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Gastro-Entero-Pancreatic Neuroendocrine Tumors (GEP-Nets): A Review

Chuangqi Chen*, Xiaojiang Yi and Yulong He

Department of Gastro-entero-pancreatic Surgery and Colorectal Surgery, the First Affiliated Hospital of Sun Yat-sen University, China

Abstract

Introduction: The diagnosis of Gastro-entero-pancreatic Neuroendocrine Tumors (GEP-NETs) is currently a common event and it has showed the highest incidence of NETs. The majority of this lesion are well differentiated and with only a minority performing a malignant behavior. However, it poses a significant challenge to diagnosis especially for the assessment of the malignant potential of well differentiated types and many aspects of the management remain unclear and controversial. Recently, some new progresses of this disease have been put into clinical practice and some are still on trail.

Methods: We will present a review of GEP-NETs on classification, pathology, clinical manifestation, biomarkers, management and follow-up.

Conclusion: This review aims to provide some new understanding of pathologic classification and clinical diagnosis in GEP-NETs. On the basis of patients' individual condition, comprehensive treatment options should be carried out to achieve a better therapeutic effect and improve the quality of life.

Keywords: Gastro-entero-pancreatic neuroendocrine tumors; Classification; Pathology; Clinical manifestation; Biomarkers; Management; Review

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originating in various anatomic locations, comprising nearly 0.49% of all malignancies. In 2003, Modlin et al. [1] analyzed 13715 NETs, gastrointestinal tract showed the highest incidence (67.5%) followed by the bronchopulmonary NETs (25.3%). And among gastrointestinal NETs, most of them occurred in the small intestine (41.8%), followed by the rectum (27.4%) and stomach (8.7%). Maggard et al. [2] including 11427 NETs reported a 5-year survival rate of 87.5% for rectal NETs, and in colorectal NETs without metastasis showed a 5-year survival of 85-99% and the rates of 54-73% and 15-30% for regional and distant metastasis, respectively. The term NETs of gastro-entero-pancreatic (GEP) tract was defined as "carcinoid" one century ago and actually known as NET. GEP-NETs have been reported to present increased incidence.

Classification

NETs arise from the neuroendocrine cell. In GI tract and pancreas, there are 14 different cells defined by hormonal reagents [3], many of NETs manifest hormonal syndromes. GEP-NETs associated with hormonal syndromes are called insulinomas, glucagonomas and gastrinomas. In addition, some can produce hormones which are ectopic to the GEP system such as vasoactive intestinal polypeptide (VIP), ACTH or GH-releasing factor. In 1963 Williams and Sandler [4] classified the GEP-NETs by embryological origin as foregut (stomach, duodenum, upper jejunum and pancreas), midgut (lower jejunum, ileum, appendix and caecum) and hindgut (colon and rectum) tumors. However, with new developments in last two decades, especially in foregut tumors, the shortcoming of this classification in diagnosis is limited. Moreover, the diagnosis of GEP-NETs can be delayed for up to 5 years, especially in asymptomatic cases [5]. As a result, a number of patients are admitted to hospital with metastatitc (up to 25%) or unresectable (60%) disease [6-8].

In 2000 and 2004 [9,10] (Table 1), WHO introduced the classification for GEP-NETs for pancreatic NETs. Step 1, it distinguishes between pure endocrine tumors and mixed endocrine-exocrine tumors. Step 2, a scheme is applied to pure GEP-NETs, identifying 3 categories: [9] 1) well-differentiated endocrine tumors with probably benign behavior; 2) well-differentiated endocrine tumors with uncertain behavior and well-differentiated endocrine carcinomas with low-grade malignant behavior and 3) poorly differentiated endocrine carcinomas with high-grade malignant behavior. Step 3, well-differentiated, low-grade proliferative GEP-NETs or islet cell tumors in pancreas, are distinguished in case of original site, size, gross and/or microscopic tumor extension, angioinvasion, proliferative index (Ki-67) and syndromatic features [9,10]. Immunohistochemically, well-differentiated, low-grade proliferative GEP-NETs are characterised by synaptophysin (Syn) and usually also for chromogranin A (CgA). Poorly differentiated NECs are characterised by their diffuse Syn, and only infrequent and sparse CgA [11].

WHO 2000	WHO 2010
1. Well-differentiated endocrine	1. NET G1
tumour (WDET)	
2. Well-differentiated endocrine	2. NET G2a
carcinoma (WDEC)	
3. Poorly-differentiated endocrine	3. NEC G3 (large cell or small cell)
carcinoma (PDEC)	
4. Mixed exocrine-endocrine	4. Mixed adenoneuroendocrine carcinoma
carcinoma (MEEC)	(MANEC)
5. Tumour-like lesions (TLL)	5. Hyperplastic and preneoplastic lesions

G, grade; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour.
a G2 NET may include WDET or WDEC of the WHO 2000 classification.

Table 1: Definitions for NETs of the digestive system according to WHO classifications.

In recent years, it was felt that WHO classification should be

***Corresponding author:** Chuangqi Chen, Department of Gastro-entero-pancreatic Surgery and Colorectal Surgery, the First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China, E-mail: chenchqi@mail.sysu.edu.cn

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Grading	Mitotic count (10 HPF*)	Ki-67 index (**)
G1	2	<2%
G2	2-20	3-20%
G3	>20	>20%

*HPF: High Power Field, 2 mm2; based on at least 50 fields (at 40× magnification) in tumor areas with higher mitotic density ("hot spots");
**MIB1 antibody; % on 500-2000 cells in tumor areas with higher density.

Table 2: Definition of tumour grading for NETs of the digestive system according to WHO 2010 classification.

supplemented by criteria that may refine the prognostic stratification of GEP-NETs to allow a better stage-adjusted treatment. Therefore, European Neuroendocrine Tumor Society (ENETS) developed TNM classifications [12,13]. Meanwhile, the definition of the proliferation grade (G1-G3) (Table 2) used both mitotic rate and Ki-67 to assess the proliferating activity. It putted out some innovative concepts with respect to the 2000 WHO classification: 1) the clinic-pathological differences among NETs according to the site of origin; 2) NETs should be considered as potentially malignant lesions; 3) the new grading and staging systems are applicable in advanced tumors without the need of surgical exploration, staging can be defined according to clinical and imaging data while grading can be established by biopsies and cytology specimens [14,15]. Several years later, North American Neuroendocrine Tumor Society (NANETS) clinical recommendations released in 2010 were highly consistence with ENETS [16-23]. However, a difference exists between ENETS and NANETS approach to staging systems propose for pancreatic and appendiceal NETs [12,13,16,24,25]. Grading system is based on mitotic count and Ki-67 index [12,13]. G1 and G2 NETs are considered well-differentiated tumors, whereas G3 characterises the poorly differentiated tumors (Table 1). Both staging and grading systems were recently tested for foregut and particularly pancreatic NETs and the biological relevance and contributions in prognosis were largely confirmed [26-30]. The 7th edition of the AJCC/UICC [31] contains a TNM classification of well-differentiated NETs that differs in a number of criteria from ENETS [32]. It did not apply to high-grade NECs and did not exactly follow ENETS for some of the anatomic sites. The result is that there now exist two parallel systems and its discrepancy may lead to confusion and limit the ability to compare researches.

The 2010 WHO classification (Table 1) was the assumption that are adopted in potential malignant tumors and the stratification in malignancy-related risk groups is based on tumor grading and TNM staging [16]. It retained the morphologic criteria of tumor differentiation of the previous classification, and added a grading and staging system. A significant terminological novelty was the introduction of 'neuroendocrine'. 'Carcinoid tumor' retained in use in tubular GEP-NETs as a synonym for well-differentiated NETs [33]. NECs were subtyped into small cell and large cell tumors (Table 1). The tumors that show in addition to neuroendocrine cells (exceeding at least 30% of all tumor cells) non-endocrine components (usually adenocarcinoma structures) are distinguished from the pure NETs and called mixed adenoneuroendocrine carcinomas (Table 1).

Pathology

GEP-NETs can occur anywhere in GEP system, in general, these lesions concentrate at the gastric fundus/corpus mucosa, the proximal segment of the duodenum, the papilla of Vater, the terminal segment of the ileum, the tip of the appendix, the lower rectum and the pancreas. In the past, the most common GEP-NETs are considered those arising in ileum and appendix. Recent studies revealed that probably the gastric NETs were the first place [34,35]. NETs usually share some pathological and clinical differences in different tumors, but well-differentiated NETs are much more common (20:1) than the poorly differentiated NECs [36]. The tumor proliferation rate is very low especially in well differentiated tumors of small intestinal origin (G1) and associated with poor responsiveness to conventional chemotherapeutic drugs [37]. Histologically, NETs can divide into types A (insular solid), B (trabecular or ribbon like), C (glandular) [37]. Different patterns may be associated with the region of tumor origin: type C is frequently found in ampullary tumors, type A is in tumors of the small intestine and appendix, and type B is in tumors of rectum or sigmoid colon.

Several markers of differentiation and more cell-specific markers emerged recently. The traditional markers are Syn, CgA and Neuron-Specific Enolase (NSE). Some new markers that are available include the following: Neuroendocrine secretory protein 55 is a polypeptide that belongs to the chromogranin family [38]. It can stain pancreatic NETs, but in other sites of GI tract it is negative. Ghrelin can be seen in oxyntic glands of the gastric mucosa. However, its expression isn't detected in the pancreas, pituitary, and heart. Ghrelin-producing NETs is reported in stomach and intestine [39]. Five somatostatin receptors are identified, but up to 90% of serotonin- and gastrin-producing NETs of the distal jejunum and ileum, and about 60% of insulin-producing pancreatic NETs, are positive for receptors 2 and 5 [40,41]. CDX-2 is essential for intestinal development and differentiation. Approximately 80% of NETs are CDX-2 positive, especially in the ileum and appendix. Gastric NETs tend to be negative. In pancreatic NETs, histidine decarboxylase is most frequently positive [42]. Xenin appears to be specific to duodenal NETs. It is shown that NETs from the duodenum, including nonfunctional, gastrin- and somatostatin-producing tumors show xenin expression [43]. Cytokeratin 19 is a shown to have prognostic value in pancreatic NET and should form part of the routine [44].

About the molecular pathology of GEP-NETs, The biology of GEP-NETs is a complex interaction of a number of factors that influence growth, differentiation, interaction with tumor environment, and secretion [45]. GI tract NETs arise via the CpG island methylator phenotype pathway, but pancreatic NETs arise as a result of chromosomal instability [46]. Several studies showed that the common oncogenes and tumor suppressor genes such as src, ras, myc, fos, jun, p53, and Rb and the DNA mismatch repair genes are not implicated in the molecular pathogenesis of GEP-NETs [46]. Combining data from the studies by Speel et al. [47] and Zhao et al. [48], it is apparent that losses of 3p, 21q and 6 and gains on 4, 7, 14q and Xq are associated with metastatic events.

Clinical Manifestation

Functioning GEP-NETs become evident when a characteristic clinical syndrome secondary to the secretion of bioactive substances [49]. However, majority of GEP-NETs are non-functioning and are diagnosed when symptoms of mass effects develop. Recently, it was reported that a number of vague and/or poorly defined symptoms may be related to the secretion of previously unrecognized substances in the form of para-neoplastic syndromes [50]. Carcinoid heart disease is observed in 3-4% of NETs and in 40-50% of those with a carcinoid syndrome and echocardiography is the gold standard for detection. Involvement of the tricuspid leaflets grade 2-3 occurs in 90%, a stenosis of the pulmonary leaflets in 50%, while regurgitation is seen in 81% of the patients during the course of the disease [51].

CT, MRI, and US can be used as diagnostic approaches. In addition sstrs scintigraphy (SRS),is used for the initial staging of disease and to evaluate sstrs status and for therapy with SS-analogs [52,53]. In recent years SRS was superseded by PET-CT performed with 68Ga-labeled

octreotide. Among several preparations of radiolabeled octreotide, 68Ga-DOTATOC is the most widely used [53]. This image provides better spatial resolution and higher ratios of tumor-to-normal tissue than SRS and its sensitivity to detect GEP-NETs exceeds that of SRS and single-photon emission CT (SPECT) [54,55]. F-18-fluoro-deoxy-glucose (18F-FDGPET) is used to detect highly metabolic tumors, which tend to be clinically more aggressive. The 92% sensitivity of 18F-FDGPET for depicting NETs with a proliferation index greater than 15% exceeds that of SRS and meta ido-benzyl guanidine (MIBG) scintigraphy that exert a sensitivity of 69 and 46%, respectively [56]. More information can be gained by combining 68Ga-DOTATOC or 68Ga-DOTATE and 18F-FDGPET. This occurs because there is a significant correlation between histologic tumor grade and predominant tumor uptake of 68Ga-DOTATE, a chelator that has higher affinity for sstr2 compared to DOTATOC in well-differentiated tumors, and 18F-FDGPET by poorly differentiated tumors [57,58]. On the other hand, PET using 5-hydroxy-L-tryptophan (5-HTP) and L-3,4-dihydroxyphenylalanine (L-DOPA) as tracers exhibit increased sensitivities and specificities of 91 and 96%, respectively [59]. Several functional imaging techniques, including dynamic contrast enchanced (DCE) MRI, diffusion weighted-MRI (DW-MRI), PET, and SPECT provide quantitative information regarding the physiologic and molecular characteristics of tumors [52,53]. 18F-FDGPET has a stronger prognostic value than traditional markers such as Ki-67, CgA and the presence of liver metastasis and correlates with reduced progression-free and overall survival [60,61]. However, the possibility of tumor de-differentiation with loss of receptors is a relative limitation and should be taken into consideration [62]. DCE-MRI permits the investigation of tumor vasculature by evaluating the transit time of an iv contrast medium from vessels to the tissue with leakage from capillaries into the interstitial tissue and re-diffusion into the venous system [58]. DW-MRI allows non-invasive characterization of biological tissues based on their water diffusion characteristics as apoptotic cells exhibit different water diffusivity [63]. However, although it represents a potentially quantifiable and reproducible method it has not been widely tested.

Biomarkers

CgA is for functional NETs of the midgut (carcinoid syndrome) and for non-functional tumors of the midgut and pancreas as it may be used to assess the speed of tumor growth [64-66]. In most metastatic hindgut tumors, CgA is negative and no tumor markers are suitable for this lesion. For gastric type 1 NETs CgA and gastrin are elevated but are not helpful for follow-up. CgA also have been associated with poor prognosis [67]. NSE may act as additional marker in patients with poorly differentiated tumors [65]. CgA is found to be clinically informative and moderately sensitive in majority of studies and more sensitive than NSE in all subgroups of a large mixed NET patient cohort [68]. Specificity of CgA in diagnosis depends on the tumor type and burden (100% specificities have been reported with metastatic disease [69-72]. Elevated CgA can be more sensitive than high urinary 5-hydroxyindole acetic acid (5- HIAA) levels with metastatic midgut lesions (87 vs. 76%, respectively).Nonetheless, the prognostic value of CgA has not been confirmed to date.

The overall sensitivity and specificity of urinary 5-HIAA in the presence of the carcinoid syndrome is of 70 and 90%, respectively [73,74]. Midgut carcinoids are most liable to produce the carcinoid syndrome with a high specificity (>90%) of 5-HIAA [75]. Recent data examined 5-HIAA as a prognostic factor, two studies including 256 and 139 patients with midgut carcinoid tumors showed that while el evated 5-HIAA levels were predictive of poor outcome at univariate analysis but did not remain significant at multivariate analysis [76].

For insulinoma, supervised 72-Hour Fast is verified as the gold standard inestablishinga biochemical diagnosis [77], although some groups propose a shorter fast of 48h [78,79]. For Zollinger-Ellison syndrome, up to two thirds of gastrinoma patients are found to have fasting serum gastrin values <10-fold normal [80]. The gold standard is the secretin test.

The use of a minimal immunohistochemical panel including CDX2, TTF1 and insulin is also recommended for NETs or NECs metastasis in liver or lymph node biopsies, in which the most common diagnostic requests refer to the primary tumor localization [81]. CDX2 suggests an intestinal origin [82], for TTF1a pulmonary origin, for insulin a pancreatic origin. The interpretation of such data requires caution because of incomplete specificity. In rectal NETs, pancreatic polypeptide, enteroglucagon and β-hCG may be useful markers in the monitoring [83]. The prostatic acid phosphatase is present in 80-100% of rectal NETs and always be requested to evaluate the therapeutic effect [84]. It is intriguing that all rectal NETs exams express both INSL5 and RXFP4, and that INSL5 and CgA are expressed reciprocally in colorectal NETs. Thus, INSL5-RXFP4 signaling may play a role in rectal NETs.

Management

Surgical resection of primary tumors

Resection is the first choice for local regional disease and in setting of impending obstruction and should still be considered for advanced disease. For gastric NETs, Type 1 can undergo endoscopic resection, and in cases with invasion beyond the sub-mucosa, positive resection margins after EMR, multiple tumors >1 cm or regional lymph node metastases, local resection or partial or total gastrostomy should be performed [85,86]. With liver metastasis (in 25-50% of the patients), it should be resected if possible to obtain R0 resection. Type 4 gastric NETs and oesophagus are diagnosed with an increasing incidence. Surgical treatment is not an option and patients should start chemotherapy immediately. However, in the few cases with localized disease surgical treatment should be considered if R0 resection can be obtained [87,88]. For duodenal NETs, tumors >3 cm are usually require a pancreaticoduodenectomy. For pancreatic NETs, while tumors to the left of the mesenteric vessels can be managed by a distal pancreatectomy with splenectomy. Tumor close to one of the major pancreatic ducts (<2-3 mm) should be avoided due to the high risk (20-30%) of damage to the ducts with formation of a pancreatic fistula [89,90]. Liver metastasis are not a contraindication, resection of liver metastasis may increase five-year survival up to 76% compared to a five-year survival of 30-40% in untreated cases. However, tumour recurrence is up to 75% within two years after surgery [91-93]. For non-functioning tumors, aggressive surgery in locally advanced tumours including nearby organ involvement may lead to a five-year survival of up to 80% [94,95]. For insulinomas, it should be resected in order to relieve hypoglycemic symptoms. For gastrinomas, sporadic gastrinomas should be removed to relieve symptoms and to prevent liver metastasis. Radical surgical treatment of sporadic gastrinomas has a high cure rate with a 20-year disease related survival of 98% vs. 74% in non-operated cases [96]. For multiple endocrine neoplasia type 1 (MEN-1), pancreaticoduodenal NET operation is only advisable when tumors exceed 2-3 cm, not to cure patients but to avoid liver metastasis. For NETs of appendix, right hemicolectomy with node dissection is considered if high risk factors present. For ileum and jejunum, resection with node dissection is indicated and full bowel examination is required during surgery in case of lateral metastasis. Ileocecal valve and right colon can be preserved for more proximal tumors in NETs of ileum. Several studies indicated that overall survival is extended from 4-5 years up to 8-10 years if the

primary and regional metastases are resected [97-99]. The treatment of colorectal NETs is complex, the incidence of metastasis ranges from 1.7-3.4% [100]. Yamaguchi et al. [101] reported complete removal in 90% of rectal carcinoids of <1 cm using ESD, with an average operation time of 45 minutes, and one case of perforation. As reported by Lee et al. [102], complete removal was achieved in 89.3% and 100% undergoing EMR and ESD. For NECs, patients should be referred to chemotherapy immediately, but despite that the median survival is only 12-18 months [103,104]. However, in few patients with localized disease surgical resection should be considered as the only hope for cure or prolonged.

Other Techniques

Percutaneous or intraoperative radiofrequency ablation (RFA) is the preferred ablative procedure and reduces local or hormone-induced symptoms in 70-80% of the patients for a period of one year [8,105], in addition, a 50% reduction in tumour markers is seen in an equivalent number of patients. However, RFA is still a supplement or a secondary treatment to liver resection. Embolization can be performed as bland-, chemo- or radioembolization with numerous liver metastases not suited for surgical resection or RFA and with tumor burden predominantly confined to the liver. One randomized prospective study showed that bland- and chemoembolization is equally effective [106]. Relief of local or endocrine symptoms is seen in 90% of the patients with duration of 14-22 months. Reduction in tumor markers is observed in approximately 75% and a radiological tumor response is seen in approximately 50% of the patients with duration of 1-2 years. In a retrospective study bland embolization seemed superior to chemoembolization with small intestinal NETs (81% vs. 44%), however, chemoembolization seemed superior to bland embolization in patients with pancreatic NETs (50% vs. 25%) [107]. Radioembolization or selective internal radiation therapy (SIRT) with 90Y-microspheres is a relatively new treatment option for liver metastasis. Radiological tumor response rates are seen in 60% [108]. Liver transplantation should be restricted to the very small group of young patients (<50 years) with WHO performance status 0, with non-resectable metastasis confined to the liver preferentially from a small intestinal NETs with severe uncontrolled endocrine symptoms. However, relapse occurs in all [109].

Hormonal Syndrome Control

In 1973 Brazeau and Guillemin discovered the somatostatin. In 1980 Bauer and co-workers synthesized an analogue named octreotide. Later development leads to the long-acting formulation of Octreotide LAR given once monthly, following by some other analogues, such as Lanreotide (BIM23014), RC160 (Octastatin) and pasireotide (SOM230) [110-112]. Octreotide and lanreotide both effectively inhibit amine and peptide secretion, hyper secretion symptoms such as carcinoid syndrome with flushing and diarrhoea, watery diarrhoea syndrome (WHDA) and the necrolytic migratory skin lesions in the glucagonoma syndrome can be relieved in most patients. However, tachyphylaxis develops after months or even years. Initially tachyphylaxis can be reversed by increasing the dose. In functioning GI-NETs, somatostatin analogues (SAs) can control clinical symptoms in 40-60% and result in remission and/or stabilization of tumor markers in approximately 60-70% of the patients [113-118]. High dose treatment has resulted in up to 50% stabilization of the disease in patients after failure on regular doses of SAs [119-121]. The PROMID trial demonstrated anti-tumor efficacy of octreotide in advanced midgut carcinoid tumors [122].

Interferon-α is used for the same indication as are SAs in GEP-NETs with carcinoid crisis being the exception. Symptomatic remission is seen in 30-70% in patients with the carcinoid syndrome with a better effect of interferon therapy on flushing compared to diarrhoea [123-128]. In patients with Verner Morrison's syndrome and secretory diarrhoea resistant to SAs, interferon-α has provided excellent response with reduction in VIP levels as well as diarrhoea [128].

There are several non-randomized and at least three randomized trial combining interferon-α with SAs [129-135]. The reason for combining them is that interferon-α might upregulate the number of somatostatin receptors on the tumor cells. Five nonrandomized trials have been published with biochemical responses in 40-77% of the patients, radiological response in single patients, but mainly stabilization of the disease [129-132].

The use of radiolabeled SAs is a relatively new treatment option for inoperable or metastasized GEP-NETs. ^{111}In-DTPA, ^{90}Y-DOTA^{0}-Tyr^{3}, ^{177}Lu-DOTA^{0}-Tyr octreotate are taken into use. Serious side effects consist of leukemia, myelodysplastic syndrome and hematological toxicity.

Chemotherapy and Targeted Therapies

Combination treatment with streptozotocin (STZ) plus 5-fluorouracil (5-FU) or doxorubicin may reduce hormonal symptoms and result in an objective tumor responsein 20-35% of patients [136]. Indication for the use is treatment of malignant inoperable GEP-NETs, when biotherapy has failed. The use of cisplatin plus etoposide is treatment of poorly differentiated NETs. It has been reported to produce objective responses in about 50% of cases. Some reported dacarbazine with malignant abdominal tumors when biotherapy and combinations with STZ have failed because this drug may induce tumor responses.

Based on two phase 3 clinical trials, sunitinib and everolimus [137,138] are FDA approved and recommended for patients with progressive metastatic pancreatic NETs. Everolimus was also studied in metastatic functional carcinoid tumors in a large phase 3 clinical trial [139]. But up to now, we do not have sufficient evidence to recommend routine use of everolimus in carcinoid tumors.

Follow-Up

Follow-up is mainly based on imaging procedures and tumor markers. A physician should judge the patient's general health and even prognosis by a careful history and examination, assessing carcinoid syndrome and possible carcinoid cardiac disease. Imaging procedures includes abdominal ultrasound, endoscopy, EUS, CT, MRI, Octreo scan and PET-CT. Accordingly, abdominal ultrasound may be recommended because it allows one to compare findings obtained during different follow-up visits. In contrasting to abdominal ultrasound, CT and MRI have greater sensitivity and resolution. Octreoscan is substituted in some centers due to its higher sensitivity [140].111In-pentetreotide Octreoscan is positive in 80-90% of the patients with midgut NETs [141]. However, caution is recommended when comparing the number of tumor lesions detected by the Octreoscan and PET-CT. Due to the higher sensitivity of PET more lesions are detected, so it is essential to use this technique when assessing for progression or regression.

Conclusion

GEP-NET types also differ in their clinical manifestation. Because of this biological diversity, the management of this disease is becoming more and more type-specific. Early and sufficient diagnosis is necessary for accurate recognition and optimal treatment. However, the long-time survival rate of this lesion still has no significant improvement. With the study of genic and molecular mechanism, a large number of tyrosine kinase, angiogenesis as well as mTOR inhibitors have recently

been developed and also attempted in the management of NETs and some new targeted drugs have been put into clinical trial. In the future, more basic and clinical trials on classification, pathology, biomarkers, management and follow-up should be the main point of research.

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