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REVIEW ARTICLE

Pancreatic Neuroendocrine Tumours

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ABSTRACT

Neuroendocrine tumours (NETs) are a heterogeneous group of malignancies that can arise in different organs. Although NETs account for only 0.5% of all malignancies, their incidence has significantly increased in recent years. In the Asia Pacific region, the most common site of primary NETs is the pancreas. Many new treatment modalities have been shown to be effective in treating NETs. This study reviews the diagnosis, management, and prognosis of pancreatic NETs.

Key Words: *Neuroendocrine tumors; Pancreatic neoplasms*

中文摘要

胰腺神經內分泌腫瘤

林河清、卓華、歐陽定勤、鄭海清、顏繼昌

神經內分泌腫瘤（NETs）是能在不同器官中出現的異質性惡性腫瘤組織。儘管NETs僅佔所有惡性腫瘤的0.5%，但其發病率近年來顯著增加。在亞太地區，原發性NETs最常見的部位為胰腺。許多新的治療方式顯示能有效治療NETs。本文回顧了胰腺NETs的診斷、治療和預後。

INTRODUCTION

Neuroendocrine tumours (NETs) constitute a heterogeneous group of tumours postulated to be originated from neuroendocrine cells of the embryological gut. They can arise from the tubular digestive tract such as the stomach, small and large intestines, rectum, and pancreas. In the United States, the gastrointestinal tract (excluding pancreas) is the most common primary location (48%), whereas in Asia Pacific and the Middle East, pancreatic NETs (pNETs) are the most common (49%).[1,2] The incidence of pNETs is one per 100,000 per year, accounting for 1% to 2% of all pancreatic tumours.[3-5] This incidence has increased over the last two decades,[5] partly due to improved diagnosis and classification. pNETs are often diagnosed at a late stage because symptoms are usually absent or vague, and thus 50% of pNETs are metastatic at the time of diagnosis.[1] The most common symptoms are abdominal pain, weight loss, anorexia, and nausea, followed by obstructive jaundice, intra-abdominal

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haemorrhage, and a palpable mass.

pNETs can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide. Carcinoid syndrome refers to a constellation of symptoms that include flushing, abdominal cramps, diarrhoea, and even carcinoid heart disease that occurs in 8% to 35% of patients with pNETs, mostly in those with hepatic metastasis.[6] 60% to 90% of pNETs are non-functioning tumours.[7,8] In a population-based study, the median overall survival for patients with non-functioning pNETs was 38 months.[1] Survival was mostly affected by the presence of distant metastasis. Patients with distant metastasis had a median survival of 23 months compared with 124 and 70 months in those with localised and regional disease, respectively.

STAGING

The American Joint Committee on Cancer (AJCC) provides no specific staging system for pNETs. The tumour / node / metastasis staging system is used for pNETs and other exocrine or endocrine tumours of the pancreas.[9] In 2006, the European Neuroendocrine Tumor Society (ENETS) developed a specific tumour / node / metastasis staging system for various NETs including pNETs.[10] The AJCC and ENETS classifications differ in their definition of tumour stages (Table 1[9,10]). In the AJCC system, T3 is distinguished from T2 by recognition of peripancreatic soft tissue invasion (difficult to determine radiologically and independent of tumour size) without specifying any particular adjacent organ. The ENETS system specifies invasion to particular adjacent organs as T3 or T4. Both staging systems are highly prognostic for overall survival. In a retrospective study of 425 patients with pNETs over 11 years, the 5-year overall survival rates for stages I, II, III, and IV disease based on the ENETS system were 100%, 88%, 85%, and 57%, respectively ($p < 0.001$), and the corresponding values based on the AJCC system were 92%, 84%, 81%, and 57%, respectively ($p < 0.001$).[11]

DIAGNOSIS

Histology

A definitive diagnosis of pNETs is based on immunohistochemical workup using neuroendocrine markers such as chromogranin A and synaptophysin. Tissue diagnosis is mandatory. According to the 2010 World Health Organization classification of gastrointestinal tumours, all pNETs are considered malignant except for the non-functioning pancreatic neuroendocrine microadenoma (<0.5 cm). The old term 'carcinoid' may incorrectly impart a benign connotation and can be confused with 'carcinoid syndrome' and thus has been abandoned. Nonetheless, in the lung and thymus, carcinoid tumour and atypical carcinoma tumour remain official terms. The behaviour of the tumour depends on its histological grade that reflects the biological aggressiveness of the tumour; low-grade pNETs are relatively indolent, high-grade pNETs are extremely aggressive, and intermediate-grade pNETs

Table 1. Comparison of American Joint Committee on Cancer (AJCC) and European Neuroendocrine Tumor Society (ENETS) in tumour (T), node (N), and metastasis (M) staging of pancreatic neuroendocrine tumours.

Staging	AJCC 2010 staging[9]	ENETS 2006 staging[10]
Tumour (T)	T1: tumour limited to pancreas and ≤2 cm	T1: tumour limited to pancreas and <2 cm
	T2: tumour limited to pancreas and >2 cm	T2: tumour limited to pancreas and 2-4 cm
	T3: tumour extends beyond pancreas but not involving celiac axis or superior mesenteric artery	T3: tumour limited to pancreas and >4 cm or invading duodenum or bile duct
	T4: tumour involves celiac axis or superior mesenteric artery	T4: tumour invading adjacent organs (stomach, spleen, colon, adrenal) or wall of large vessels (celiac axis or superior mesenteric artery)
Lymph node (N)	N0: no regional lymph node metastasis	
	N1: regional lymph node metastasis	
Distant metastasis (M)	M0: no distant metastasis	
	M1: distant metastasis	
Stage grouping	Stage IA: T1 N0 M0	Stage I: T1 N0 M0
	Stage IB: T2 N0 M0	Stage IIa: T2 N0 M0
	Stage IIA: T3 N0 M0	Stage IIb: T3 N0 M0
	Stage IIB: T1-3 N1 M0	Stage IIIa: T4 N0 M0
	Stage III: T4 any N M0	Stage IIIb: any T N1 M0
	Stage IV: any T any N M1	Stage IV: any T any N M1

Table 2. World Health Organization (WHO) classification for gastro-intestino-pancreatic neuroendocrine tumours or carcinoma (NET or NEC)

WHO classification for gastro-intestino-pancreatic NET or NEC	Differentiation	Grade	Mitotic count (per 10 high-power fields)	Ki-67 index (%)
NET, grade 1	Well	Low	<2	<3
NET, grade 2	Well	Intermediate	2-20	3-20
NEC, grade 3, small cell	Poor	High	>20	>20
NEC, grade 3, large cell	Poor	High	>20	>20

are less predictable and moderately aggressive.[12] Well-differentiated pNETs are either grade 1 or grade 2; poorly differentiated pNETs are grade 3 and can be large-cell or small-cell carcinoma.

The sole criterion for histological grading of pNETs is the proliferation rate, calculated by counting either mitotic figures in 50 high-power fields or the Ki-67 index in 500 to 2000 cells (Table 2 and Figure 1). The one with a higher grade (usually the Ki-67 index) should be used. pNETs with grade-2 mitotic count and grade-3 Ki-67 index (well-differentiated discordant tumours) fare better than poorly differentiated NETs but worse than tumours with grade-2 mitotic count and grade-2 Ki-67 index (well-differentiated concordant tumours).[13] Morphologically well-differentiated pNETs with an elevated Ki-67 index may represent a distinct entity and demonstrate intermediate behaviour.[13]

Biomarkers

Serum chromogranin A is the most useful biomarker for diagnosing pNETs. Its sensitivity and specificity are 43% to 100% and 10% to 96%, respectively.[14-20] It is associated with tumour size and patient survival.[21,22] Nonetheless, increased serum chromogranin A can be a result of renal or hepatic insufficiency and the use of proton pump inhibitors.[21]

Biomarkers for specific tumour types (e.g. insulin for insulinoma and gastrin for gastrinoma) are only useful in monitoring disease activity of few specific pNETs with distinct clinical syndromes. Urine 5-hydroxyindoleacetic acid (a metabolite of serotonin) is a marker for carcinoid syndrome of the midgut origin. It provides poor prognostic information and has a sensitivity of 35% and thus requires adherence to a restricted diet.[23] Other biomarkers useful in diagnosing NETs include neuron-specific enolase, tachykinins, and pancreatic polypeptides (Table 3).[14-20,23-31]

Table 3. Neuroendocrine tumour biomarkers

Biomarker	Sensitivity (%)	Specificity (%)
Chromogranin A[14-20]	43-100	10-96
Urine 5-hydroxyindoleacetic acid[23]	35	Up to 100
Insulin[24]	Up to 100	<20
Gastrin[24]	Up to 100	<20
Neuron-specific enolase[23]	33	Up to 100
Neurokinin A[25]	88	Not reported
Substance P[26]	32	85
Pancreatic polypeptide[27-29]	31-63	Up to 67
Pancreastatin[14,15,20]	64	58-100
Circulating tumour cells[30,31]	<40	95

Technological advances facilitate the detection of circulating tumour cells in the blood of patients with various cancers including NETs. In a study of 176 patients with metastatic NETs, 49% had detectable circulating tumour cells, and their presence was associated with increased tumour burden, tumour grade, and serum chromogranin A, as well as worse progression-free survival (PFS) and overall survival.[30]

Imaging

Multiphasic contrast-enhanced computed tomography (CT) has a sensitivity of >80% in detecting primary pNETs.[32] Endoscopic ultrasonography provides high-resolution imaging of the pancreas. Endoscopic ultrasonography–guided fine-needle biopsy can provide a histological diagnosis but requires a highly skilled endoscopist, and tumours in the pancreatic tail are difficult to visualise. Somatostatin receptor scintigraphy (SRS), also known as In111-pentetreotide scan, can be an alternative. Many pNETs express high levels of somatostatin receptors and can be imaged with a radiolabelled form of the somatostatin analogue octreotide. SRS has a sensitivity of 90% and specificity of 80% for pNETs.[33,34] Poorly differentiated pNETs express low somatostatin receptor levels and are

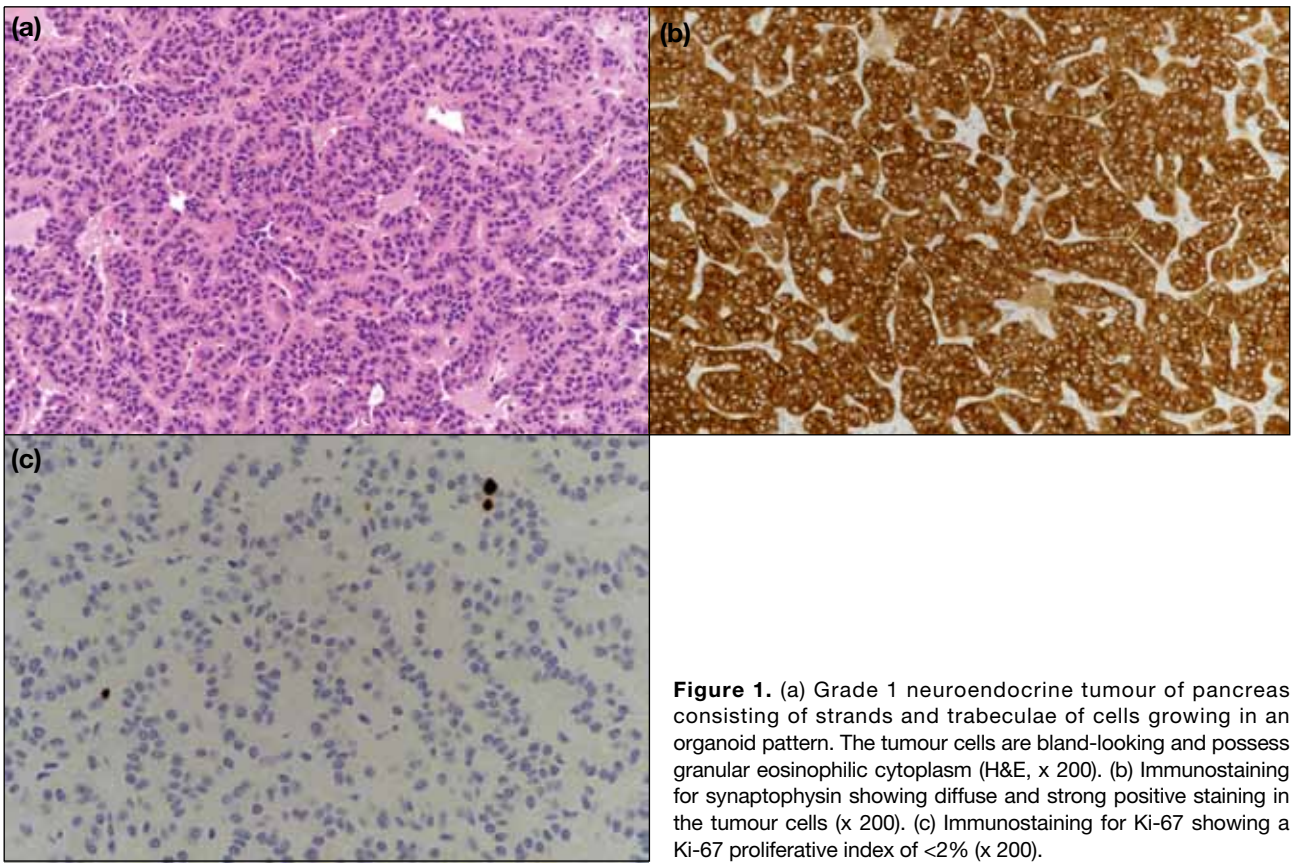

Figure 1. (a) Grade 1 neuroendocrine tumour of pancreas consisting of strands and trabeculae of cells growing in an organoid pattern. The tumour cells are bland-looking and possess granular eosinophilic cytoplasm (H&E, x 200). (b) Immunostaining for synaptophysin showing diffuse and strong positive staining in the tumour cells (x 200). (c) Immunostaining for Ki-67 showing a Ki-67 proliferative index of <2% (x 200).

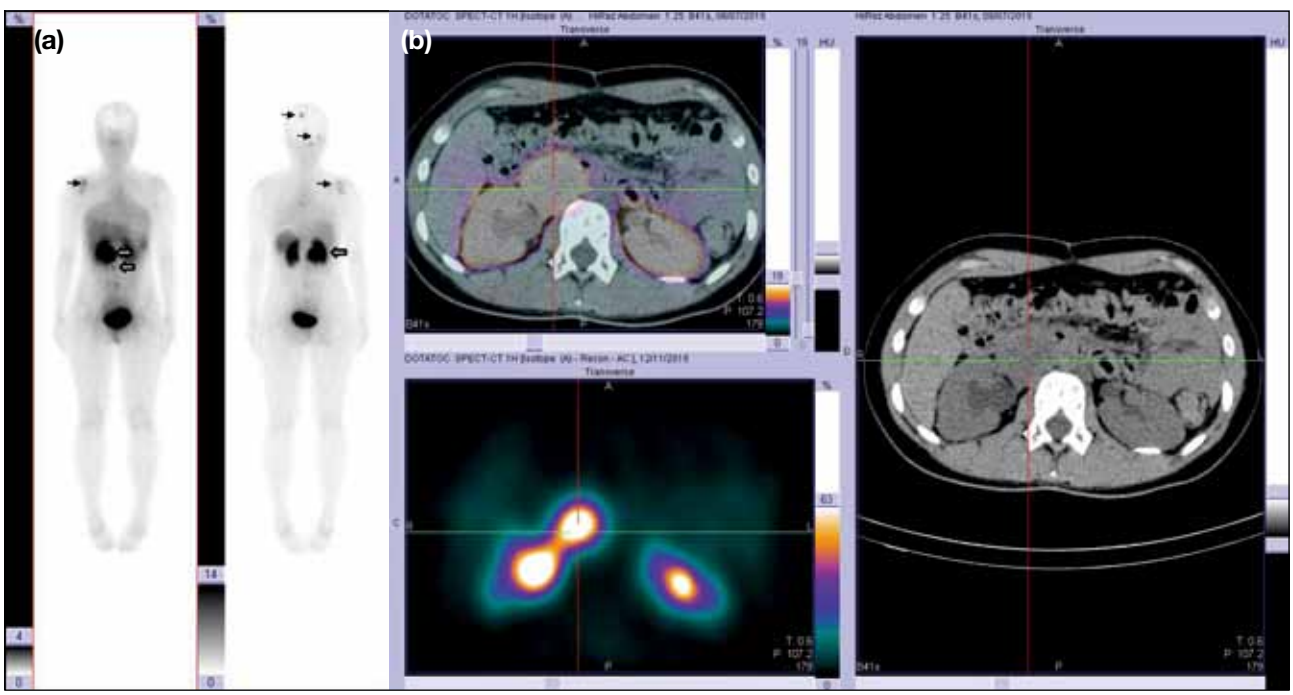

Figure 2. In a patient with neuroendocrine tumour: (a) ^{111}In-DOTATOC whole-body planar scanning and (b) transaxial single-photon emission computed tomography–computed tomography at the renal pelvis level showing the retroperitoneal metastases (block arrows and cross-hairs) and bone metastases (arrows).

unlikely to be detected on SRS. SRS is essential in peptide receptor radioligand therapy (PRRT) using radiolabelled somatostatin analogues, because levels of radiotracer uptake predict response to treatment (Figure 2). Functional positron emission tomography (PET) has begun to replace SRS in modern nuclear medicine imaging. Combined use of CT and PET tracers (^{18}F-DOPA, ^{11}C-5-HTP, ^{68}Ga-DOTATOC) improves detection and staging of NETs. These novel PET modalities provide higher spatial resolution than SRS and higher sensitivity for small lesions.

MANAGEMENT

Surgery

Curative surgery is the treatment of choice for patients with pNETs. Aggressive resection of pNETs results in acceptable morbidity and mortality and improved survival in all stages (localised, locoregional, and metastatic) of disease.[35] Nonetheless, grade-3 pNETs are often widely disseminated and thus inoperable.[36-38]

For most malignancies, there is little rationale to resect the primary tumour when there is widespread unresectable disease. For NETs, resection of the primary tumour may be beneficial when it causes physical symptoms (such as bleeding, pain, and obstruction) or hormone-related symptoms. Most patients with advanced pNETs have liver metastasis; surgical resection of liver metastasis is recommended in the absence of diffuse bilobar involvement, compromised liver function, or extrahepatic metastasis, particularly when the metastasis is of low volume or from low-grade tumours, and systemic therapy is available and the disease is indolent. Resection is recommended if at least 90% of tumour can be resected.[39] Nonetheless, the long-term benefits of hepatic resection versus a non-surgical approach are not well known. The indolent nature of the disease and the potential patient selection bias render comparison of various approaches difficult.

In a study of 172 patients with neuroendocrine liver metastasis at a single institute over 30 years, 144 patients underwent resection with or without ablation and their median overall survival was 9.6 years, and 5-year and 10-year overall survival rates were 77% and 55%, respectively.[40] Although nearly 50% of patients had liver recurrence, most underwent repeated resection or ablation.[40] In a study of 339 patients who underwent hepatic resection for neuroendocrine liver metastasis (60% had bilobar disease) in eight institutes over 24 years, the median survival was 125 months, and 5-year and 10-year overall survival rates were 74% and 51%, respectively.[41] Recurrence occurred in 94% of patients at 5 years. Although the rates of intrahepatic disease progression and recurrence were high, resection is still preferred for symptom control and to increase survival.[41]

Ablation

Radiofrequency ablation is most commonly used, followed by cryoablation and microwave ablation. Ablative techniques may be applicable to smaller lesions only. In patients with multifocal and bilateral disease, ablation may serve as an adjunct to surgical resection when major hepatectomy alone might compromise residual liver function. Ablation is particularly useful for patients with intrahepatic disease recurrence in whom surgical options are limited due to prior hepatectomy.

In a study of 89 patients who underwent laparoscopic radiofrequency ablation for neuroendocrine hepatic metastasis, the mean number of liver lesions treated per patient was 6 (range, 1-16) and the mean lesion size was 3.6 (range, 1-10) cm.[42] There was one postoperative death and 6% had perioperative morbidity, mainly due to haemorrhage.[42] Among patients with hormonal symptoms (44%), 73% had significant or complete symptom relief.[42] After a median follow-up of 30 months, the median disease-free survival was 1.3 years and overall survival was 6 years.[42] Of the patients, 22% developed local liver recurrence, and 59% developed extra-hepatic disease.[42]

Hepatic Artery Embolisation

Hepatic artery embolisation is a palliative procedure for patients with predominantly hepatic metastatic NETs who are not candidates for surgical resection. It is most suitable for patients with a slow-growing grade 1 to grade 2 tumour refractory to medical therapy to reduce tumour burden or control tumour progression in non-functioning tumours. Embolisation can be performed via infusion of gel foam powder (bland embolisation), in conjunction with chemotherapy (chemo-embolisation), or radioactive isotopes (yttrium-90) that are tagged to glass or resin microspheres (radio-embolisation). All three techniques for liver predominant disease result in comparable response rates of >50% in terms of decreased hormone secretion, symptomatic relief, or radiographic regression.[43-52] Contraindications and complications of these techniques are similar to those for hepatocellular carcinoma. In contrast to hepatocellular carcinoma, the presence of extra-hepatic disease is not a contraindication to hepatic artery embolisation for

NETs, particularly in highly symptomatic patients.[50]

SYSTEMIC TREATMENT FOR METASTASIS

Observation

For locally advanced or metastatic NETs, close observation can be considered if the patient has a low tumour burden, stable disease, and no symptoms. Treatment can be initiated if the disease progresses significantly (Table 4[53-59]).

Somatostatin Analogues

Somatostatin analogues are standard therapy for functioning NETs of any size and most effective for symptom control, but their anti-tumour efficacy is weak with only a 5% to 10% reduction in tumour size. Nonetheless, they enable disease stabilisation in 50% to 60% of patients and thus are first-line therapy for non-functioning and functioning progressive grade 1 or grade 2 NETs but are not for metastatic grade 3 NETs. Two somatostatin analogues have been shown to be effective in treating NETs in phase III clinical trials.

In the PROMID trial, patients with treatment-naïve, well-differentiated, advanced midgut NETs were randomised to receive octreotide LAR (Novartis Pharma AG, Switzerland) every 4 weeks or placebo until disease progression.[53] Octreotide LAR significantly reduced the risk of progression by 66%, doubling the median time to progression (14.3 vs. 6 months, hazard ratio [HR] = 0.34, $p < 0.001$).[53] It also reduced the median time to progression in patients with non-functioning NETs (28.8 vs. 5.91 months).[53]

In the CLARINET trial, patients with advanced well- or moderately differentiated (grade 1 or 2), non-functioning NETs (gastrointestinal and pancreatic NETs) were randomised to receive Lanreotide Autogel (Ipsen Pharma, France) every 4 weeks or placebo for 96 weeks or until progressive disease or death.[54] The PFS (but not overall survival) was significantly longer with the use of Lanreotide.[54] At 2 years, the median PFS was not reached in patients with Lanreotide, compared with 18 months in patients with placebo (HR = 0.47, $p < 0.001$).[54] The most common treatment-related adverse effect was diarrhoea (26% vs. 9%).[54]

Somatostatin analogues are well tolerated with only mild side-effects. Common side-effects include nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption, although symptoms tend to subside.

Molecular Targeted Therapy

Molecular targeted therapy is considered in patients with progressive advanced pNETs who are neither symptomatic from large tumour bulk nor having rapidly progressive metastatic disease. In a phase III trial to compare placebo with sunitinib (a multi-targeted tyrosine kinase inhibitor) in patients with advanced, well-differentiated pNETs, accrual was stopped prematurely prior to the first pre-planned interim efficacy analysis.[55] Although the objective responses were only observed in 9.3% of patients receiving sunitinib, the median PFS was significantly longer (11.4 vs. 5.5 months, HR = 0.42, $p < 0.001$), and overall survival was superior (HR = 0.41, $p = 0.02$).[55] With 69% of patients subsequently crossed over to the sunitinib arm, overall survival of the two arms were comparable (30.5 vs. 24.2 months, HR = 0.74, $p = 0.19$).[55] Hand-foot skin reactions and hypertension of any grade occurred in 23% and 26% of patients, respectively, and the most common grade 3 and 4 adverse events were neutropenia

Table 4. Summary of phase III clinical trials: systemic treatment for advanced neuroendocrine tumours (NETs).

Trial	Drug	Control arm	Progression-free survival (%)	Hazard ratio
Pancreatic NETs				
CLARINET*[54]	Lanreotide autogel	Placebo	Not reached vs. 18	0.47
SUN-1111[55]	Sunitinib	Placebo	11.4 vs. 5.5	0.42
RADIANT-3[56]	Everolimus	Placebo	11 vs. 4.6	0.35
Non-pancreatic NETs				
PROMID[53]	Octreotide LAR	Placebo	Time to progression: 14.3 vs. 6 months	0.34
RADIANT-2[57]	Octreotide LAR + everolimus	Placebo + octreotide LAR	16.4 vs. 11.3	0.77
RADIANT-4[58]	Everolimus	Placebo	11 vs. 3.9	0.48
NETTER-1[59]	^{177}Lu-DOTATATE + octreotide LAR 30 mg	Placebo + octreotide LAR 60 mg	Not reached vs. 8.4	0.21

* Including NETs originated in pancreas, midgut, hindgut, and unknown primary.

(12%) and hypertension (10%), respectively.[55]

In the RADIANT-3 trial, everolimus (which targets the mTOR pathway) has demonstrated its activity in pNETs.[56] Patients with progressive advanced low or intermediate-grade pNETs were randomised to receive everolimus or placebo. The objective responses were low (5%), but patients with everolimus had longer PFS (11.4 vs. 5.4 months, $p < 0.001$) and comparable overall survival, with a disease control rate of 77.7%.[56] Nonetheless, 85% of patients crossed over from the placebo to everolimus arm and might confound the ability to detect a difference. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (64% vs. 17%), rash (49% vs. 10%), diarrhoea (34% vs. 10%), fatigue (31% vs. 14%), and infection (23% vs. 6%) [mainly upper respiratory tract infection], whereas the most common grade 3 or 4 drug-related adverse events were stomatitis (7%), anaemia (6%), and hyperglycaemia (5%).[56]

In the RADIANT-2 trial, patients with advanced gastrointestinal NETs of low or intermediate grade were randomised to receive everolimus or placebo, together with octreotide LAR.[57] The median PFS was higher in the everolimus group (16.4 vs. 11.3 months, HR = 0.77, 95% confidence interval [CI] = 0.59-1.00, $p = 0.026$). In the RADIANT-4 study, patients with advanced, non-functional lung or gastrointestinal NETs with radiological progression within 6 months were randomised to receive everolimus or placebo.[58] The PFS was higher in the everolimus group (11 vs. 3.9 months, HR = 0.48, 95% CI = 0.35-0.67, $p < 0.001$).[58] Common drug-related adverse events included stomatitis (63% vs. 19%), diarrhoea (31% vs. 16%), fatigue (31% vs. 24%), infection (29% vs. 4%), rash (27% vs. 8%), and peripheral oedema (26% vs. 4%), whereas the most common grade 3 or grade 4 adverse events were stomatitis (9%), diarrhoea (7%), and infections (7%).[58]

Cytotoxic Chemotherapy

Chemotherapy enables a higher response rate and thus is a first-line treatment for patients with symptomatic large tumour bulk or rapidly enlarging metastasis. Streptozocin-based combination chemotherapy is the standard systemic treatment for patients with advanced pNETs. Streptozocin plus doxorubicin has been shown to result in a combined biochemical and radiological response rate of 69% and a median overall survival of 2.2 years.[60] In a retrospective study of patients with locally advanced or metastatic pNETs treated with streptozocin, 5-fluorouracil plus doxorubicin, the radiological response rate was 39% and the median overall survival was 37 months.[61] In a retrospective study of patients with pNETs treated with streptozocin plus 5-fluorouracil, the objective response rate was 43%, and an additional 41% had stable disease as the best response.[62] Although streptozocin-based regimens are effective in patients with advanced pNETs, their widespread use is limited by the cumbersome administration schedule and serious toxicity profile (such as nausea, hair loss, and renal dysfunction).

Dacarbazine is an alkylating agent that shows activity against pNETs. In an ECOG phase II trial of 42 patients with advanced pancreatic islet cell carcinomas, the objective response rate was 33%.[63] The toxicity of dacarbazine-based regimens has limited their widespread use. Temozolomide is a less toxic orally active analogue of dacarbazine. In prospective studies of temozolomide combined with thalidomide, bevacizumab or everolimus, the response rate ranged from 24% to 45%.[64-66] In a retrospective study of 30 patients treated with temozolomide plus capecitabine, the response rate was 70%.[67] Some patients continued treatment until disease progression, and some were treated until a maximal response was achieved or when a break from chemotherapy was recommended. The median duration of treatment was 8 cycles.[67] The median PFS was 18 months. In a phase II trial of temozolomide plus capecitabine, the overall response rate was 43% (including 11% complete response) and the stable disease rate was 54%, with an overall clinical benefit rate of 97%, whereas the median PFS was >20 months and overall survival was >25.3 months.[68] The most common grade 3 / 4 toxicities were lymphopenia (32%), hyperglycaemia (15%), thrombocytopenia (3%), and diarrhoea (3%); there was no hospitalisation, opportunistic infection, or death.[68] Nonetheless, the relative contribution of temozolomide in combination with capecitabine in terms of anti-tumour activity is unknown. It is not conclusive whether temozolomide is more effective with or without capecitabine. An ongoing phase II trial by ECOG is evaluating the relative efficacy of temozolomide plus capecitabine versus temozolomide alone.[69] Based on its clinical efficacy and administrative convenience as an oral drug, temozolomide is still recommended by various international guidelines.[70-74]

Peptide Receptor Radioligand Therapy

A unique feature of NETs is their over-expression

of different receptors: growth-regulating factor receptors (such as vascular endothelial growth factor, epithelial growth factor) and peptide hormones (such as somatostatin, cholecystokinin, and gastrin-releasing peptide). This makes them an ideal molecular target for imaging and therapy. Of these, somatostatin receptor over-expression, in particular the type-2 receptor, is most commonly found in NETs. The receptor-ligand complex is internalised into the tumour cells and disintegrated by lysosomes, leaving the radioactive ligand in the cells. The long retention time enables a high radiation dose to the tumour. The most frequently used radionuclides include yttrium-90 and lutetium-177 that are labelled to somatostatin analogues through a bisfunctional ligand. Change to the structure of any one of these three components in the complex can significantly alter their affinity for somatostatin receptors. In the DOTATOC and DOTATATE studies, the higher beta energy of yttrium-90 makes it potentially more effective for larger-size tumours, at the expense of more toxic effects, including renal and marrow toxicity, whereas lutetium-177 may be more suitable for small-size tumours.[75,76] Both radionuclides have been used in alternate cycles, tandem treatment, and have shown better overall survival.[75,76] PRRT can be considered in both functioning and non-functioning NETs as long as SRS is positive in which the levels of radiotracer uptake predict the response to PRRT. PRRT is recommended for patients with metastatic or inoperable NETs that show positive somatostatin tracer uptake (e.g. ^{111}In-octreotide or ^{68}Ga-DOTATATE scan), and preferably World Health Organization grade 1 or 2 tumours. Other considerations include the performance status and life expectancy of the patient.[77] Renal radiation dose can be reduced by lysine / arginine infusion, plasma expanders, and colchicine. Careful consideration or pretreatment dosimetry should be performed in patients with renal impairment, particularly with yttrium-90 therapy. Complete remission is seldom achieved in PRRT; the objective response rate was approximately 30% and stable disease rate was approximately 50%, similar to PRRT using yttrium-90 or lutetium-177. Overall survival and PFS are generally improved after PRRT.[78-81] Long-term side-effects of PRRT include impaired renal function, pancytopenia, and myelodysplastic syndrome. Hormonal crisis is rare but close monitoring is required.

In the phase III NETTER-1 study of PRRT, ^{177}Lu-DOTATATE plus octreotide LAR 30 mg was compared with octreotide LAR 60 mg alone in patients with inoperable, somatostatin receptor-positive, midgut grade-1 or 2 NETs who progressed under octreotide LAR 30 mg.[59] Four doses of 7.4 GBq of ^{177}Lu-DOTATATE administered every 8 weeks together with octreotide resulted in higher PFS (median PFS not reached vs. 8.4 months, HR = 0.21, $p < 0.001$) and objective response rate (18% vs. 3%, $p < 0.001$).[59] Although data were not mature enough for a definitive analysis, the number of deaths suggested improved overall survival (14 vs. 26, HR = 0.4, $p = 0.004$).[59] Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9% of patients, respectively, in the ^{177}Lu-DOTATATE group as compared with no patient in control group, with no evidence of renal toxic effects.[59]

MANAGEMENT OF HIGH-GRADE NEUROENDOCRINE TUMOURS

Unlike well-differentiated NETs, grade 3 NETs behave more aggressively and conventional cytotoxic chemotherapy is the first-line treatment. Evidence for selection of a chemotherapy regimen for grade 3 NETs is limited, and most experts extrapolate from their experience of treating small-cell lung cancer, owing to the close histological and clinical resemblance.

The most commonly used regimen for grade 3 NETs is cisplatin plus etoposide. The response rate to first-line chemotherapy has been reported to be 31% and the stable disease rate 33%.[82] Patients with a Ki-67 index of >55% had a higher response rate (42% vs. 15%, $p < 0.001$) but worse survival (10 vs. 14 months, $p < 0.001$), compared with those with a Ki-67 index of ≤55%.[82]

There is no established second-line chemotherapy for grade 3 NETs. The overall response rate is lower compared with that for first-line treatment. In a retrospective study of temozolomide alone or in combination with capecitabine +/- bevacizumab, the partial tumour response rate has been reported to be 33%.[83] Retreatment with platinum can be considered provided that there have been durable responses to first-line platinum-based chemotherapy, PFS of >3 months, and no cumulative neuro- and oto-toxicities.[83]

CONCLUSION

Systemic treatments including somatostatin analogues and molecularly targeted therapies are effective in treating NETs. PRRT is an emerging treatment option. Future clinical trials should focus on exploring a sequence of various systemic therapies, possible

benefits of their combination (somatostatin analogue with targeted agents), and PRRT in combination with targeted therapies.

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