all 5 sst subtypes, whereas the related synthetic analogues, octreotide, octreotate(used for imaging) and Lanreotide interact with very high affinity only with sst₂ and intermediate affinity with sst₃/sst₅[2, •120].

As stated in the previous section, in a proportion of gastrointestinal F-NETs, octreotide/Lanreotide do not initially control the hormone-excess syndromes and furthermore, with time, in some patients that initially responded, they develop increasing resistance. Many of these NETs express the other classes of somatostatin receptors(sst_{1, 3, 4}) which interact only with low affinity with these drugs[121, •122, •123], raising the possibility that a broad acting somatostatin analog might be more effective[121, •122, •123, 124].

Pasireotide interacts with high affinity with all SST subtypes except sst₃ and recent studies demonstrate it may have increased utility in some of the gastrointestinal NETs and F-NET syndromes, in that it controlled the hormone-excess state, in some cases in patients with resistance to octreotide/lanreotide[121, •122, •123, 124, 125]. In an animal model of MEN1 patients with insulinomas, pasireotide treatment was able to control the hormone-excess state as well as the insulinoma growth[126]. While a once monthly injection of Pasireotide-LAR has been generally well-tolerated[127], hyperglycemia occurs at a higher frequency than seen with octreotide-LAR(28 vs 5%), as well as fatigue(11 vs 3.5%) and nausea(9.4 vs 0%)[124]. In two other studies hyperglycemia was seen in 16% and 79% of patients[121, •122]. In a study of normal volunteers[128], the pasireotide-associated hyperglycemia was related to a decrease in insulin secretion and incretin hormone response, without changes in hepatic/peripheral insulin sensitivity[128].

3.9.3. Use of newer agents to treat Cushing's syndrome due to pancreatic ACTHomas or other causes of ectopic Cushing's syndrome, to control symptoms—In various studies 4–16% of ectopic Cushing's syndrome (EAS) is due to pancreatic ACTHomas. Although uncommon in pNETs[2, 129], Cushing's syndrome can be the only sign of a F-pNET and it occurs in 4–5% of patients with sporadic ZES in which its development is associated with a poor prognosis, because the tumors are usually aggressive[2, 30, 130].

Until relatively recently the treatment of the EAS involved the use of bilateral adrenalectomy(preferably after period of control of the EAS), and medical treatment of the hypercortisolemia using mitotane, metapyrone and ketoconazole[131, •132, 133, 134]. Recently other classes of drugs have been used and reported to be helpful including glucocorticoid receptor antagonists(mifepristone[•135], etc.); adrenal specific therapy(etomidate, osilodrostat and fluconazole=11 β -hydroxylase inhibitors); somatostatin analogues including pasireotide; and dopamine receptor agonists(cabergoline, etc.)[131, •132, 133, 134]. In addition PRRT has been reported to be helpful in controlling the hypercortisolism with EAS and will be discussed under the specific syndromes in a later section.

4. Summary of recent advances in management of specific hormone-excess states of functional NETs(Tables 1)

4.1. General

For each of the F-NETs the hormone-excess state needs to be controlled as quickly as possible while the diagnosis, extent of manifestations of the hormone-excess state established (carcinoid heart disease, etc.) and treatment strategy are being formulated. The latter includes establishing the location of the primary tumor and extent of disease; with F-pNETs, the possible presence of an inherited syndrome such as MEN1[2, 136, 137]; whether surgical resection is possible, and the treatment of advanced disease, if present[2, ••8, 17, 27, 28, 136, 138, 139].

Control of the hormone state is needed during tumor localization, which is particularly important to formulating management steps. The tumor localization can be time-consuming and can be difficult with F-NET syndromes. The primary tumors can be small and therefore not localized by conventional cross-sectional imaging(CT, ultrasound, MRI)[2, ••8, 28, 140, 141] and frequently requires specified studies such as somatostatin receptor scintigraphy(SRS)(using ^{68}Ga or ^{111}In -labeled somatostatin analogues[••8, 52, 142], endoscopic ultrasound[2, ••8, 28, 142], and rarely, specific hormonal gradient sampling[2, 28, 143, 144]).

4.2. Carcinoid syndrome

4.2.1. Current standard treatment of carcinoid syndrome—Long acting somatostatin analogues(Octreotide-LAR, Lanreotide-autogel) supplemented during breakthrough with subcutaneous octreotide, are the standard therapies for controlling the principal carcinoid syndrome symptoms of diarrhea, flushing, and asthma[2, •96, 98, •120, 145, •146]. With time, refractory cases may develop and therefore, there is a need for new treatments[2, •96, 98, •120, 145, •146]. Treatment of the carcinoid heart disease involves standard treatment for heart failure/arrhythmias and in advanced cases, heart valve replacement[147]. Whether long-term somatostatin treatment prevents the development or progression of the carcinoid heart disease is not established[147].

4.2.2. Newer treatments of carcinoid syndrome(Table 1)—Almost all of the new therapies for F-NETs listed in Table 1 have been used successfully patients with carcinoid syndrome, some with refractory disease, although in many cases only small numbers of patients have been treated.

Both studies and case reports have reported the successful use in patients with carcinoid syndrome of the control of the symptoms of the hormone-excess state by using: everolimus[•38]; PRRT[•56, 57, 66, 95, •96, •148]; liver-directed therapies including TACE/TAE[70, 72, •73, 77, 95, 98, 149]; radioembolization[70, 150, 151]; RFA[80, 81, 83, 95, 152]; by increasing the dosage of octreotide/Lanreotide in refractory cases[94, 97, 153–155]; use of cytoreductive surgery[23, 95, 156–160]; use of ^{131}I -MIBG[95, 105, 106, 108, 110, •161, 162–164]; with the use of the tryptophan hydroxylase inhibitor, Telotristat[108, 113, 114, ••116, •117, 118, 119] and with pasireotide in octreotide resistant cases[•122].

In one series[•56] of 35 patients with refractory carcinoid syndrome symptoms, PRRT with ¹⁷⁷Lu-DOTA-Octreotate resulted in 63% of patients having a significant improvement in flushing and/or diarrhea. The TELESTAR study[•115, ••116] is ongoing and is a phase 3 randomized trial of the efficacy/safety of the 11B-hydroxylase inhibitor required for serotonin synthesis, in patients with carcinoid syndrome, Telotristat resulted in a 29%(250 mg) and 35%(500 mg) decrease in bowel movement frequency and was well tolerated[•115, ••116], suggesting it may be a valuable addition to control some aspects of the carcinoid syndrome. In a Phase 2, multicenter study[•122] involving 45 patients with carcinoid syndrome with refractory symptoms to octreotide-LAR, pasireotide controlled the diarrhea and/or flushing in 27%.

The carcinoid crisis is an emergency which can occur in patients with carcinoid syndrome [2, 24]. It is usually precipitated by procedures such as surgery and is characterized by extreme changes in blood pressure, flushing, diarrhea, CNS symptoms and cardiac arrhythmias[2]. High doses of somatostatin analogues are used prophylactically prior to these procedures, as well as intravenously during the procedure, but are not always successful [2]. Whether telotristat[••116, •117, 118] will prevent the development of carcinoid crises is unclear at present.

4.3. Insulinoma

4.3.1. Current standard treatment of Insulinoma—In >90% of patients with insulinoma the treatment is curative surgical resection[2, ••8, 28, 136]. This is the exception with the F-pNETs and occurs because insulinomas are usually solitary, almost all intrapancreatic in location, this is the only pNET syndrome in which almost of the tumors are benign, and in <3% of all patient, s insulinomas occur in patients with MEN1 in which they can be recurrent and multiple[2, ••8, 28, 136]. Therefore, control of the hormone-excess state in patients with insulinomas is usually only needed during the pre-operative period and in the minority of patients with malignant insulinomas. Currently, the primary treatment is frequent small feedings and the use of diazoxide, which can control symptoms in 50–60%. Somatostatin analogues are also used and are effective in 50%[99, 165, 166, •167] however, in some patients they can exacerbate symptoms, by inhibiting counter-regulatory mechanisms such as glucagon/growth-growth hormone release[2, 168, 169].

4.3.2. Newer treatments of insulinoma hormone-excess state(Table 1)—Many of the new therapies for F-NETs listed in Table 1 have been used successfully in patients with insulinoma, some with refractory disease, although in many cases only small numbers of patients have been treated.

Both studies and case reports have reported the successful use in patients with insulinomas, particularly in patients with malignant insulinoma which comprise<10% of all cases, but in whom the hormone-excess state can be difficult to control[•167]. Included in the recent literature are reports of the control of the symptoms of the insulinoma hormone-excess state by using: everolimus[•39, 40–46, 170, 171]; tyrosine kinase inhibitor sunitinib[•50]; PRRT[44, 55, 58–60, •61, •76, 170, 172]; liver directed therapies including TACE/TAE[44, 70, 72, •73, 74.75, •76, 172–174]; radioembolization[44, 70, 172]; RFA and use of ablative

treatment(ethanol, microwave of primary/metastases[81, 83–87, •89, 90, 92, •93, 175, •176, 177, 178]; by increasing the dosage of octreotide/Lanreotide in refractory cases[153, 155]; use of cytoreductive surgery[157, 158, 160, 172, 174]; use of ^{131}I -MIBG[•111] and with pasireotide in octreotide resistant cases[125].

In one report[55] involving 5 patients with metastatic insulinomas, with poorly controlled hypoglycemia on standard therapies, treatment with ^{177}Lu -DOTA-octreotate or ^{111}In -octreotide resulted in stable disease for a mean follow-up of 27 months with no hypoglycemic episodes. In three reports of 8[•89], 4[90] and 4[92] patients with insulinomas which were not operable in a number of cases, ethanol injection of the primary insulinoma controlled the symptoms of the insulinoma in all cases.

4.4. Zollinger-Ellison syndrome

4.4.1. Current standard treatment of Zollinger-Ellison syndrome(ZES)—At present approximately 25–40% of all patients with ZES are cured long-term[2, 6, ••8, 27], thus the majority require life-long treatment of the gastric acid hypersecretion. This occurs because 70–85% of patients with sporadic ZES (i.e.no MEN1) have small, duodenal tumors which are frequently missed at surgery, 25–35% have non-resectable liver metastases at diagnosis and 25% have MEN1 with multiple, small gastrinomas frequently with lymph node metastases[2, 6, ••8, 27, 37, 141, 179].

The medical control of the gastric acid hypersecretory state is highly effective with proton pump inhibitors(PPIs) and histamine H_2 receptor antagonists are also effective in most patients if high, frequent dosing is used[6, 27, •33]. Somatostatin analogues are also effective but rarely used because they require parental administration compared to the orally active PPIs and histamine H_2 receptor antagonists[27, •33]. Because tachypylaxis is not a problem with PPIs, these drugs remain effective and if sufficient drug is given, except for low vitamin B_{12} levels in some patients, there are very rarely any side-effects limiting their use, and acid secretion can be controlled in all patients with ZES long-term.[6, 27, •33, 180]. Therefore, these newer therapies to control the hormone-excess state have been rarely used in ZES patients.

4.4.2. Newer treatments to control Zollinger-Ellison syndrome(ZES) symptoms(Table 1)—Only a few of the new therapies for F-NETs listed in Table 1 have been used successfully patients with ZES, some with refractory disease, and only small numbers of patients have been treated.

Both studies and case reports have reported the successful use in patients with ZES of the control of the symptoms of the hormone-excess state by using: PRRT[65]; liver directed therapies including TACE/TAE[70, 173, 174, 181]; radioembolization[70], RFA[81, 83, •176, 182]; by increasing the dosage of octreotide/Lanreotide in refractory cases[155, 183]; use of cytoreductive surgery[156, 160, 174]; use of ^{131}I -MIBG[110, 164] and with pasireotide in octreotide resistant cases[•122].

4.5. VIPoma syndrome

4.5.1. Current standard treatment of VIPoma symptoms—Patients with VIPoma syndrome are uncommonly cured (<20–30%) because most adults present with metastatic disease, therefore life-long treatment of the hormone-excess state is usually required[2, ••8, 28, 102]. The main stay of treatment is the use of somatostatin analogues(octreotide/lanreotide), which control the large-volume diarrhea in 70–90%, and although some patients become refractory, in most, with dose adjustments, these drugs continue to have some efficacy[2, ••8, 28, 101, 102, •120]

4.5.2. Newer treatments of VIPoma symptoms(Table 1)—A number of the new therapies for F-NETs listed in Table 1 have been used successfully patients with VIPomas, many with refractory disease, although in many reports only small numbers of patients have been treated.

Both studies and case reports have reported the successful use in patients with VIPomas of the control of the symptoms of the hormone-excess state by using: tyrosine kinase inhibitor sunitinib[47, 49]; liver directed therapies including TACE/TAE[70, 100, 173, 174, 184, 185]; radioembolization[70, 150], RFA [81, 83, •186, 187, 188]; by increasing the dosage of octreotide/Lanreotide in refractory cases[185] and the use of cytoreductive surgery[100, 102, 134, 158, 160, 174, •186, 189].

4.6. Other less frequent F-pNET syndromes(glucagonomas, pancreatic ACTHomas, etc)

4.6.1. Current standard treatment of other F-pNET-syndrome symptoms—Conventional therapies include the use of long-acting somatostatin analogues and various therapies directed at Cushing's syndrome(see.section.3.9.3 above)

4.6.2. Newer treatments of other F-pNET symptoms(Table 1)—A number of the new therapies for F-NETs listed in Table 1 have been used successfully patients with other, less frequent F-NETs, some with refractory disease, although in many cases only small numbers of patients have been treated.

Both studies and case reports have reported the successful use in patients with a number of the other F-pNET syndromes for of the control of the symptoms of the hormone-excess state by using: PRRT [glucagonoma[•63], reninoma[64], ACTHoma[62, 65]] ; liver-directed therapies including TACE/TAE [70] [glucagonoma[174], ACTHoma[181], SIADH[•78]]; radioembolization[70, 174][glucagonoma, SSoma[150]]; RFA [glucagonoma[80, 81], ACTHoma[80], SSoma[83], PTHrPoma[81]]; by increasing the dosage of octreotide/lanreotide in refractory cases [glucagonoma[183]]; use of cytoreductive surgery [glucagonoma[•63, 156–158, 160, 174], ACTHoma[62, 190], PTHrPoma[160]] ; and use of ¹³¹I-MIBG [SSoma[107]].

5. Controversies/unresolved issues in current management of hormone-excess states of functional gastrointestinal NETs(F-NETs)(Table 2)

5.1. General

Despite the numerous advances in treatment of the functional states of F-NETs discussed above, as well as advances in treatments directed at the tumor itself, a number of areas of controversy and/or unresolved issues remain in the management of the hormone-excess states which are summarized in Table 2. These will be briefly discussed.

5.2. Controversies/unresolved issues pertain to most F-NETs

For the new therapies there are no studies, which have established the order with which they should be applied, whether drug combinations are more helpful if one fails, or even if therapy with one new medical treatment such as everolimus or sunitinib fails, is the other efficacious for controlling the hormone-excess state.

Although at present in most cases different medical therapies including the newer drugs, such as sunitinib or everolimus, are used before PRRT or liver-directed therapies, especially with the excellent results with PRRT with some F-NET syndromes, it may be appropriate to use it earlier. Furthermore, in patients that are requiring higher doses with medical management, PRRT or liver-directed therapies may be used earlier to facilitate control of the hormone-excess state.

The present place of cytoreductive surgery is really not well defined because its use is often not for the hormone-excess-state but for its effect on tumor itself. It is unclear in most studies how often it is required in patients with F-NETs for symptom control of the hormone-excess state, how effective it is for this, and whether liver-directed therapies or PRRT would not be just as effective.

5.3. Controversies/unresolved issues pertain to a specific F-NET syndrome

While the TELESTAR study established that telotristat, by inhibiting the synthesis of serotonin[115, 116], markedly ameliorated the diarrhea in patients with carcinoid syndrome, its effect on a number of other important manifestations of carcinoid syndrome will be very important, and are at present unclear. Part of the uncertainty is due to the release of numerous other biologically active amines/peptides by the carcinoid tumor, which are reported to contribute to the symptoms of the hormone-excess state[2]. These include various tachykinin(substance P, neurokinin A, neuropeptide K), prostaglandins, bradykinin, and kallikreins[2, 191, 192]. Whether the flushing and asthmatic symptoms in patients also can be ameliorated by telotristat, as well as the development and/or reversal of the carcinoid heart disease, is unclear. Also the pathogenesis of the fibrosis associated with the carcinoid syndrome is not clear[191], and it is unclear whether telotristat will reverse this or stops its progression, both in the heart and in the mesentery. The availability of telotristat should help to answer these questions and define the role of serotonin excess in mediating these manifestations of the carcinoid syndrome.

The role of the long-term use of pasireotide in F-pNETs at present is unclear. There is only one study[•122] on its effectiveness in small number of patients with carcinoid syndrome whose symptoms were octreotide/Lanreotide resistant. Because of the small size of this study, it remains unclear in a larger group of patients with different types of F-NET syndromes who develop resistance for on octreotide/Lanreotide, in what percentage will pasireotide be effective. It also is unclear if initially effective, whether it will remain effective, or similar to octreotide/Lanreotide, in many cases increasing resistance will develop. There is also the question of the long-term complications of the use of pasireotide. In a number of studies hyperglycemia developed in 16% to 79% of patients in different studies[121, •122]. Whether this is going to be a major problem and limit its usefulness in these patients, especially if combined with previous pancreatic resections, is unclear.

The majority of patients with pancreatic ACTHomas have malignant disease[30, 130, 193], in most cases with diffuse liver metastases, and the Cushing's syndrome can be rapidly developing, fulminant, difficult to control and has been shown to be an independent variable for poor prognosis[30, 130, 193]. Whether medical therapy[194], even with the newer drugs, will be successful in the majority of these patients is unclear, as is the role of PRRT, liver-directed therapies or cytoreductive surgery.

6. Conclusions

With widespread use of somatostatin analogs and the development of potent gastric acid anti-secretory agents (PPIs, H₂ receptor antagonists) the medical treatment of the hormone-excess states of F-NETs has become possible in most cases. However, in the case of the somatostatin analogues, resistance can develop over time, initially resistant cases exist, and the long-term treatment may not prevent or reverse all aspects of the hormone-excess state such as fibrosis in carcinoid syndrome or carcinoid heart disease. Control of the hormone-excess state can be particularly difficult in some patients with carcinoid syndrome, insulinomas and VIPomas. In this paper newer options for treatment of the hormone-excess state are reviewed with a number showing much promise. Despite these advances, a number of unanswered questions still exist as well as controversies on management of the hormone-excess states. Each of these are reviewed in depth in this paper.

7. Expert opinion

In the last few years there have been considerable attention paid to advances in anti-tumor treatments of patients with neuroendocrine tumors. This has resulted in a large number of reviews and consensus papers incorporating these advances. This is appropriate because the incidence of NETs is increasing in almost all countries, and increasingly the natural history of the NET per se is becoming the primary determinant of long-term survival. However, a proportion of these patients with F-NETs has two problems requiring management: antitumor treatment and treatment of the hormone-excess state. The antitumor treatments, for example chemotherapy, while effective against tumor growth, may not be useful to control the hormone-excess state, and therefore these two problems; controlling the hormone-excess state and the tumor growth may not be adequately dealt with by one approach.

Treatments directed at controlling malignant NET growth have received increased attention, in part because of the development of effective treatments for the hormone-excess state in patients with F-NETs. Particularly important has been medical treatment with somatostatin analogues with F-NETs, and for patients with gastrinoma, potent gastric antisecretory drugs, which control the hormone-excess state initial in most patients. The result of this increasingly effective control of the hormone-excess state is that, it is no longer a leading cause of early death, with the result that tumor growth is becoming the major factor for long term survival. While these treatments have been highly successful, the long-term treatment of the hormone-excess states remain a problem in many patients, because of drug-resistance developing, resistance existing at the initial treatment or because all manifestations of the hormone-excess states are not controlled. Particularly, in patients with insulinomas not controlled surgically, carcinoid syndrome or some cases of VIPomas and pancreatic ACTHomas, these later problems arise and new treatments are needed. These newer treatments for the hormone-excess states, in general, have received little attention. This paper reviews the evidence that a number of new treatments (medical, surgical, radiological) are effective in controlling the hormone-excess states and their increased use may markedly facilitate management. Because of the rarity of these syndromes, there are few large perspective trials, but nevertheless, in many cases of the different new treatments, there are sufficient number of cases to support the usefulness of the different approaches. However, there are a number of unresolved issues and controversies that will likely require additional studies, which in some cases will need to be controlled studies to completely resolve the issues.

Abbreviations

pancreatic ACTHoma	adrenocorticotrophic hormone-secreting neuroendocrine tumor of pancreas
CgA	chromogranin A
CT	computed tomography
F-NET	NET with a specific functional syndrome
GRFoma	growth-hormone releasing factor secreting NET
NET	neuroendocrine tumor
NF-pNET	pNET not associated with a functional syndrome
GI-NET	neuroendocrine tumor of the gastrointestinal tract not including pNETs
MIBG	meta-iodobenzylguanidine
MEN-1	Multiple Endocrine Neoplasia-type 1
MRI	magnetic resonance imaging
NF-PNET	nonfunctional pNET

PPI	proton pump inhibitors
VHL	von Hippel Lindau disease
pNET	pancreatic neuroendocrine tumor
PRRT	Peptide Radio-receptor therapy
RFA	radiofrequency ablation
TAE	trans-arterial embolization
TACE	trans-arterial chemoembolization
SIRT	selective internal radiation therapy
SSoma	somatostatinoma
sst₁₋₅	somatostatin receptor subtypes
VIPoma	vasoactive intestinal peptide secreting NET
ZES	Zollinger-Ellison syndrome

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Article Highlights

- Patients with functional neuroendocrine tumors(F-NETs) have two treatment problems: treatment of the hormone-excess state and directed at tumor growth/malignancy
- Recently there are many advances in antitumor therapies, which are well covered in reviews, but little analysis of advances in treatments of hormone-excess states
- In contrast to antitumor studies, most advances in treatment of hormone-excess states are in small series, case series, case reports.
- Numerous new treatments of the hormone-excess states are reported including: medical therapies [mTor-inhibitors (everolimus), tyrosine-kinase inhibitors (sunitinib), increases dosages of convention agents (somatostatin-analogs)]; peptide-radioreceptor therapy and increased use of ¹³¹I-MIBG; cytoreductive surgery; ablation of F-NET primaries; liver-directed therapies (embolization, chemoembolization, radioembolization, RFA); therapies directed at specific syndromes [serotonin-synthesis inhibitors(telotristat), pasireotide, new agents for Cushing's syndrome with ACTHomas]
- The evidence for the use of each approach is reviewed and the unresolved areas and controversies discussed

Table 1

Advances in management of hormone-excess states of functional gastrointestinal NETs (F-NETs)

In refractory cases, control of symptoms of F-NET hormone-excess state by:	
1	Use of a mTor inhibitor such as everolimus (carcinoid syndrome, F-pNETs)
2	Use of a tyrosine kinase inhibitor such as sunitinib (F-pNETs)
3	Use of PRRT to reduce tumor mass/hormone release and increase response to medical therapy (F-pNETs/carcinoid syndrome)
4	Use of liver-directed therapies (TACE, TAE, Radioembolization (SIRTs), RFA) to reduce tumor mass/hormone release and increase response to medical therapy (F-pNETs/carcinoid syndrome)
5	Use of percutaneous/endoscopic ablative therapies (ethanol, etc.) for primary or metastases (F-pNETs)
6	Use of a supra-maximal doses of conventional therapies (carcinoid syndrome, F-pNETs)
7	Use of cytoreductive surgery to control symptoms and/or (increase response to medical therapy (F-pNETs/carcinoid syndrome)
8	Increased use of ^{131}I MIBG (carcinoid syndrome)
9	Use of a new specific syndrome therapy
a.	Telostristat, a a tryptohan hydroxylase inhibitor, to inhibit serotonin synthesis (carcinoid syndrome)
b.	Pasireotide, a broad spectrum sst receptor agonist (F-pNETs/carcinoid syndrome)
c.	Newer agents to treat Cushing's syndrome due to pancreatic ACTHoma(and other causes of ectopic Cushing's syndrome)

Table 2

Controversies/unresolved issues in current management of hormone-excess states of functional gastrointestinal NETs(F-NETs)

In refractory cases, control of symptoms of F-NET hormone-excess state:	
1	What order of new therapies (which first, second, etc).
2	Do combinations of new therapies enhance response (i.e. everolimus +sunitinib, etc).
3	If initial treatment with everolimus or sunitinib fails, can the alternate drug be used to control the hormone-excess state
4	Should PRRT be used before completely refractory to decrease dosage/frequency of drugs.
5	Can PRRT be repeated with similar benefit to control the hormone-excess state if refractoriness to drugs develops after an initial treatment
6	What role of cytoreductive surgery to increase sensitivity to drug therapies.
7	Use of a new specific syndrome therapy
a.	Does Telotristat therapy continue to remain effective for long periods of time? Does it prevent the development/or progression of carcinoid heart disease?
b.	Will Telotristat therapy prevent the development of mesenteric fibrosis or its progression?
c.	Will Telotristat therapy prevent the development of carcinoid crises?
d.	Will Pasireotide, remain effective and are side-effects such as hyperglycemia longterm a problem?
e.	What proportion of pancreatic ACTHoma patients become refractory to all drugs and what should be their treatment?