Review Article

A systematic review of management of neuroendocrine tumors: An experience from a tertiary care centre from India

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ABSTRACT

Neuroendocrine tumors (NETs) encompass a heterogeneous group of tumors demonstrating varied clinical behavior. The field has recently witnessed several important developments stemming from improvements in the histopathological classification schemes, advanced imaging techniques, and a deeper understanding of the molecular mechanisms underlying tumor progression. These tumors have indolent clinical courses, with long survival rates even for the patients with metastatic disease. The mainstay of treatment is surgery. Somatostatin analogs play a key role in controlling the symptoms; however, they are seldom associated with tumor regression. Traditional cytotoxic chemotherapies have a very limited role in well-differentiated NETs, but platinum-based chemotherapy is highly effective in neuroendocrine carcinomas. Recently, the biological targeted agents have shown promise in patients with metastatic disease. Evolving modalities like peptide receptor targeted therapies and radioembolization have opened up new avenues in refractory and advanced disease.

Key words: Neuroendocrine tumors, octreotide, targeted therapy

INTRODUCTION

Neuroendocrine tumors (NETs) encompass a heterogeneous group of neoplasms demonstrating varied clinical presentation. NETs can arise from neuroendocrine cells present in most epithelial organs of the body, but they are particularly well-recognized in lung, tubular gastrointestinal (GI) tract, and pancreas. These tumors are characterized by the ability to secrete hormones and biogenic amines. Though NETs commonly have an indolent clinical course, a significant number of patients present with metastatic disease. Because of this fortunate indolent biology, NETs can often be cured when detected early. However, the same indolent nature makes an early diagnosis unlikely. For patients with localized disease surgical resection is often curative. On the other hand, patients with metastatic disease often present a therapeutic challenge. Since the metastatic disease is generally incurable, most patients are treated for many years. Although somatostatin analogs are highly effective in controlling the symptoms due to endocrine secretions, they are seldom associated with tumor regression. The development of molecular therapies targeting the mammalian target of rapamycin (mTOR) and tyrosine kinase, like everolimus and sunitinib, respectively, has led to improved survivals even in patients with advanced disease. Evolving modalities like peptide receptor targeted therapies and radioembolization have opened up new avenues in refractory and advanced disease.

Because of the higher probability of cure in early stages, it will be of utmost importance to diagnose the neuroendocrine tumors at an early stage.

Access this article online	
Quick Response Code:	Website: www.ccij-online.org
	DOI: 10.4103/2278-0513.138052

PATHOLOGICAL CLASSIFICATION AND NOMENCLATURES

Since the initial description by Oberdorfer[1] in 1907, who coined the term "carcinoid" to describe the presence of

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a group of tumors in the small intestine that behaved better than conventional carcinomas, numerous attempts have been made to arrive at a more specific classification system to provide a more accurate prognosis of these tumors. For the most part, such a unifying approach had failed. Updated guidelines have been proposed by several organizations like the World Health Organization (WHO), the European Neuroendocrine Tumor Society (ENETS), the American Joint Committee on Cancer (AJCC), and the North American Neuroendocrine Tumor Society.[2-4] While no standard nomenclature could be established, modifications have largely aimed to incorporate Ki-67 as a fundamental component of grading, making a clear distinction between poorly differentiated and well-differentiated NETs.

The term "carcinoid tumor" was originally proposed to mean "carcinoma like," a reflection of the relatively less aggressive clinical course of well-differentiated NETs, compared to exocrine carcinomas of the same organs. However, carcinoid tumor has been criticized as a diagnostic nomenclature,[5,6] because of mistaken assumption of benign behavior. Organ specific terms like islet cell tumor or insulinoma no longer exist today. The 2010 WHO classification of tumors of the GI tract, pancreas and liver specifies that well-differentiated neuroendocrine neoplasms be classified as "NETs."[4,7,8] The term "neuroendocrine carcinoma" is limited to high-grade (G3), poorly differentiated neoplasms (high-grade neuroendocrine carcinomas [HGNEC]).[7,9] It also includes small cell carcinoma and large cell neuroendocrine carcinomas. Table 1 compares the various synonyms that exist for these different categories of NETs. The classification system separates NET into two clinically meaningful groups (G1/G2, well-differentiated NET and G3, poorly differentiated NET), which are characterized by vastly different clinical behavior and response to therapy. The grade of NET is a major determinant of the treatment outcome and grading parameters are a part of most classification systems. Table 2 summarizes the grading system of NETs.

Table 1: Nomenclature of different neuroendocrine tumour

Grade	Traditional	ENETs, WHO	Moran *et al*
Low	Carcinoid Tumour	Neuro endocrine tumour, grade 1	Neuroendocrine carcinoma grade 1
Intermediate	Carcinoid Tumour	Neuro endocrine tumour grade 2	Neuroendocrine carcinoma grade2
High	Small cell carcinoma,	Neuroendocrine carcinoma grade 3, small cell carcinoma	Neuroendocrine carcinoma grade 3, small cell carcinoma
	Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3, large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3, large cell neuroendocrine carcinoma

*Taken from North American Neuroendocrine Tumour Society guidelines,
WHO: World Health Organization

Table 2: Grading system of neuroendocrine tumors

Grade	Lung, Thymus (WHO)	GEP-NETs (ENETS, WHO)
Low	<2 mitosis/10 hpf and no necrosis	<2 mitoses/10 hpf and Ki 67 index<3%
Intermediate	2-10 mitoses/10 hpf or foci of necrosis	2-20 mitoses/10 hpf or Ki 67 index 3-20%
High	>10 mitoses/10 hpf	>20 mitoses/10 hpf or Ki-67 index>20%

WHO: World Health Organization

STAGING

Previously, there was no tumor node metastasis (TNM) based staging system in existence for NETs for any anatomical site. The AJCC and ENETS have each recently published TNM staging systems for NETs of the small intestine, large bowel, and appendix. These staging systems are provided in Tables 3 and 4.

PATHOGENESIS, GENETICS AND MOLECULAR BIOLOGY

The majority of NETs are sporadic but some of them may be associated with several familial syndromes like multiple endocrine neoplasia type 1 (MEN-1), MEN-2, von Hippel-Lindau (VHL) syndrome, neurofibromatosis and tuberous sclerosis. Little is known about the pathogenesis of sporadic NETs. NETs contain a number of genetic alterations, but it is only in the setting of MEN-2 syndrome, that an activating mutation of RET proto oncogene driving the tumor progression, with a direct genotype-phenotype correlation could be deciphered. A recent study showed that more than 40% of sporadic pancreatic NETs harbor MEN-1 gene mutation, in addition to those associated with MEN-1 syndrome.[10] The study by Jiao *et al*. showed that ATRX/DAXX genes involved in chromatin remodeling are mutated in a significant number of tumors. They have also identified mutations in genes encoding components of the mTOR pathway in up to 14% of tumors.[11] Understanding of this tumor biology has encouraged the emergence of mTOR inhibitors in the treatment of this tumor; however, the predictive value of such mutations remains uncertain at present. Genetic abnormalities in pathways involved in angiogenesis have also been described. Loss of VHL gene expression is known to be associated with increased vascular endothelial growth factor (VEGF) expression and angiogenesis. In fact, germline mutations of the VHL gene in VHL syndrome, has also been linked to the development of islet cell carcinomas. Multiple genes in the VEGF pathway are located in regions where frequent allelic deletions occur in NETs, making anti-angiogenic therapy plausible.

Table 3: AJCC and ENET staging for NETs of small intestine and large bowel

AJCC (Bowel)	ENETS (Bowel)
Primary tumour (T)	Primary Tumour (T)
TX Primary tumour cannot be assessed	TX Primary tumour cannot be assessed
T0 No evidence of primary tumour	T0 No evidence of primary tumour
T1 Tumour invades lamina propria or submucosa and size<1 cm	T1 Tumour invades mucosa or submucosa and size<1 cm
T2 Tumour invades muscularis propria or size>1 cm	T2 Tumour invades muscularis propria or size>1 cm
T3 Tumour invades through muscularis propria into subserosa or into the nonperitonealised tissue	T3 Tuour invades subserosa
T4 Tumour invades visceral peritoneum or any other organs or structures	T4 Tumour invades peritoneum or other organs
Regional Lymphnodes (N)	Regional Lymphnodes (N)
NX Regional lymphnodes cannot be assessed	NX Regional lymphnodes cannot be assessed
N0 No regional lymphnode metastasis	N0 No regional lymphnode metastasis
N1 Regional lymphnode metastasis	N1 Regional lymphnode metastasis
Distant Metastasis (M)	Distant Metastasis
M0 No distant metastasis	M0 No distant metastasis
M1 Distant metastasis	M1 Distant metastasis

Stage grouping (AJCC)				Stage grouping (ENETS)			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
0	Tis	N0	M0	-	-	-	-
I	T1	N0	M0	I	T1	N0	M0
IIA	T2	N0	M0	IIA	T2	N0	M0
IIB	T3	N0	M0	IIB	T3	N0	M0
IIIA	T4	N0	M0	IIIA	T4	N0	M0
IIIB	Any T	N1	M0	IIIB	Any T	N1	M0
IV	Any	T Any	N M1	IV	Any T	Any N	M1

Table 4: AJCC & ENET Staging for appendix

AJCC	ENETS
Primary tumour (T)	Primary tumour (T)
TX Primary tumour cannot be assessed	TX Primary tumour cannot be assessed
T0 No evidence of primary tumour	T0 No evidence of primary tumour
T1 Tumour<2 cm in greaest dimension	T1 Tumour<1 cm invading submucosa and muscularis propria
T1a Tumour 1 cm or less in greatest dimension	T2 Tumour<2 cm invading submucosa , muscularis propria and or minimally (upto 3 mm) invading subserosa or mesoappendix
T1b Tumour>1 cm but not >2 cm	T3 Tumour invades subserosa/ pericolic/perirectal fat
T2 Tumour>2cm but not>4cm or with extension to caecum	T4 Tumour invades peritoneum or other organs
T3 Tumour>4 cm or with extensions to ileum	
T4 Tumour directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscles	
Regional lymphnodes (N)	Regional lymphnodes (N)
NX Regional lymphnodes cannot be assessed	NX Regional lymphnodes cannot be assessed
N0 No regional lymphnode metastasis	N0 No regional lymphnode metastasis
N1 Regional lymphnode metastasis	N1 Regional lymphnode metastasis
Distant metastasis (M)	Distant metastasis (M)
MX ————	MX Distant metastasis cannot be assessed
M0 No distant metastasis	M0 No distant metastasis
M1 Distant metastasis	M1 Distant metastasis

Stage grouping (AJCC)				Stage grouping (ENETS)			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
I	T1	N0	M0	I	T1	N0	M0
II	T2	N0	M0	IIA	T2	N0	M0
	T3	N0	M0	IIB	T3	N0	M0
III	T4	N0	M0	IIIA	T4	N0	M0
	Any T	N1	M0	IIIB	Any T	N1	M0
IV	Any T	Any	N M1	IV	Any T	Any N	M1

CLINICAL PRESENTATION

Presenting symptoms are generally attributable to a well-differentiated (low or intermediate grade) NET metastatic to liver, often present for years prior to diagnosis. Symptoms may be isolated flushing or diarrhea.[12] As early symptoms are vague and nonspecific, misdiagnosis or a delay in diagnosis may occur even in patients presenting with advanced disease.[13] Carcinoid diarrhea is typically secretory in nature, may be nocturnal and is not responsive to fasting. Patients may present with a facial rash mimicking rosacea, cardiac valvular disease (tricuspid insufficiency, pulmonic stenosis), wheezing or malaise.[14] Patients with gastrinomas present with abdominal pain, dyspepsia, diarrhea, and GI bleeding.[15] Presentation of insulinoma are often confusing and constitute an unusual spectrum including hypoglycemia, syncope, involuntary weight gain, and unexplained seizure disorder.[14] High volume secretory diarrhea that persists during fasting and is accompanied with electrolyte imbalance (hypokalemia, hypomagnesemia, and hypocalcemia), dehydration, nausea, emesis, muscle weakness, cramps, and sometimes flushings are classic symptoms of VIPoma.[16] Diabetes accompanied by the 4D s-dermatosis (necrolytic migratory erythema) depression, diarrhea and deep vein thrombosis-is diagnostic for glucagonomas that should be considered malignant despite a benign histologic appearance.[17] The triad of cholelithiasis, hyperglycemia and steatorrhea triggers the suspicion for a somatostatinoma.[14]

DIAGNOSIS

Tumor localization

A number of techniques including GI endoscopy, barium radiography, chest radiography, imaging studies (ultrasonography, computed tomography [CT], magnetic resonance imaging [MRI], angiography), endoscopic ultrasonography, selective venous sampling

for various hormones, positron emission tomography (PET) and various forms of radionuclide scanning (radiolabelled somatostatin receptor scintigraphy (SRS), iodinated metaiodobenzylguanidine [MIBG] scanning) have all been used to determine the location of primary tumor as well as tumor extent.[18]

Bronchial carcinoid tumors are usually detected by chest radiography, CT or occasionally bronchoscopy. They appear frequently as opacities with sharp or often notched margins. They are slow growing and often induce airway compression with resultant atelectasis. Enlarged hilar lymph nodes from metastasis are rare. Rectal, duodenal, colonic and gastric NETs are almost always detected by GI endoscopy, with barium radiograph results being generally negative. Positive barium radiograph results show dilated loops of small bowel or extrinsic filling defects, but rarely detects a mucosal lesion, whereas ileal, cecal and right colon tumors are often diagnosed on radiographic studies.[19]

The major problem lies in localizing the small bowel carcinoid tumors, which may be very small and hence frequently missed by barium studies. Some of those tumors can be picked up by angiography, SRS or CT, but many are not seen even with these imaging modalities.

Neuroendocrine tumors are usually hypervascular and are typically well-visualized as avidly enhancing masses during the early (arterial) phase of multiphasic contrast-enhanced CT. The lesions are typically of low density on noncontrast CT. They have variable appearances on MRI: Hypo or isointense on T1-weighted and hyperintense on T2-weighted images.

Conventional imaging modalities have a limitation in detection of NETs due to their small size, their variable anatomic location and the slow metabolic rate of well-differentiated forms. Here comes the role of nuclear imaging studies, which have been proven useful in diagnosing and staging the somatostatin receptor (SSTR) positive NETs.

SOMATOSTATIN RECEPTOR SCINTIGRAPHY

Somatostatin receptors have been demonstrated in NETs, many of which are derived from cells belonging to the amine precursor uptake and decarboxylation system. Octreotide binds with high affinity to SSTR-2 and SSTR-5, and to a lesser extent to SSTR-3.[20] Octreotide, substituted N-terminally by DTPA, can be efficiently labeled with ^{111}In. The preferred dose of ^{111}In Octreotide is about 5-6 mci and planar and single photon emission computed tomography images are obtained with a large field of view gamma camera equipped with a medium energy parallel-hole collimator.

Octreotide scan can be used for the following:

- Diagnosis of primary or recurrent NETs; a negative scan however cannot be used to exclude gastrinoma, insulinoma or medullary carcinoma thyroid
- Prediction of therapeutic response to octreotide
- Staging and differentiation of NETs from other tumors including benign lesions
- Therapeutic guidance for ^{90}Y octreotide or analogs.

The diagnostic sensitivity of ^{111}In DTPA octreotide scans in patients who have gastroenteropancreatic tumors have been reported to be in the range of 80% to 90% with the highest reported results for glucagonoma.[21]

ROLE OF POSITRON EMISSION TOMOGRAPHY SCAN IN NEUROENDOCRINE TUMOURS

Recently, with the widespread use of PET/CT and development of novel PET tracers (Ga-68 DOTA peptides) that specifically bind to SSTRs over expressed on the surface of NETs, the visualization of NET with Ga-68 DOTA PET/CT scans[22] has been shown to be advantageous over conventional SRS. Firstly Ga-68 is generator produced and labeling of Ga-68 with DOTA is relatively easy. Secondly, resolution of PET/CT imaging is far better than gamma camera, thus better visualization of lesion is a benefit. It has higher sensitivity for the detection of well-differentiated NETs than SRS. Furthermore, this is less time-consuming than SRS (roughly 1.5 h instead of up to 24 h acquisition in SRS). In addition, PET/CT provides the advantage of semi-quantification of the lesions. Ga-68 DOTATATE PET/CT is useful in characterization, localization, staging, restaging, recurrence detection, and assessment of response to treatment in NET.[23]

But one should be aware of the fact that positive findings on Ga-68 DOTATATE PET/CT reflect an increased density of SSTRs rather than malignant disease. Thus, a poorly differentiated NET that is, poorly SSTR expressing tumor may not show tracer uptake.[23] Fluorodeoxyglucose PET should be used for poorly differentiated and undifferentiated tumors or when [^{111}In-DTPA] octreotide or ^{123}I-MIBG are negative or equivocal. [18F]-fluorodeoxyglucose PET imaging may also be used to characterize tumor aggressiveness with higher FDG uptake (expressed as SUV values) having a worse prognosis.

TUMOUR MARKERS

Frequently measured tumor markers in NETs include serum chromogranin A (CgA) and 5-hydroxyindole acetic acid (5-HIAA) levels in a 24 h urine sample.

Chromogranin A is an acidic glycoprotein with a molecular mass of 49 kD that is widely expressed by neuroendocrine cells and constitutes one of the most abundant components of secretory granules. In particular circulating CgA levels have been claimed to be useful markers for NETs with a high specificity and sensitivity ranging from 27% to 81%. Because it does not rely on serotonin secretion, serum CgA is a more sensitive and broadly applicable marker than urinary 5-HIAA and may be used not only in patients who have metastatic small bowel and appendiceal carcinoid tumors, but also in patients who have bronchial and rectal carcinoid tumors in whom urinary 5-HIAA levels are less likely to be elevated. Plasma Cg A levels have also been shown to correlate with treatment response and may also have a prognostic value.[24]

Twenty-four hour urinary 5-HIAA quantification is a useful laboratory test for carcinoid tumors. It is a surrogate measure of serotonin metabolism that is tightly linked to the presence of carcinoid syndrome. It is also perhaps more useful than the direct measurement of serotonin, as serum serotonin levels vary considerably during the day according to physical activity and stress levels. The specificity of this test has been reported to be 88%.

In addition to CgA and 5-HIAA, NETs synthesize other bioactive amines and peptides such as 5-hydroxytryptamine, 5-hydroxytryptophan, serotonin, insulin, gastrin, glucagon, somatostatin, vasoactive intestinal peptide, growth hormone, adrenocorticotropic hormone, melanocyte-stimulating hormone, pancreatic polypeptide, calcitonin, substance *P* and pancreastatin, etc.[25]

MANAGEMENT

Optimal management requires a multidisciplinary approach. Because of the limited amount of definitive data from random-assignment studies, much of the management decisions are based on experience and expert recommendations. Surgery remains the standard and only potentially curative therapy for patients with localized well-differentiated NETs. Adjuvant therapy is currently not indicated in patients with completely resected localized NETs. Presently, there is insufficient data to recommend the use of adjuvant therapy after complete resection of local-regional disease.

MANAGEMENT OF ADVANCED WELL DIFFERENTIATED NEUROENDOCRINE TUMOURS

Though surgery remains the mainstay of treatment in localized well-differentiated NETs, a reasonable number of patients present with disease that is already advanced or unresectable. Appropriate management of patients with advanced surgically unresectable neuroendocrine carcinomas remains a therapeutic dilemma. Advanced unresectable NETs are generally not curable. The goals of treatment for nonfunctional tumors include palliation of symptoms and cytoreduction of bulky tumors in an effort to prolong the survival. There are a handful of options for advanced well-differentiated NETs; however, there is no consensus guidelines regarding the optimum utilization of these modalities.

SOMATOSTATIN ANALOGS

Somatostatin analogs have been widely used in NETs for the control of hormone related symptoms. The biological effects of commonly used somatostatin analogs like octreotide or lanreotide are mediated primarily by binding with SSTR-2.[26] Pasireotide is a novel somatostatin analog, that not only binds to SSTR-2, but it also binds with subtype 1, 3 and 5. It is not yet known if the expanded binding affinity will translate into improved efficacy either in first-line setting or as a salvage therapy.[27]

Octreotide is an intermediate acting somatostatin analog that can be administered subcutaneously every 6-12 hourly. It produces complete resolution or partial relief of flushing or diarrhea in about 85% of the patients with carcinoid syndrome and produces a biochemical response rate up to 72%. Long acting somatostatin analogues have obviated the need for daily injections in most patients. Depot octreotide (10, 20 or 30 mg) is given intramuscularly once a month.[28] Although somatostatin analogs have been also widely used for presumed cytostatic activity, until recently, there have been no prospective data to support the antiproliferative role of somatostatin analogs. An antiproliferative effect associated with somatostatin analogs has been demonstrated in patients with advanced small bowel carcinoid tumors in the PROMID study, where 80 patients with unresectable or metastatic small bowel carcinoid tumors were randomized to receive either a long acting octreotide or placebo. Those patients randomized to receive octreotide experienced a median time to tumor progression of over 14 months as compared with only 6 months for patients receiving placebo.[29] Based on these results somatostatin analogs are now widely used for their antiproliferative effects in patients with advanced NETs.

SYSTEMIC THERAPY

Cytotoxic chemotherapy

Cytotoxic chemotherapy has contributed in only a limited fashion to the treatment of patients with advanced well-differentiated NETs. Single agent therapy with

5-fluorouracil, streptozocin or doxorubicin had shown response rates of approximately 20%.[30] Combination chemotherapy does not seem to be significantly superior to single agent therapy. Various studies[31-36] showed varied response rates of combination chemotherapeutic agents used in advanced carcinoid tumors [Table 5].

Peptide receptor targeted therapy

Majority of the NETs express SSTRs and octreotide scan with ^{111}In labeled somatostatin analogs has been widely used as a diagnostic modality in NET patients. A similar strategy with different radioisotopes also can be used for therapeutic purposes in patients with advanced disease and SSTR expression. The most frequently used radionuclides for targeted radiotherapy are yttrium (^{90}Y) and lutetium (^{177}Lu). A retrospective series of more than 500 patients showed good tolerability and overall tumor response of up to 30% in patients with various types of NET where ^{177}Lu-DOTA tyr-3 octreotide has been used.[37] ^{90}Y-DOTA also has been extensively used for the treatment of advanced NETs and showed similar results as compared to ^{177}Lu-DOTA.[38] Most recently, the combination of ^{90}Y-DOTA and ^{177}Lu-DOPA was evaluated in 249 patients and compared retrospectively to the results in 237 patients receiving ^{90}Y-DOTA alone. Longer survival durations in patients who were exposed to both agents suggested potential promise associated with this strategy.[39] These radioisotope therapies have been associated with hematologic and renal toxicity.[40] Prospective randomized controlled studies evaluating both the antitumor activity and long-term toxicity of radiolabeled somatostatin analogs are necessary and anticipated.

Table 5: Response to different cytotoxic chemotherapies and biological targeted agents in advanced carcinoid and pancreatic endocrine tumours

Chemotherapy regimes	Response (%)	Median OS/ PFS (months)	Authors
Doxorubicin[a]	21	Not reported	Engstrom *et al.*[31]
Streptozocin/5FU[a]	33	16.8 (OS)	Moertel *et al.*[32]
Streptozocin/ Doxorubicin/5FU[b]	39	37 (OS)	Kouvaraki *et al.*[33]
Temozolamide/ Thalidomide[b]	45	Not reported	Kulke *et al.*[34]
Gemcitabine	8	Not reported	Kulke *et al.*[35]
Paclitaxel	0	Not reported	Ansell *et al.*[36]
XELOX+Bevacizumab	30	Not reported	Kunz *et al.*[45]
FOLFOX+Bevacizumab	60	Not reported	Bergsland *et al.*[46]
Temozolamide+ Bevacizumab	24	Not reported	Kulke *et al.*[34]
Temozolamide+ Everolimus	35	Not reported	Kulke *et al.*[47]
Sunitinib	9	11.4 (PFS)	Raymond *et al.*[44]
Sorafenib	11	11.9 (PFS)	Hobday *et al.*[48]
Pazopanib	17	11.7 (PFS)	Phan *et al.*[49]
Everolimus	9	9.7 (PFS)	Yao *et al.*[50]
Temsirolimus	7	10.6(PFS)	Duran *et al.*[51]

[a]Advanced carcinoid tumours, [b]Advanced pancreatic neuroendocrine tumours, OS: Overall survival, PFS: Progression free survival

INTERFERONS

Interferon alpha has been historically used as a treatment for patients with advanced carcinoid tumors for a long time. Low dose interferon has been reported to reduce symptoms of hormonal hypersecretion and, in some cases, to arrest or slow the tumor growth. In some studies tumor regression has been reported in up to 15%.[41] Interferon doses in most studies ranged from 3-9 million units subcutaneously, administered 3-7 times per week.[42] It is not routinely used now because of its toxicity.

TARGETED THERAPIES

In contrast to primary NETs of other sites, significant progress has been made in the development of novel treatments for pancreatic NETs over the past decade. Everolimus and sunitinib were both approved as single agents for the treatment of progressive pancreatic NET in 2011. mTOR functions downstream a number of receptor tyrosine kinases and is thought to integrate the signal cascade of several growth factors. Several lines of evidence support the role of mTOR inhibitors in controlling the growth of NETs. The RADIANT-3 study compared everolimus with placebo in progressive pancreatic NETs and showed a significant improvement in progression free survival (11.6 months vs. 4.6 months, hazard ratio 0.35; $P < 0.0001$).[43]

Sunitinib is an oral tyrosine kinase inhibitor that inhibits a variety of kinases including VEGFR 1 and 2, platelet derived growth factor receptors, Flt-3 and RET. In a phase III trial by Raymond *et al*. sunitinib was compared to placebo in progressive pancreatic NET and accrual was stopped prior to a preplanned efficacy analysis; analysis of the enrolled patients showed median progression free survival was significantly longer with sunitinib as compared with placebo (11.4 vs. 5.5 months; hazard ratio 0.42; $P < 0.001$).[44] Though preliminary analysis predicted an improvement of overall survival (OS) with sunitinib, an updated analysis showed no significant improvement in OS. Response rates and survival with different biological agents reported in literature [45-51] have been shown in Table 5.

LIVER DIRECTED THERAPIES

Treatment options for NETs have historically centered around surgical resection. Hepatic metastatic lesions can be resected even if the primary is not identified. Hepatic metastatic lesions can be resected even if the primary is not identified. Because hepatic metastasis are responsible for most of the morbidity and mortality of these diseases, liver directed therapies can be of great benefit for those whom resection is not indicated.

Cytoreduction of liver NET also can be achieved with a variety of nonsurgical procedures. Ablative therapy, transarterial embolization (TAE), transarterial chemoembolization (TACE), or selective internal radiation therapy using ^{90}Y microspheres can be performed as the primary liver directed treatment for patients with diffuse disease or in poor surgical candidates.

RADIOFREQUENCY ABLATION

The growing experience with radiofrequency ablation (RFA) in hepatocellular carcinoma and colorectal cancer metastasis has led to its use in in NETs also. The largest prospective study of 89 patients by Akyildiz *et al*. showed within 1 week of the procedure there was partial symptom relief in 97% patients and complete or significant symptom relief in 73% patients with a median progression free survival of 15 months.[52] This large experience showed that RFA is an effective tool for cytoreduction in NETs.

TRANSARTERIAL EMBOLISATION

Neuroendocrine tumors tend to form highly vascular metastatic lesions in the liver and derive more than 90% of their blood supply from the hepatic artery, whereas approximately 50% of the oxygen supply to normal liver is from the portal system.

In addition, nutrient flow from the hepatic artery to a tumor is twice that from the portal vein. Thus, the hepatic artery offers an avenue for introduction of antitumor agents while sparing the surrounding normal liver tissue from the brunt of the toxic effects. TAE causes tumor ischemia by occluding the intratumoral hepatic arterial branches with embolic agents like polyvinyl alcohol and gelatin microspheres.

Transarterial chemoembolization theoretically augments the effects of embolization with localized infusion of chemotherapeutics. TACE allows for intratumoral concentration of a chemotherapeutic agent that is 10-20 times higher than that which can be achieved with systemic chemotherapy.[53] Different chemotherapeutic agents have been used for TACE in NETs which include streptozocin, mitomycin, doxorubicin and cisplatin. There are very few studies in the literature comparing the efficacy of TAE and TACE and they have shown similar results with both the procedures in terms of symptomatic relief, radiological response or median survival. Vogl *et al*. summarized the recent literature on efficacy of TAE and TACE, where symptomatic response has been described in 64-93% of patients after TAE, compared to 53-95% of patients following TACE. Five-year survival rates following TAE ranged from 40% to 54% compared to 48-83% following TACE.[53]

RADIOEMBOLIZATION

Radioembolization with ^{90}Y microspheres has been tried in the treatment of metastatic NETs to liver. This kind of therapy involves the administration of resin or glass microspheres labeled with ^{90}Y into the hepatic artery. ^{90}Y is a pure beta particle emitter with average penetration of 2.5 mm in liver tissue and a physical half-life of 64.2 h. With use of radioembolization, radiological objective responses (complete and partial responses combined) at 3-6 months have been observed in 39-70% of patients, whereas disease stabilization can be expected in 15-40% of patients. NETs take 4-6 months to respond maximally to this therapy and duration of response is around 15 months.[54,55]

TREATMENT OF HIGH GRADE NEUROENDOCRINE CARCINOMAS

High-grade neuroendocrine carcinomas constitute a wide spectrum of aggressive malignancies and are morphologically and clinically distinct from well-differentiated NETs (NETs low and intermediate grade). They have a universally poor prognosis irrespective of the primary site of origin. Median survival ranges from 4 to 16 months with treatment.[56]

There is scarcity of data regarding the treatment of localized extrapulmonary HGNEC. Retrospective studies have shown that surgery alone is rarely curative.[57] Based on treatment algorithms of localized small cell lung cancer, concurrent chemoradiation can be a treatment option and it may be beneficial where surgical resection is not feasible. The optimal sequencing of this multimodality treatment is yet to be determined; however, extrapolating from the results of pulmonary HGNEC, it appears that concurrent chemoradiation offers a better disease control as compared to sequential treatment.[58] There are no prospective studies addressing the benefit of adjuvant therapy following surgical resection.

Platinum-based chemotherapy is the treatment of choice-based on trials from metastatic pulmonary HGNEC.[59] Cisplatin and etoposide constitute the most utilized regimen; however, it is reasonable to substitute carboplatin for cisplatin or irinotecan for etoposide.[60] A paucity of data exists on second-line therapy for patients who have progressed on platinum-based therapy. Temozolomide, topotecan, taxanes, vinorelbine, gemcitabine, amrubicin all have demonstrated some responses in pulmonary as well as nonpulmonary HGNEC. When progression follows a chemotherapy holiday, it may be possible to re-initiate the platinum-based chemotherapy, particularly when a good response was previously achieved in the first-line setting.

OUR EXPERIENCE WITH NEUROENDOCRINE TUMOURS

We have treated 51 patients of NETs between 2007 and 2012. The median age at presentation of our patients was 44 years. Most of the patients were males with a male to female ratio of 2.2 [Table 6].

The median OS for all cases was 14 months (range: 0-60 months), and the survival closely paralleled the stage at diagnosis. Patients with functional tumors survived longer than patients with nonfunctional tumors in a univariate analysis, where the median OS was 12 months for the functional tumors versus 7 months for nonfunctional ones ($P < 0.001$). Male sex predicted a shortened survival in a univariate analysis. Higher grade also predicted a worse survival. The median OS was 11 months for patients with either Grade 1 or 2 tumors; 8 months for patients with tumors that were not assigned a grade; and 2.5 months in patients with Grade 3 or 4 tumors. Resection of any type predicted better outcome with a median OS of 13 months in the surgery group versus 4 months in the group who did not undergo surgery.

Table 6: Our Experience

Patient characteristics	No of patients	Patient characteristics	No of patients
Age	Mean 44 years (25-66)	Adjuvant treatment post radical surgery	7
Sex		Follow up only	23
Male	35	Chemotherapy with Cisplatin and etoposide	13
Female	16	Somatostatin anologue Octreotide	6
Stage		Everolimus	5
Localized	11	Palliative Chemotherapy (No surgery)	4
Regionally advanced	18	Lu177 DOTA	3
Metastatic	22	Paliative radiation alone (No surgery)	14 months
Grade		Median OS	12 months
1	5	Median OS of patients with functional tumours	7 months
2	15	Median OS of patients with nonfunctional tumours	13 months
3	23	Median PFS with Octreotide	7 months
4	8	Median PFS with Everolimus	
Primary site			
Head/Neck of Pancreas	18		
Periampullary	11		
Jejunum/Ileum	7		
Stomach	3		
Retroperitoneum	5		
Metastatic to liver with unknown primary	5		
Others	2		

PFS: Progression free survival, OS: Overall survival

CONCLUSION

Neuroendocrine tumors are rare, but their incidence has been increasing over the past 30 years. The last decade had witnessed a major change in our understanding of the biology of the disease, its classification and treatment. Early localized well-differentiated NETs are curable and surgery remains the mainstay of treatment. However, treating advanced or metastatic NETs is a major therapeutic challenge and we have a plethora of options ranging from somatostatin analogs to peptide receptor targeted therapy to radio or chemoembolization. These tumors are incurable and have an indolent course with waxing and waning of symptoms. In those cases, the main goal of treatment is to achieve palliation. Hence, it is of utmost importance to diagnose NETs at an early stage. Unfortunately, there is no consensus regarding the screening guidelines for NETs due to the rarity of these tumors. However, the authors suggest that those patients who have a strong family history, predictive of mutations in RET or VHL genes, should undergo strict surveillance with measurement of possible tumor markers or with imaging.

REFERENCES

1. Modlin IM, Shapiro MD, Kidd M, Eick G. Siegfried oberndorfer and the evolution of carcinoid disease. Arch Surg 2007;142:187-97.
2. Edge S, Byrd D, Carducci M. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
3. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: A review of nomenclature, grading, and staging systems. Pancreas 2010;39:707-12.
4. Rindi G, Arnold R, Bosman F. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. Lyon: IARC Press; 2010.
5. Chetty R. Requiem for the term 'carcinoid tumour' in the gastrointestinal tract? Can J Gastroenterol 2008;22:357-8.
6. Soga J. The term "carcinoid" is a misnomer: The evidence based on local invasion. J Exp Clin Cancer Res 2009;28:15.
7. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, *et al*. TNM staging of midgut and hindgut (neuro) endocrine tumors: A consensus proposal including a grading system. Virchows Arch 2007;451:757-62.
8. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, *et al*. TNM staging of foregut (neuro) endocrine tumors: A consensus proposal including a grading system. Virchows Arch 2006;449:395-401.
9. Shia J, Tang LH, Weiser MR, Brenner B, Adsay NV, Stelow EB, *et al*. Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol 2008;32:719-31.
10. Öberg K. The genetics of neuroendocrine tumors. Semin Oncol 2013;40:37-44.
11. Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A,

et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science 2011;331:1199-203.
12. Creutzfeldt W. Historical background and natural history of carcinoids. Digestion 1994;55 Suppl 3:3-10.
13. Vinik A, Moattari AR. Use of somatostatin analog in management of carcinoid syndrome. Dig Dis Sci 1989;34:14S-27.
14. Anthony LB. Practical guide to supportive care of patients with functional neuroendocrine tumors. Semin Oncol 2013;40:45-55.
15. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: Pancreatic endocrine tumors. Gastroenterology 2008;135:1469-92.
16. Smith SL, Branton SA, Avino AJ, Martin JK, Klingler PJ, Thompson GB, *et al*. Vasoactive intestinal polypeptide secreting islet cell tumors: A 15-year experience and review of the literature. Surgery 1998;124:1050-5.
17. Chastain MA. The glucagonoma syndrome: A review of its features and discussion of new perspectives. Am J Med Sci 2001;321:306-20.
18. Gibril F, Jensen RT. Diagnostic uses of radiolabelled somatostatin receptor analogues in gastroenteropancreatic endocrine tumours. Dig Liver Dis 2004;36 Suppl 1:S106-20.
19. Doherty GM. Neuroendocrine (carcinoid tumours) and the carcinoid syndrome. In Cancer Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2011:1503-15.
20. Reubi JC, Laissue J, Krenning E, Lamberts SW. Somatostatin receptors in human cancer: Incidence, characteristics, functional correlates and clinical implications. J Steroid Biochem Mol Biol 1992;43:27-35.
21. Kubo H, Chijiiwa Y, Akahoshi K, Hamada S, Matsui N, Nawata H. Pre-operative staging of ampullary tumours by endoscopic ultrasound. Br J Radiol 1999;72:443-7.
22. Kaltsas G, Rockall A, Papadogias D, Reznek R, Grossman AB. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. Eur J Endocrinol 2004;151:15-27.
23. Mittal BR, Agrawal K, Shukla J, Bhattacharya A, Singh B, Sood A, *et al*. Ga-68 DOTATATE PET/CT in neuroendocrine tumours: Initial experience. J Postgrad Med Educ Res 2013;47:1-6.
24. Janson ET, Holmberg L, Stridsberg M, Eriksson B, Theodorsson E, Wilander E, *et al*. Carcinoid tumors: Analysis of prognostic factors and survival in 301 patients from a referral center. Ann Oncol 1997;8:685-90.
25. Ardill JES, Erikkson B. The importance of the measurement of circulating markers in patients with neuroendocrine tumours of the pancreas and gut. Endocr Relat Cancer 2003;10:459-62.
26. de Herder WW, Hofland LJ, van der Lely AJ, Lamberts SW. Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. Endocr Relat Cancer 2003;10:451-8.
27. Schmid HA. Pasireotide (SOM230): Development, mechanism of action and potential applications. Mol Cell Endocrinol 2008;286:69-74.
28. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. N Engl J Med 1986;315:663-6.
29. Rinke A, Muller HH, Schade-Brittinger C. Placebocontrolled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrin midgut tumors: A report from the PROMID study group. J Clin Oncol 2009;27:4656-63.
30. Moertel CG. Treatment of the carcinoid tumor and the malignant carcinoid syndrome. J Clin Oncol 1983;1:727-40.
31. Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO Jr. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol 1984;2:1255-9.
32. Moertel C, Martin J, O"Conell M. Phase II trials in the malignant carcinoid tumour and carcinoid syndrome. Proc Am Soc Clin Oncol 1982;2:169.
33. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, *et al*. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004;22:4762-71.
34. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, *et al*. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 2006;24:401-6.
35. Kulke MH, Kim H, Clark JW, Enzinger PC, Lynch TJ, Morgan JA, *et al*. A Phase II trial of gemcitabine for metastatic neuroendocrine tumors. Cancer 2004;101:934-9.
36. Ansell SM, Pitot HC, Burch PA, Kvols LK, Mahoney MR, Rubin J. A Phase II study of high-dose paclitaxel in patients with advanced neuroendocrine tumors. Cancer 2001;91:1543-8.
37. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, *et al*. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3] octreotate: Toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124-30.
38. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0, Tyr3] octreotate. J Nucl Med 2011;52:1361-8.
39. Villard L, Romer A, Marincek N, Brunner P, Koller MT, Schindler C, *et al*. Cohort study of somatostatin-based radiopeptide therapy with [(90) Y-DOTA]-TOC versus [(90) Y-DOTA]-TOC plus [(177) Lu-DOTA]-TOC in neuroendocrine cancers. J Clin Oncol 2012;30:1100-6.
40. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, *et al*. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011;29:2416-23.
41. Oberg K, Eriksson B. The role of interferons in the management of carcinoid tumors. Acta Oncol 1991;30:519-22.
42. Kulke MH. Systemic therapy for advanced pancreatic neuroendocrine tumors. Semin Oncol 2013;40:75-83.
43. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, *et al*. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514-23.
44. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, *et al*. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501-13.
45. Kunz P, Kuo T, Zahn J. A phase II study of capecitabine, oxaliplatin, and bevacizumab for metastatic or unresectable neuroendocrine tumors. ASCO Annual Meeting; 2010. Abstract 4104.
46. Bergsland E, Ko A, Tempero M. A phase II trial of FOLFOX plus bevacizumab in advanced, progressive neuroendocrine tumors. ASCO Gastrointestinal Cancer Symposium; 2008. Abstract 216.
47. Kulke M, Blaszkowsky L, Zhu A. Phase I/II study of everolimus (RAD001) in combination with temozolomide (TMZ) in patients (pts) with advanced pancreatic neuroendocrine tumors (NET). 2010 Gastrointestinal Cancer Symposium; 2010. Abstract 127.
48. Hobday TJ, Rubin J, Holen K. MC044h, a phase II trial of sorafenib in patients with metastatic neuroendocrine tumors (NET): A Phase II Consortium (P2C) study. J Clin Oncol 2007;25:4504-5.
49. Phan A, Yao J, Fogelman AD. A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (sandostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC). J Clin Oncol 28:15s; 2010 (suppl; abstr 4001).
50. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E,

et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514-23.
51. Duran I, Kortmansky J, Singh D, Hirte H, Kocha W, Goss G, *et al*. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. Br J Cancer 2006;95:1148-54.
52. Akyildiz HY, Mitchell J, Milas M, Siperstein A, Berber E. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: Long-term follow-up. Surgery 2010;148:1288-93.
53. Vogl TJ, Naguib NN, Nour-Eldin NE, Eichler K, Zangos S, Gruber-Rouh T. Transarterial chemoembolization (TACE) with mitomycin C and gemcitabine for liver metastases in breast cancer. Eur Radiol 2010;20:173-80.
54. King J, Quinn R, Glenn DM, Janssen J, Tong D, Liaw W, *et al*. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer 2008;113:921-9.
55. Rhee TK, Lewandowski RJ, Liu DM, Mulcahy MF, Takahashi G, Hansen PD, *et al*. 90Y Radioembolization for metastatic neuroendocrine liver tumors: Preliminary results from a multi-institutional experience. Ann Surg 2008;247:1029-35.
56. Smith J, Reidy-Lagunes D. The management of extrapulmonary poorly differentiated (high-grade) neuroendocrine carcinomas. Semin Oncol 2013;40:100-8.
57. Shia J, Tang LH, Weiser MR, Brenner B, Adsay NV, Stelow EB, *et al*. Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol 2008;32:719-31.
58. Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, *et al*. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: Results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054-60.
59. Oze I, Hotta K, Kiura K, Ochi N, Takigawa N, Fujiwara Y, *et al*. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: Disappointing results. PLoS One 2009;4:e7835.
60. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, *et al*. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85-91.

Cite this article as: Kapoor R, Bhattacharyya T, Gupta R, Mittal BR, Kalra N. A systematic review of management of neuroendocrine tumors: An experience from a tertiary care centre from India. Clin Cancer Investig J 2014;3:363-72.
Source of Support: Nil, **Conflict of Interest:** None declared.