**NEUROENDOCRINE TUMOURS:**

**EVOLVING ROLE OF THE MULTIDISCIPLINARY TEAM APPROACH IN MANAGEMENT**

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**INTRODUCTION**

Neuroendocrine cells are widely dispersed around the body: in the gastrointestinal tract, the lungs, larynx, thymus, thyroid, adrenal, gonads, skin and many other organs and tissues

The characteristics of neuroendocrine cells are that[1]

1. They produce a neurotransmitter, neuromodulator or neuropeptide hormone
2. They possess a of dense-core secretory granules from which the hormones are released by exocytosis in response to an external stimulus and
3. They do not possess axons and synapses.

These neuroendocrine cell aggregates dispersed in non-neuroendocrine tissues constitute the diffuse neuroendocrine system.

The neuroendocrine cells produce polypeptide hormones and biogenic amines identical to those found in neurons. The gastro-entero-pancreatic system has the richest source of regulatory peptides outside the brain.

Molecular markers essentially define neuroendocrine cells, and these include chromogranin A, the subtilase proprotein convertases (SPC), particularly SPC2 and SPC3. [1]

Tumours arising from the cells of the diffuse neuroendocrine system are defined as neuro endocrine tumours (NETs). NETs have been increasingly described in recent years.

Challenges of NETs include [101]

* Heterogeneity of tumours
* Wide variety in clinical presentations
* Late clinical presentation
* Different terminologies and classifications
* Difficulties in Histological diagnosis
* Availability of a variety of therapeutic options/approaches

A multidisciplinary team of physicians is essential for the successful treatment of NETs. The benefits of multidisciplinary disease management of patients include reducing recurrent disease, optimizing timing of surgery, prolonging survival for the patient and enhancing response to therapies.

**NEUROENDOCRINE TUMOURS**

The various neuroendocrine tumours and are listed in **Table 1**.

**Table 1**

**Neuroendocrine tumours**

|  |  |
| --- | --- |
| Tumours | Examples |
| * Gastro-entero-pancreatic tumours * Carcinoid * Non-carcinoid | * Gastrinoma * VIP (vasoactive intestinal polypeptide) oma * Insulinoma * **Glucaganoma** * **Somatastatinoma** * **GRFoma** * **ACTHoma** |
| * Catecholamine-secreting tumours | * Phaeochromocytoma * Paraganglioma * Ganglioneuroma * Ganglioneuroblastoma * Sympathoblastoma * Neuroblastoma |
| * Thyroid | * Medullary carcinoma of the thyroid |
| * Pitutary | * Chromophobe pituitary tumour |
| * Lung | * Small cell lung cancer |
| * Skin | * Merkel cell tumour |

**Epidemiology**

Neuroendocrine tumours account for about 0.5% of all malignancies. The incidence of NETs diagnosed during life is rising, with gastrointestinal carcinoids making up the majority; earlier estimates were of fewer than 2 per 100 000 per yearbut more recent studies have found rates approaching 3 per 100 000, with a continuing slight predominance in women. The risk of NET in an individual with one affected first degree relative has been estimated to be approximately four times that in the general population; with two affected first degree relatives, this risk has been estimated at over 12 times that in the general population. The main primary sites are the gastrointestinal tract (62-67%) and the lung (22-27%). Other sites include larynx, thymus, thyroid, adrenal, gonads and skin.

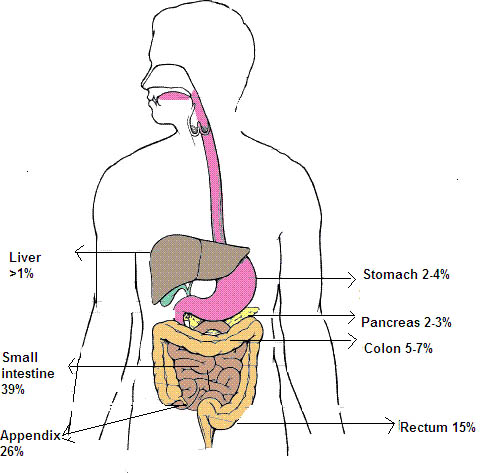
Presentation with metastatic disease accounts for 12-22%. Most neuroendocrine tumours are mainly sporadic, but association with the multiple endocrine neoplasia type 1 syndrome and clustering within families is known. An increased risk of secondary cancers has been reported, but numbers are small. The 5-year survival is mainly associated with stage: [2, 3]

|  |  |
| --- | --- |
| Stage | 5YSR |
| Local disease | 93% |
| Regional disease | 74% |
| Metastatic disease | 9% |

**Sites of occurrence**

NETs predominantly are seen in the gut wall but can be seen in other organs, including the lungs, mediastinum, thymus,liver, pancreas, bronchus, ovaries, prostate,and kidneys. In children, most tumours occur in the appendix.

The sites of occurrence of gut NETs and their frequencies is presented in **Fig.1** [102]

[](javascript:showrefcontent(%22refimage_zoomlayer%22);)

**Fig.1: NETs in the gut** [102]

**Aetiopathology**

Gastrointestinal and pancreatic neuroendocrine tumours originate from cells of the diffuse endocrine system. Most Gastrointestinal and pancreatic neuroendocrine tumours are sporadic, however, some of them, especially pancreatic endocrine tumours, may occur as part of familial syndromes.

In sporadic endocrine pancreatic tumours, losses of chromosome 1 and 11q as well as gain on 9q appear to be early invents in development of pancreatic tumours. Multiple genetic defects may accumulate with time and result in pancreatic neuroendocrine tumour progression and malignancy. Gastrointestinal endocrine tumours mostly show genetic alterations concentrated on chromosome 18. There are losses of the entire chromosome as well as smaller deletions. The most frequently reported mutated gene in gastrointestinal neuroendocrine tumours is b-catenin. Overexpression of cyclin D1 and cMyc has also been reported. A set of genes NAP1L1, MAGE-2D and MTA1 has been correlated with malignant behaviour of small intestinal carcinoids.

Pancreatic endocrine tumours, may occur as part of inherited syndromes such as multiple endocrine neoplasia type 1 (MEN1 syndrome), von Hippel-Lindau disease, neurofibromatosis type 1 and tuberous sclerosis [103]

NETs appear as small firm nodules. These tumours have a yellow, tan, or gray-brown appearance. The yellow colour is a result of cholesterol and lipid accumulation within the tumour. Tumours can have a polypoid appearance and occasionally become ulcerated. The tumours can expand and infiltrate locally. Metastases to the mesenteric lymph node and liver, ovaries, peritoneum, and spleen can occur.



**Fig.2: Gross appearance of Pancreatic NET** [104]

**Classification of NETs**

1. Classification by site of origin: Most NETs are characterized as arising in the GI tract (stomach, appendix, duodenum, and small intestine), the bronchopulmonary system (lungs and thymus), the pancreas, and the colon and rectum
2. Functional vs. non functional tumours. Pancreatic neuroendocrine tumours can be either functional or non-functional. Functional pancreatic neuroendocrine tumours can secrete biologically active peptides like insulin, gastrin, glucagon, somatostatin, vasoactive intestinal polypeptide (VIP), whereas non-functional tumors also express and secrete peptides like neurotensin or chromogranin A, which are not active.
3. Classification by tumour stage: NETs are staged using TNM criteria

**Clinical features**

The clinical picture varies from asymptomatic patients to abdominal pain and symptoms secondary to complications. The various clinical presentations are outlined in **Table 2**.[3]

**Table 2**

**Clinical presentations of NETs**

|  |
| --- |
| * Asymptomatic |
| * Obstructive symptoms - pain, nausea, and vomiting |
| * Cardinoid syndrome (metastases to the liver with the subsequent release of serotonin, tachykinins, and other vasoactive compounds) - Flushing , diarrhoea. lacrimation, rhinorrhoea, , episodic palpitations. intermittent abdominal pain, , wheezing and pellagra |
| * Bronchial cardinoid- Bronchospasm, pneumonitis, pleuritic pain, atelectasis, difficulty with breathing; cough , haemoptysis, weakness, nausea, weight loss, night sweats, neuralgia, and Cushing’s syndrome. |
| * Carcinoid crisis - profound flushing, bronchospasm, tachycardia, and widely and rapidly fluctuating blood pressure |
| * Phaeochromocytoma: Hypertension (high blood pressure), anxiety attacks, fever, headaches, sweating, nausea, vomiting, palpitations |

Pancreatic NETs may cause symptoms specific to the substance overproduced. These symptoms are indicated in **Table 3**. [105]

**Table 3**

**Symptoms of functional NETs of the pancreas**

|  |  |  |
| --- | --- | --- |
| **Functional endocrine tumour of the pancreas** | **Substance overproduced** | **Symptoms** |
| Gastrinoma (Zollinger-Ellison Syndrome) | Gastrin | Burning abdominal pain, acid reflux, diarrhea and weight loss. |
| Glucaganoma | Glucagon | High blood sugar can cause severe swelling or irritation of the skin, sore mouth, anaemia, and weight loss. |
| Insulinoma | Insulin | Hypoglycemia can cause palpitations, tremors, sweating, confusion and seizures. |
| Multiple Endocrine Neoplasia Type-1  (MEN1)  (Wermer Syndrome) | Various hormones including: gastrin, insulin, glucagon and parathyroid | Ulcers and blood sugar problems are common. Hyperparathyroidism, can cause hypercalcemia which can lead to generalized weakness, bone abnormalities, constipation and changes in mental state. |
| Somatostatinoma | Somatostatin | Somatostatin suppresses production of a variety of other hormones which can cause diabetes, gallstones, weight loss, diarrhea, excess fat in the stools, steatorrhea, nausea and vomiting. |
| Vasoactive Intestinal Peptide-Releasing Tumor  (VIPoma or Verner-Morrison Syndrome) | Vasoactive intestinal peptide (VIP) | Severe watery diarrhoea can lead to low blood potassium levels causing muscle weakness, fatigue and nausea. |

Non-functional islet cell tumours do not overproduce pancreatic hormones.  They are generally detected because of pain or jaundice caused by the large tumour size

**Diagnosis**

The diagnosis is based on clinical symptoms, hormone concentration, radiological and nuclear medicine imaging, and histological confirmation. The gold standard in diagnosis is detailed histology and this should be obtained whenever possible.[2]

***Blood***

* Serum calcium,
* T3, T4, TSH
* PTH
* Calcitonin
* Prolactin
* α-fetoprotein, CEA, β-HCG.
* pancreatic polypeptide
* Plasma chromogranin A (CgA) may be useful in gastric carcinoids with metastases

***Recommendations for diagnosis* [3]**

If a patient presents with symptoms suspicious of a gastroenteropancreatic NET:

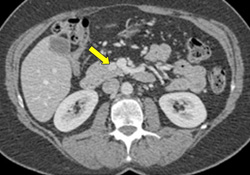
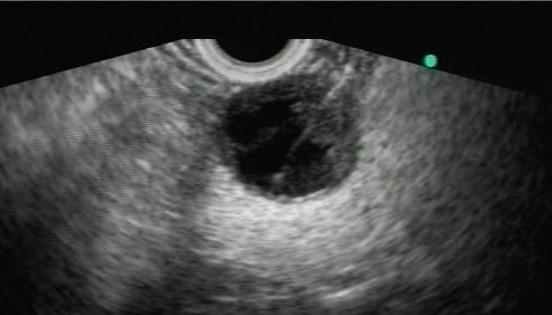
* Baseline tests should include CgA and 5-HIAA (grade C).
* Other tests that may be appropriate include TFTs, PTH, calcium, calcitonin, prolactin, α-fetoprotein, CEA, and β-HCG (grade D).
* Specific biochemical tests should be requested depending on which syndrome is suspected
* Certain foods and drugs will affect urinary excretion of 5-HIAA if they are taken just before collection of the urine sample. banana, pineapple, plums, walnut, paracetamol, fluorouracil, methysergide, naproxen, and caffeine may cause false positive results. Levodopa, aspirin, adrenocorticotrophic hormone (ACTH), methyldopa, and phenothiazines may give a false negative result..

***Imaging***

*For suspected NETs:* [3]

Imaging helps in the localization of the primary tumour, the detection of metastases, and the assessment of response to treatment.

Computed tomography (CT) or magnetic resonance imaging (MRI)are primary modalities. Endoscopic ultrasound has an important role in the preoperative assessment of the pancreas where a small functioning tumour or the possibility of multiple tumours is suspected.

**Fig.3:CT scan showing insulinoma[106] Fig.4: EUS showing neuroendocrine tumour in body**

**of pancreas [107]**

*When the patient has already presented with metastases**with no known primary site* [3]: Investigations for localising the primary site may include (depending on the type of tumour and symptoms): ultrasound scans of the abdomen, testes, and ovaries; EUS; CT scan of the chest (bronchial carcinoid), abdomen, and pelvis; endoscopy-colonoscopy and gastroscopy; barium studies; and nuclear medicine functional imaging.

Neuroendocrine tumours express somatostatin receptors (SSTR) and this has led to the development of radiolabeled somatostatin analogues for diagnostic imaging

* For detecting the primary tumour, a multimodality approach is best and may include CT, MRI, SSRS, EUS, endoscopy, DSA, and venous sampling (grade B/C).
* For assessing secondaries, SSRS (somatostatin receptor scintigraphy) is the most sensitive modality (grade B).
* When a primary has been resected, SSRS may be indicated for follow up (grade D).
* A CT scan is the best modality for localising lung lesions but this could be followed by SSRS (octreoscan) to assess the full extent of the disease.
* Intra-arterial calcium with digital subtraction angiography may be particularly important for localising gastrinomas. , insulinomas. The sensitivity is further increased by combining it with imaging modalities such as intraoperative ultrasonography.

*Searching for secondaries:*[3]

The diagnostic test of choice to locate secondaries is SSRS ( octreoscan)

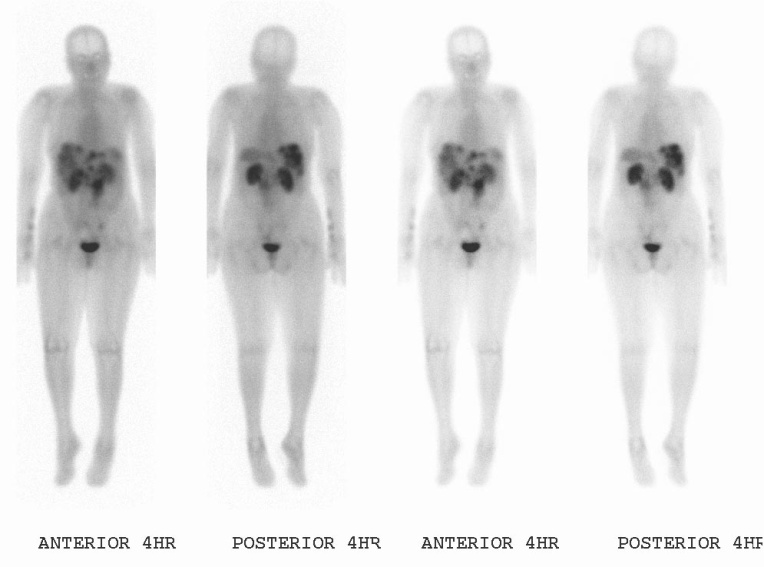


Fig.6: Octreoscan demonstrating abnormal uptake [108]

*Monitoring progression of disease:* [3]

Spiral CT scanning, MRI, and ultrasound scans are useful for monitoring lesions.

*Biopsy*: Specimen for biopsy can be obtained by

* Endoscopic biopsy with or without EUS guidance
* Percutaneous biopsy under CT scanning or ultrasonographic guidance

***Histology***

On histological examination, NETs have 5 distinctive patterns:

1. Solid, nodular, and insular cords
2. Trabecular or ribbons with anastomosing features
3. Tubules and glands or rosettelike patterns
4. Poorly differentiated or atypical patterns
5. Mixed patterns. A combination of these patterns is often observed.

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Distribution of carcinoid tumors.

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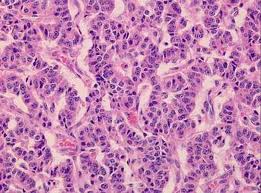
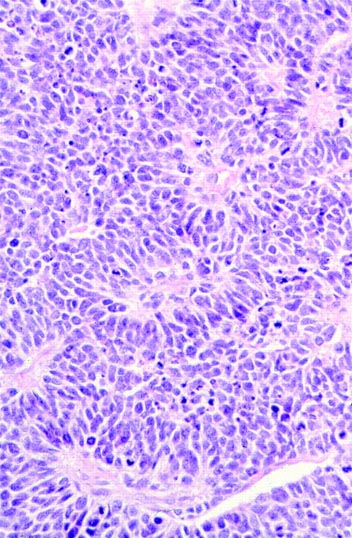
 

Fig.7: Well differentiated NET of duodenum [109] Fig.8:Poorly differentiated NET[110]

*Histochemical methods* for the recognition of neuroendocrine differentiation in pancreatic tumours include the use of silver stains and cytoplasmic labeling with the Grimelius, Sevier-Munger, or Churukian-Schenk procedure.[111]

*Ultrastructural characteristics* of pancreatic NETs include presence of dense-core neurosecretory granules in the cytoplasm, ranging from 80 to 300 nm in diameter, andwith a tendency for clustering near Golgi complexes, which may be prominent in their own right. Endoplasmic reticulumis are visualized easily in pancreatic NETs, but other metabolic organelles are relatively nondescript. The tumour cells are joined to one another by well-defined attachment plaques.[111]

*Immunohistologic features*: Panceratic endocrine tumours have immunoreactivity for keratin proteins keratins 8 and 18. Adjunctive immunohistochemical indicators of neuroendocrine differentiation include chromogranin A , synaptophysin , protein gene product 9.5, neuron-specific (gamma-dimer) enolase, and CD57 (HNK-1 antigen), [111]

**WHO classification of gastro-entero-pancreatic endocrine tumours based on histology**

World Health Organization’s definition of neuroendocrine tumours is ‘morphofunctional’ and is primarily based on microscopic characteristics, but incorporates immunohistological data (with such markers as the chromogranins, synaptophysin and non-specific enolase),

special stains (e.g. silver), in addition to immunohistochemical stains for specific hormones which result in endocrine hyperfunction syndromes.

Categorizing the tumour takes into consideration

1. Presence of well-defined [histological](http://en.wikipedia.org/wiki/Histology) features
2. Size of the tumour
3. [Lympho](http://en.wikipedia.org/wiki/Lymphatic_system)[vascular](http://en.wikipedia.org/wiki/Circulatory_system) invasion,
4. [Mitotic](http://en.wikipedia.org/wiki/Mitosis) counts
5. [Ki-67](http://en.wikipedia.org/wiki/Ki-67_(protein)) labelling index,
6. Invasion of adjacent organs,
7. Presence of [metastases](http://en.wikipedia.org/wiki/Metastasis) and
8. Production of [hormones](http://en.wikipedia.org/wiki/Hormone).

WHO classification of gastro-entero-pancreatic endocrine tumours based on histology is represented in **Table 4**.

**Table 4**

**WHO classification of gastro-entero-pancreatic endocrine tumours based on histology**[4]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Site | Well differentiated  >endocrine tumour  >(Benign behaviour) | Well differentiated  >endocrine tumour  >(Uncertain behaviour) | Well differentiated  >endocrine carcinoma  >(Low grade malignant) | Poorly differentiated  >endocrine carcinoma  >(High grade malignant) |
| HPF, high power field. | | | | |
| Pancreas | Confined to pancreas | Confined to pancreas | Well to moderately differentiated | Small cell carcinoma |
|  | <2 cm | ≥2 cm | Gross local invasion and/or metastases | Necrosis common |
|  | <2 mitoses per 10 HPF | >2 mitoses per 10 HPF | Mitotic rate often higher (2–10 per 10 HPF) | >10 mitoses per 10 HPF |
|  | <2% Ki-67 positive cells | >2% Ki-67positive cells | Ki-67 index >5% | >15% Ki-67 positive cells |
|  | No vascular invasion | or vascular invasion |  | Prominent vascular and/or perineural invasion |
| Stomach | Confined to mucosa-submucosa, | Confined to mucosa-submucosa, | Well to moderately differentiated | Small cell carcinoma |
|  | ≤1 cm. No vascular invasion | >1 cm or vascular invasion | Invasion to muscularis propria or beyond or metastases |  |
| Duodenum, upper jejunum | Confined to mucosa-submucosa, | Confined to mucosa-submucosa, | Well to moderately differentiated | Small cell carcinoma |
| ≤1 cm. No vascular invasion | >1 cm or vascular invasion | Invasion to muscularis propria or beyond or metastases |  |
| Ileum, colon, rectum | Confined to mucosa-submucosa, | Confined to mucosa-submucosa, | Well to moderately differentiated | Small cell carcinoma |
|  | ≤1 cm (small intestine) | >1 cm (small intestine) | Invasion to muscularis propria or beyond or metastases |  |
|  | ≤2 cm (large intestine). No vascular invasion | >2 cm (large intestine) or vascular invasion |  |  |
| Appendix | Non-functioning | Enteroglucagon-producing | Well to moderately differentiated | Small cell carcinoma |
|  | Confined to appendiceal wall | Confined to subserosa | Invasion to mesoappendix or beyond or metastases |  |
|  | ≤2 cm. No vascular invasion | >2 cm or vascular invasion |  |  |

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## Staging

The American Joint Committee on Cancer (AJCC) staging by TNM classification to define neuroendocrine tumours **is given in** Tables 5-12.

**Table 5**

**AJCC TNM classification and disease staging for gastric endocrine tumours** [5]

**Primary Tumour (T)a**

|  |  |
| --- | --- |
| TX | Primary tumour cannot be assessed. |
| T0 | No evidence of primary tumour. |
| Tis | Carcinoma *in situ*/dysplasia (tumour size <0.5 mm), confined to mucosa. |
| T1 | Tumour invades lamina propria or submucosa and ≤1 cm in size. |
| T2 | Tumour invades muscularis propria or >1 cm in size. |
| T3 | Tumour penetrates subserosa. |
| T4 | Tumour invades visceral peritoneum (serosal) or other organs or adjacent structures. |
| For any T, add (m) for multiple tumors. |

**Regional Lymph Nodes (N)**

|  |  |
| --- | --- |
| NX | Regional lymph nodes cannot be assessed. |
| N0 | No regional lymph node metastasis. |
| N1 | Regional lymph node metastasis. |

**Distant Metastases (M)**

|  |  |
| --- | --- |
| M0 | No distant metastases. |
| M1 | Distant metastasis. |

**Table 6**

**AJCC TNM classification and disease staging for endocrine tumours of the duodenum/ampulla/proximal jejunum**[5]

**Primary Tumour (T)**

|  |  |
| --- | --- |
| TX | Primary tumour cannot be assessed. |
| T0 | No evidence of primary tumour. |
| T1 | Tumour invades lamina propria or submucosa and size ≤1 cm (small intestinal tumors); tumour ≤1 cm (ampullary tumors). |
| T2 | Tumour invades muscularis propria or size >1 cm (small intestinal tumours); tumour >1 cm (ampullary tumors). |
| T3 | Tumour invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into nonperitonealized tissues. |
| T4 | Tumour invades visceral peritoneum (serosa) or invades other organs. |
| For any T, add (m) for multiple tumors. |

|  |
| --- |
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|  |

**Regional Lymph Nodes (N)**

|  |  |
| --- | --- |
| NX | Regional lymph nodes cannot be assessed. |
| N0 | No regional lymph node metastasis. |
| N1 | Regional lymph node metastasis. |

**Distant Metastases (M)**

|  |  |
| --- | --- |
| M0 | No distant metastases. |
| M1 | Distant metastasis. |

**Table 7**

**AJCC TNM classification and disease staging for endocrine tumors of the colon and rectum**[5]

**Primary Tumour**

|  |  |
| --- | --- |
| TX | Primary tumour cannot be assessed. |
| T0 | No evidence of primary tumour. |
| T1 | Tumour invades lamina propria or submucosa and size ≤2 cm. |
| T1a | Tumour size <1 cm in greatest dimension. |
| T1b | Tumour size 1–2 cm in greatest dimension. |
| T2 | Tumour invades muscularis propria or size >2 cm with invasion of lamina propria or submucosa. |
| T3 | Tumour invades through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissues. |
| T4 | Tumour invades peritoneum or other organs. |
| For any T, add (m) for multiple tumors. |

**Regional Lymph Nodes (N)**

|  |  |
| --- | --- |
| NX | Regional lymph nodes cannot be assessed. |
| N0 | No regional lymph node metastasis. |
| N1 | Regional lymph node metastasis. |

**Distant Metastases (M)**

|  |  |
| --- | --- |
| M0 | No distant metastases. |
| M1 | Distant metastasis. |

**Table 8**

**Anatomic stage/prognostic groups for stomach, duodenum/ampulla/jejunum/ileum,**

**and colon or rectum**

| **Stage** | **T** | **N** | **M** |
| --- | --- | --- | --- |
| 0 | Tis | N0 | M0 |
| I | T1 | N0 | M0 |
| IIA | T2 | N0 | M0 |
| IIB | T3 | N0 | M0 |
| IIIA | T4 | N0 | M0 |
| IIIB | Any T | N1 | M0 |
| IV | Any T | Any N | M1 |

**Table 9 [5]**

**AJCC TNM classification and disease staging for appendiceal NETs**

**Primary Tumour (T)**

|  |  |
| --- | --- |
| TX | Primary tumour cannot be assessed. |
| T0 | No evidence of primary tumour. |
| T1 | Tumour ≤2 cm in greatest dimension. |
| T1a | Tumour ≤1 cm in greatest dimension. |
| T1b | Tumour >1 cm but not >2 cm. |
| T2 | Tumour >2cm but not >4 cm or with extension to the cecum. |
| T3 | Tumour >4 cm or with extension to the ileum. |
| T4 | Tumour directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle.c |

|  |
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|  |

**Regional Lymph Nodes (N)**

|  |  |
| --- | --- |
| NX | Regional lymph nodes cannot be assessed. |
| N0 | No regional lymph node metastasis. |
| N1 | Regional lymph node metastasis. |

**Distant Metastasisa**

|  |  |
| --- | --- |
| M0 | No distant metastasis. |
| M1 | Distant metastasis. |

**Table 10****Anatomic stage/prognostic groupsfor appendiceal NETs**

| **Carcinoid** | | | |
| --- | --- | --- | --- |
| **Stage** | **T** | **N** | **M** |
| I | T1 | N0 | M0 |
| II | T2, T3 | N0 | M0 |
| III | T4 | N0 | M0 |
| Any T | N1 | M0 |
| IV | Any T | Any N | M1 |

**Table 11**

**TNM classification and disease staging for endocrine tumors of the pancreas**[5]

**Primary Tumour (T)**

|  |  |
| --- | --- |
| TX | Primary tumour cannot be assessed. |
| T0 | No evidence of primary tumour. |
| Tis | Carcinoma *in situ* |
| T1 | Tumour limited to the pancreas, ≤2 cm in greatest dimension. |
| T2 | Tumour limited to the pancreas, >2 cm in greatest dimension. |
| T3 | Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery. |
| T4 | Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour). |

|  |
| --- |
|  |
|  |

**Regional Lymph Nodes (N)**

|  |  |
| --- | --- |
| NX | Regional lymph nodes cannot be assessed. |
| N0 | No regional lymph node metastasis. |
| N1 | Regional lymph node metastasis. |

**Distant Metastasis (M)**

|  |  |
| --- | --- |
| M0 | No distant metastasis. |
| M1 | Distant metastasis. |

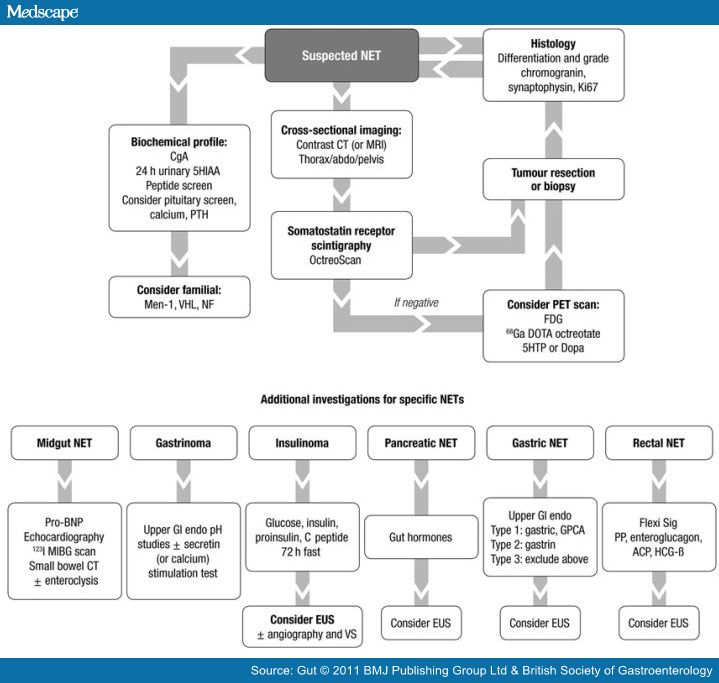
**Table 12**

**Anatomic Stage/Prognostic Groupsfor neuroendocrine tumours of the pancreas**

| **Stage** | **T** | **N** | **M** |
| --- | --- | --- | --- |
| 0 | Tis | N0 | M0 |
| IA | T1 | N0 | M0 |
| IB | T2 | N0 | M0 |
| IIA | T3 | N0 | M0 |
| IIB | T1 | N1 | M0 |
| T2 | N1 | M0 |
| T3 | N1 | M0 |
| III | T4 | Any N | M0 |
| IV | Any T | Any N | M1 |

**Algorithm for the investigation of neuroendocrine tumours (NETs)** [6]

An algorithm for the investigation of neuroendocrine tumours is given in **Fig.9.**



**Fig. 9: Algorithm for the investigation of neuroendocrine tumours [7]**

ACP, Acid Phosphatase; BNP, brain natriuretic peptide; CgA, chromogranin A; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; GI, gastrointestinal; GPCA, gastric parietal cell autoantibody; HCG, human chorionic gonadotrophin; 5HIAA, 5-hydroxyindoleacetic acid; 5HTP, 5-hydroxytryptophan; Men-1, multiple endocrine neoplasia 1; MIBG, meta iodobenzylguanidine; NF, neurofibromatosis; PET, positron emission tomography; PP, pancreatic polypeptide; PTH, parathyroid hormone; VHL, Von Hippel Lindau.

**Assessment of a patient with NET** [101]

The factors to be considered while assessing a patient with NET include

* Clinical picture
* Hormonal peptides
* Imaging
* Anatomical imaging
* Molecular imaging
* SSR scanning
* Octreotide SPECT/CT
* New tracers e.g. 68- Ga-DOTA-octreotide PET

**Treatment**

*Treatment goals* include

* Total eradication by surgery
* Control of tumour growth
* Alleviation of clinical symptoms
* Improving and preserving quality of life

*Treatment options* include

* Surgery
* Embolization (+/- chemotherapy)
* Medical treatment
* Somatostatin analogues
* α interferon therapy
* Chemotherapy
* PRRT
* Biological targeted therapies

***Prevention of carcinoid crises***

A potential carcinoid crisis is prevented by prophylactic administration of octreotide, given by constant intravenous infusion at a dose of 50 μg/h for 12 hours prior to and at least 48 hours after surgery. Patients who develop life threatening cardiorespiratory complications inspite of octreotide therapy may need alpha and beta blocking drugs. [3]

***Surgery***

The clinical management of metastatic NE tumours requires a multidisciplinary approach including surgery and other means of cytoreductive treatment, radiotherapy and medical treatment.

Surgery is the treatment of choice and is the only approach that can achieve a complete cure in patients with NETs.

In patients with metastases, surgery has been used to improve hormone-mediated symptoms; quality of life and survival in certain groups of patients, as well as to reduce tumours bulk and prevent further local and systemic effects.

Surgical resection of primary tumours as well as lymph nodes and liver involvement can improve survival. [7, 8]

Surgery can also be employed after medical treatment to achieve substantial tumour reduction in an attempt to maximize the disease-free interval [7, 8].

Liver resection surgery and ablation methods for treatment of liver metastases have resulted in significant clinical improvement and reduction in tumour size [7, 8]

Liver transplantation has been suggested in selected patients without residual extrahepatic manifestations. However, long-term results are not that encouraging at the moment and the liver transplantation should only be reserved for a very few patients, where other means of therapy cannot control the disease. [9,10]

The various surgical options are summarized in **Table 13.**

**Table 13**

**Surgical options in NETs** [3]

|  |  |
| --- | --- |
| **Lung** | Major lung resection or wedge resection plus node dissection |
| **Emergency abdominal presentations** | Appendicitis, intestinal obstruction, or other gastrointestinal emergencies- Resection, histology followed by radical resection- hemicolectomy+/- locoregional lymphadenectomy |
| **Stomach** | Type 1 -hypergastrinaemia with chronic atrophic gastritis- limited surgery with endoscopic polypectomy and/or antrectomy  Type 2 - hypergastrinaemia due to Zollinger-Ellison syndrome in combination with MEN type1- and Type 3- sporadic without hypergastrinemia- Need resection and clearance of regional lymph nodes |
| **Small intestinal carcinoid** | Resection of the primary and extensive resection of associated mesenteric lymph nodes |
| **Colorectum** | Standard resection with locoregional lymphadenectomy |
| **Pancreas** | Insulinoma – enucleation/ Whipple pancreatoduodenectomy/ left pancreatectomy, / total pancreatectomy depending on case |
| **Liver** | Curative” liver resection in lesion(s) confined to one lobe  Debulking operation for palliation in bilobar metastases and one very dominant lesion causing symptoms  Liver transplantation in end stage carcinoid disease and uncontrollable symptoms that are unresponsive to any other therapy |

***Embolization/chemoenbolization***

In patients with liver metastases at diagnosis, treatment aimed at reducing the tumour bulk in the liver may significantly improve quality of life and survival. Such procedures include embolization of liver metastasis with or without concomitant cytotoxic agents. The aim is to provide symptomatic benefit but the method has to be repeated to achieve long-lasting responses.

There are two types of embolisation: particle and chemoembolisation. Particles used include polyvinyl alcohol and gel foam powder. For chemoembolisation, agents such as doxorubicin and cisplatin are used

Embolization of (90) Y-embedded spheres (radioembolization) represents a novel approach to managing liver metastases.[11]

Chemoembolization for unresectable NETs metastatic to liver is useful for tumour size reduction, symptom palliation and can be associated with prolonged survival.[12]

***Radiotherapy***

Targeted radiotherapy is a useful palliative option for symptomatic patients with inoperable or metastatic tumour.

Tumour-targeted radioactive treatment using peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs have been applied with encouraging results. The different compounds have been 111Indium-DTPA-octreotide, 90Y-DOTA-octreotide, 90Y-DOTATOC and MAURITIUS . Other isotopes such as Lutetium 177 and Rhenium-186 are being used [13, 14]

Options to improve PRRT may include combinations of radioactive labeled somatostatin analogs, intra-arterial administration, and the use of radiosensitizing drugs combined with PRRT. Other therapeutic applications of PRRT may include additional therapy cycles in patients with progressive disease after benefit from initial therapy, PRRT in adjuvant or neoadjuvant setting, or PRRT combined with new targeted therapies, such as sunitinib or everolimus [15]

***Ablation therapies***

Radiofrequency ablation may be performed in patients with inoperable bilobar metastases in whom hepatic artery embolisation has failed. It can be performed percutaneously or laparoscopically. Radiofrequency ablation has been utilized with good results and minimal morbidity for treating patients with advanced neuroendocrine disease.[16] The main limitation for radiofrequency ablation is the size and number of tumours.

***Medical treatment***

Medical treatment of NE tumours includes treatment with both chemotherapy and biological agents, such as somatostatin analogues and interferon-alfa.

*Chemotherapy*

Cytotoxic treatment is predominantly used in patients with tumours that show high proliferative capacity and large tumour burden; a proliferation index analyzed by the antibody Ki67 should be above 10% to 15%. Classical midgut carcinoids with low proliferating capacity (Ki67) usually <2%) have not benefited from regular cytotoxic treatment. The most common chemotherapy in endocrine pancreatic tumour is a combination of Streptozotocin plus 5-fluorouracil or doxorubicin. For anaplastic tumours and high proliferative capacity (Ki67 above 15%) combination with cisplatinum and etoposide has been particularly useful[17]

New temozolomide-based chemotherapy regimens have demonstrated considerable activity in pancreatic NETs.[12]

*Somatostatin analogues*

High-affinity somatostatin receptors are present in in 80% to 90% of NE tumours. Somatostatin analogues inhibit the release of various peptide hormones in the gut, pancreas, and pituitary, antagonise growth factor effects on tumour cells, and at very high dosage may induce apoptosis.

Regular octreotide is associated with a symptomatic, biochemical and tumour response. It is administered by subcutaneous injection starting at 50–100 μg twice or three times a day to a maximum daily dose of 1500 μg.

Slow-release formulations of octreotide haves hown to been effective.These include , lanreotide (fortnightly injection), octreotide acetate LAR (monthly), and Lanreotide Autogel (also monthly), and have as good or better efficacy compared with short acting octreotide.

Somatostatin analogue SOM230 has a prolonged half-live, (approximately 24h) and exerts a more potent inhibitory effect than currently available compounds.

Side effects of somatostatin analogues include fat malabsorption, gall stones and gall bladder dysfunction, vitamin A and D malabsorption, headaches, diarrhoea, dizziness, and hypo and hyperglycaemia.

In advanced low malignant tumours the application of somatostatin analogues not only may control symptoms but they also have direct anti-tumour effect. The use of higher doses of somatostatin analogues or new subtype selective agonists, and chimeric or pan-somatostatin analogues will probably improve the clinical management of the patients who fail to respond to standard somatostatin analogue treatment. [18]

*Interferon*

Interferons are biological response modifiers as they interact with other soluble or cell-associated regulatory factors. Interferon α or slow release formulation pegylated interferon α have reported a symptomatic and biochemical response and a significant tumour reduction. [19]

*Combination therapy with IFNα and somatostatin analogue*

Patients for whom mono-therapy with interferon alone or octreotide alone could not control the disease have received the combination. Data show that somatostatin analogues and interferon have a synergistic effect. [19]

***Novel therapies***

The availability of novel agents and expression of targets, such as growth factor receptors, different subtypes of somatostatin receptors, and the mammalian target of rapamycin (mTOR) have led to the exploration of different classes of drugs and offer new treatment opportunities in neuroendocrine tumors.

Everolimus is a an oral mTOR inhibitor with broad antitumour activity and antiangiogenic activity.Daily dosing with everolimus resulted in continuous inhibition of mTOR activity.[20]

Dense vascularisation is a feature of nETs. VEGF abd VEGF R are overexpressed in NETs. Elevating circulating VEGF correlates with tumour progression. Sutinib is an angiogenesis which has been studied in the management of NETS and has demonstrated good results.

Use of bevacizumab has also shown promise in a phase II study, and results of an ongoing phase III trial comparing it to interferon are eagerly expected. Use of radiolabeled somatostatin analogues is still under investigation, though several phase II studies are encouraging. New cytotoxic agents, most notably temozolomide and capecitabine, are already in use, but their relative effectiveness compared to streptozocin in pancreatic NETs is yet to be determined.[21]

***Drugs in various syndromes***

Drugs are available for patients displaying symptoms due to hormones/peptides secreted by a secretory tumour. These include somatostatin analogues, proton pump inhibitors for gastrinomas, and diazoxide for insulinomas, which are indicated in patients with secretory tumours and distressing symptoms from peptide production. They could be commenced immediately in patients with inoperable disease or preoperatively in patients who have operable disease (liver resection with or without resection of the primary). (**Table 14**) [3]

**Table 14**

**Treatment of various syndromes**

|  |  |
| --- | --- |
| **Tumour** | **Treatment** |
| **VIPomas** | * Rehydration * Somatostatin analogues |
| **Glucagonomas** | * Somatostatin analogues |
| **Gastrinomas** | * High dose proton pump inhibitor drugs |
| **Insulinomas** | * Glucose infusion and glucagon intramuscularly for immediate correction of hypoglycemia * Diazoxide * Somatostatin analogues |

**Recommendations for treatment** [3]

* The extent of the tumour, its metastases, and secretory profile should be determined as far as possible before planning treatment (grade C)
* Surgery should be offered to patients who are fit and have limited disease—primary with or without regional lymph nodes (grade C)
* Surgery should be considered in those with liver metastases and potentially resectable disease (grade D)
* Where abdominal surgery is undertaken and long term treatment with SMS analogues is likely, cholecystectomy should be considered
* For patients who are not fit for surgery, the aim of treatment is to improve and maintain an optimal quality of life (grade D)
* The choice of treatment depends on the symptoms, stage of disease, degree of uptake of radionuclide, and histological features of the tumour (grade C)
* Treatment choices for non-resectable disease include SMS analogues, biotherapy, radionuclides, ablation therapies, and chemotherapy (grade C)
* External beam radiotherapy may relieve bone pain from metastases (grade C)
* Chemotherapy may be used for inoperable or metastatic pancreatic and bronchial tumours, or poorly differentiated NETs (grade B)

**NCCN treatment guidelines for gastro-entero-pancreatic NETs**

NCCN guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours are given in **Table 15** [110]

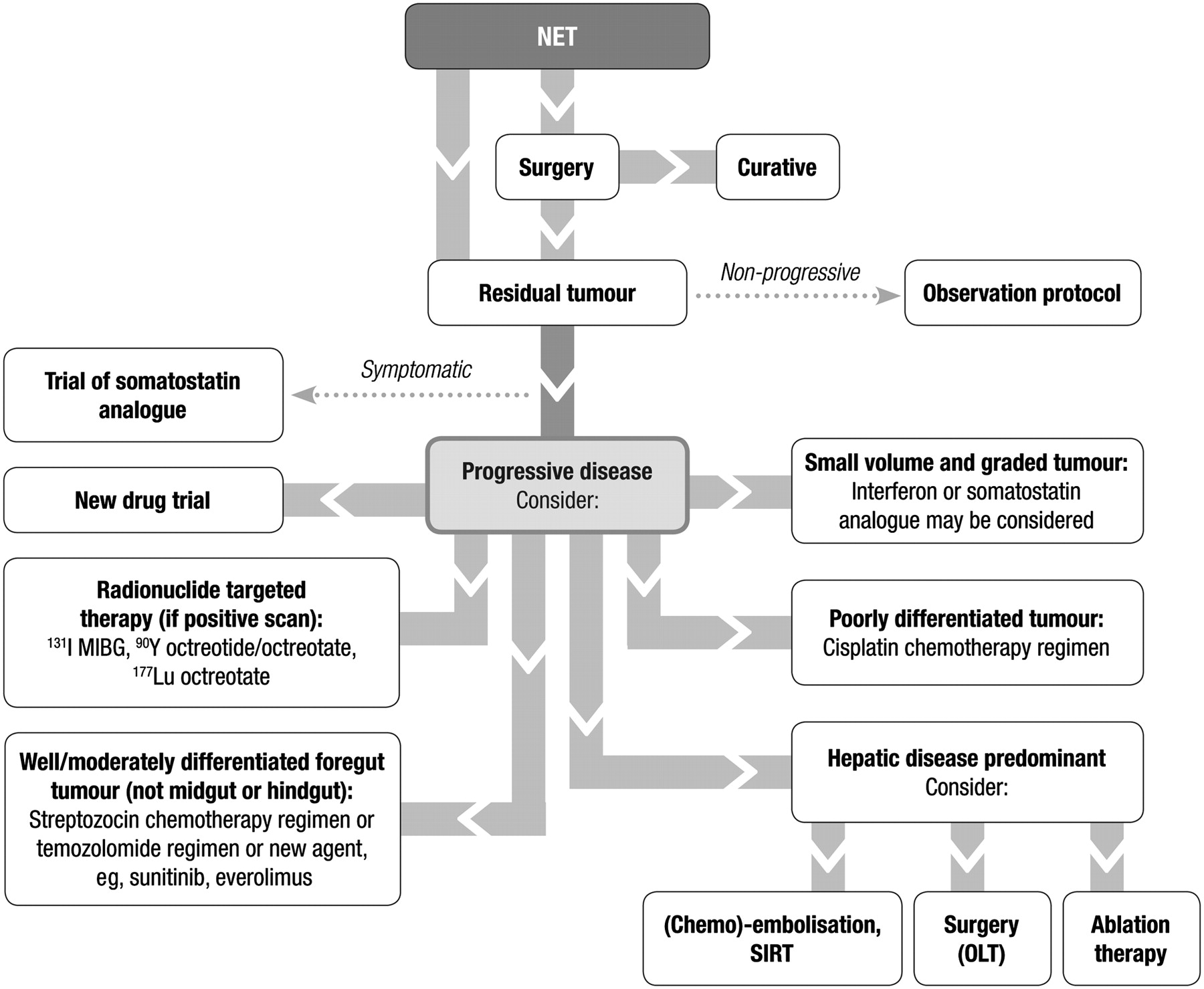
**Table 15**

**NCCN treatment guidelines for gastro-entero-pancreatic NETs** [112]

|  |  |  |
| --- | --- | --- |
|  | Loco regional disease | Metastatic disease/ metastatic disease discovered |
| Jejunum/ileum/colon | Bowel resection with local lymphadenectomy, prophylactic cholecystectomy if appropriate | **If complete resection possible**-  resect primary + metastasis  **Asymptomatic distant metastasis**- Observe with markers and scans every 3-4 months/octerotide  **Locally symptomatic from primary tumour** – consider resection of primary tumour  **Clinically significant tumour burden-** octreotide  Carcinoid tumour- octreotride, ECHO  **Progressive disease**-  octreotide if not already given,  consider hepatic regional therapy- embolization, ablative therapy, cytoreductive surgery (stage 2B), everolimus(category 3),  cytotoxic chemotherapy (category 3) |
| Duodenum | Endoscopic resection  Local resection(trans- duodenal) +/- lymph node sampling  Pancreaticoduodenectomy | **-do-** |
| Appendix | **</= 2 cm and confined to the appendix**- Simple appendicectomy  **>/=2 cms, incomplete resection**(nodes, margins)- Re-exploration, Rt. hemicolectomy | **-do-** |
| Rectal | **</= 2cms**- Resection- trans anal or endoscopic excision if possible  **>2 cms**- Low anterior resection or abdomino perineal resection | **-do-** |
| Gastric | ***Hyper gastrinemic patients***  **Tumour < 2 cms** – solitary or multiple- Observe or endoscopic resection + endoscopic biopsy of tumour and adjacent mucosa or octreotide for  Z E patients, (Category 2B)  **Tumour >2cms**- Endoscopic resection or surgical resection  ***Patients with normal gastrin***  Radical gastric resection with lymph node removal | **-do-** |

**Algorithm for the management of NETs** [6]

An algorithm for the management of NETs is presented in **Fig. 10**



**Fig. 10: Algorithm for the treatment of neuroendocrine tumours [6]**

**ROLE OF THE MULTIDISCIPLINARY TEAM IN MANAGEMENT OF**

**NEURO ENDOCRINE TUMOURS**

**Multi-disciplinary approach in cancer care**

Multidisciplinary care is described as “an integrated team approach to health care in

which medical and allied health care professionals consider all relevant treatment

options and develop collaboratively an individual treatment plan for each patient”[22]

Multidisciplinary cancer care teams include representatives from core specialties (e.g. surgery, medical oncology, radiation oncology, pathology, radiology and general practice), who are supported by non-core team members as needed (e.g. genetic counselling, physiotherapy, nuclear medicine, palliative care, social work) [23]

**Principles of multidisciplinary care** [24, 25]

* A team approach to care
* Communication among team members
* Access to full therapeutic range
* Provision of care in accord with nationally agreed standards
* Patient involvement in decision-making

Multidisciplinary teams are involved in

* The diagnosis and staging of cancer
* Treatment plans and delivery
* Ensuring patient involvement in the decision making process

Regular meetings of the cancer management team are conducted where patients are presented and their management reviewed.

Multidisciplinary teams ensure an integrated care and improved quality of cancer care. It has a patient-centred approach. The care is strenghthened and coordinated and health professionals are better equipped to support patients The process of reviewing patient management issues through multidisciplinary meetings benefits both patients and team members.

Delivery of Multidisciplinary cancer care is usually by one stop multidisciplinary clinics where patients can see all relevant specialists in one visit. [26]

**Advantages of multidisciplinary Teams**

**Benefits to patients**

Potential advantages of using a multidisciplinary team approach to tumour management may include

* Better patient treatment
* Accurate diagnosis and staging
* Consensus regarding treatment plan. A full therapeutic range of options are considered, so patients receive appropriate and timely treatment [27]
* Decisions resulting from multidisciplinary discussions are more likely to result in practice of evidence-based medicine than those made by individual clinicians.[28]
* Cohesive delivery of support, treatment modalities, and information on prognosis to patients
* Continuous reassessment, discussion and peer review of the individualized treatment plan
* Reduction in delays in treatment and referral [29, 30].
* Lower mortality, improved quality of life and reduced cost of cancer care. [31, 32]
* Greater adherence treatment plans by patients when management decisions are made at multidisciplinary meetings and understoodby all care providers.[33]
* Better co-ordination of services, leading to more efficient health processes.
* Prevention of unnecessary duplication of investigations, thus saving time and resources.[34]
* Improvements in treatment access, waiting times and continuity of care lead to better quality of life and greater patient satisfaction.[35]
* Better identification of patient’s emotional needs, paving the way for appropriate provision of psychosocial support [36]
* All medical facilities are available to the patient under one roof

**Benefits to healthcare professionals**

* Multidisciplinary team approach fosters stronger relationships between disciplines which assist in efficiently sharing information
* With regular team meetings facilitating communication between specialties, there are frequent opportunities to discuss management issues [37, 38]
* Multidisciplinary meetings provide reassurance and professional support for decision making.[36]
* Discussion with peers from different disciplines allows individuals to learn about the wide spectrum of management beyond their own specialty
* Multidisciplinary meetings facilitate continuing education of specialist clinicians, they offer valuable opportunities for the education of medical students, junior doctors and trainees.[29]

**NET – A candidate for the MDT approach**

* In NET, the underlying pathophysiology is well understood allowing more accurate diagnosis and staging of disease to be made based on morphology and on the immunohistochemistry of biopsy specimens
* As there are a variety oftherapeutic options available for patients with NETs, a multidisciplinary team is essential for management. Each specialist brings a different perspective thus helping to optimize care for each patient. Individualized care is integrated in a MDT set up and used it in a timely fashion

**The core MDT in NET**

A multidisciplinary team of physicians is essential to the successful treatment of NET. The evidence supports clinical management by multiple disciplines, including pathology, radiology, surgery, medical oncology, gastroenterology, endocrinology, and nuclear medicine

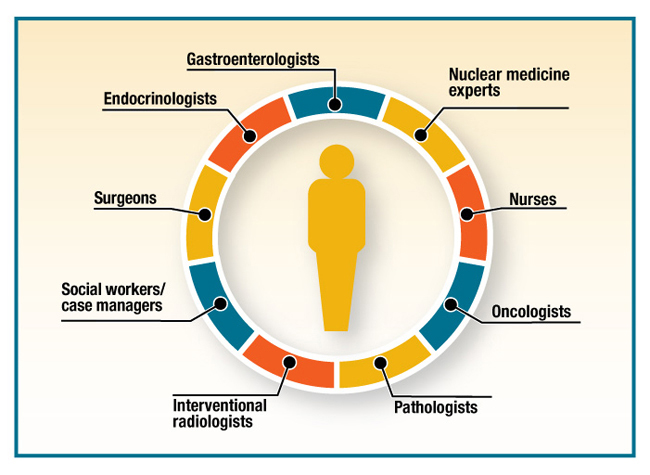
The core MD team includes gastroenterologists, endocrinologists, surgeons, medical oncologists, pathologists, interventional radiologists, nuclear medicine specialists, nurses, and social workers.

All team members play a specific role in the multi-step diagnostic work-up and all of them contribute to different extents to the decisional process leading to a “tailor- made” therapy based on patients’ specific disease and health status.

* + **Surgeon** – As surgery is the primary treatment for localized NET, the surgeon is a critical MDT member. Their role is to consider information gathered from the other MDT members when determining whether a NET is suitable for resection and when formulating a surgical plan.
  + **Pathologist** – Confirmation of NET diagnosis through examination and analysis of biopsied or resected tissue from a potential NET is undertaken by the pathologist.
  + **Radiologist** is involved in patient management throughout the course of the disease since a number of imaging modalities, including CT, PET, and MRI may be used for the detection, staging, surgical planning, and follow-up monitoring of patients with NET.
  + **Interventional radiologist** provides expertise in procedures such as embolization, chemoembolization and ablative treatments in patients with liver metastasis
  + **Medical oncologist** has an integral role within the multidisciplinary team by contributing to the prognostic assessment of patients with NET and long-term patient management, including monitoring for post-surgical recurrence or metastasis.
  + **Gastroenterologist** - the gastroenterologist's role in the early detection of NET is carried out primarily through visualization techniques such as endoscopic ultrasound (EUS).
  + **Endocrinologist** - the endocrinologist helps to develop a diagnostic and treatment plan for NETs. He has expertise in the treatment of hormone secreting tumours
  + **Nuclear medicine specialist** is experienced in diagnostic and therapeutic modalities such as PET scan, somatostatin-receptor scintigraphy, palliative radiotherapyusing radiolabeled somatostatin analogues -111Indium-DTPA-octreotide, 90Y-DOTA-octreotide, 90Y-DOTATOC etc.
  + **Oncology nurses** are involved in the long-term care of patients with NET.

Treatment options for the patient require discussion by a multidisciplinary team. Option may depend on type of NET

* TNM stage
* Tumour grade
* Extent of disease including liver disease
* Functional status of tumour
* Patient: organ status, Eastern Cooperative Oncology Group criteria,, Performance Status, comorbities
* Access to various options

[](javascript:void(0);)

**Individual roles and communication** [3, 40, 41]

Consultations between the surgeon and the gastroenterologist, radiologist, pathologist, medical oncologist, and nuclear medicine specialist are essential to ensure optimal care of patients with NET;

**Surgeon**

***Role:***

* Resection of primary tumours as well as lymph nodes
* In metastatic tumours to reduce tumours bulk and prevent further local and systemic effects.
* After medical treatment to achieve substantial tumour reduction in an attempt to maximize the disease-free interval
* Resection of liver metastases
* Liver transplantation in selected patients without residual extrahepatic manifestations

***Consultations:***

* *Gastroenterologist:* Share information for surgical planning, including [the location and size of the lesion](http://www.gistthefactsinfo.com/health-care-professional/gastroenterologist/submucosal-lesion.jsp) and [EUS results](http://www.gistthefactsinfo.com/health-care-professional/gastroenterologist/submucosal-lesion.jsp)
* *Radiologist:*
* Evaluation of imaging procedures information about the extent of the tumour and the presence of any metastases prior to surgery.
* Guiding the decision of whether or not to resect a NET.
* *Pathologist*
* Biopsy prior to surgery- input from the pathologist is necessary to provide confirmation of the lesion as a NET.
* Following resection- surgeon reports on the size and location of the tumour, the type of surgical procedure utilized, and resection margins; this is required for completion of the pathology report
* *Medical oncologist-*  Prior to surgery, consultation is essential to help determine the malignant potential of the NET and its resectability

**Medical oncologist**

***Role***

* Contributing to the interpretation of patient-specific [prognostic](http://www.gistthefactsinfo.com/health-care-professional/resources/glossary.jsp#Prognostic) factors, monitoring for disease recurrence, and progression.
* Administering Chemotherapy- Streptozotocin plus 5-fluorouracil or doxorubicin, cisplatinum and etoposide (analplastic tumours)
* Administering somatostatin analogues (regular octreotide, slow-release formulations of octreotide), interferons, combination therapy with IFNα and somatostatin analogues, Novel therapies

***Consultations***

* *Gastroenterologist* An evaluation of prognostic considerations will guide how the patient should be managed
* *Radiologist* Assess the results of CT scans and/or other imaging done during the initial evaluation, staging, and surveillance of a suspected NET
* *Surgeon* Determine whether or not a NET should be resected
* *Pathologist*
* size and location of the tumour, whether the [resection](http://www.gistthefactsinfo.com/health-care-professional/resources/glossary.jsp#ResectionID) was complete, and whether any rupture occurred
* Evaluating any [biopsy](http://www.gistthefactsinfo.com/health-care-professional/resources/glossary.jsp#Biopsy) results prior to surgery
* pathology results from the resected tumour following surgery

**Pathologist**

***Role***

* Contributing to the diagnosis – biopsy report- histologic examination, ultrastructural characteristics, immunohistochemistry- chromogranin A , synaptophysin
* Disseminating report results, need for sufficient tissue samples or additional tests
* WHO classification and TNM classification and grading system of NET tumours.
* Providing important information with regard to the future therapy of patients

**Radiologist** [109]

***Role***

* Contributing to the diagnosis – Imaging- abdominal/pelvic CT with contrast, , EUS, FNA, enteroclysis, capsule endoscopy
* Follow up imaging

**Gastroenterologist**

***Role***

* Early detection of NET through visualization techniques such as endoscopic ultrasound (EUS).
* Shares information for surgical planning, including [the location and size of the lesion](http://www.gistthefactsinfo.com/health-care-professional/gastroenterologist/submucosal-lesion.jsp) and [EUS results](http://www.gistthefactsinfo.com/health-care-professional/gastroenterologist/submucosal-lesion.jsp)
* Helps in of prognostic consideration and guiding how the patient should be managed

**Endocrinologist**

***Role:***

* Help to develop a diagnostic and treatment plan
* Experienced in the use of standard and investigational therapies for the treatment of hormone secreting tumours

**Nuclear medicine specialist**

***Role:***

* PET scan
* Somatostatin-receptor scintigraphy [SSRS]
* Palliative radiotherapy**-** Tumour-targeted radioactive treatment using radiolabeled somatostatin analogues -111Indium-DTPA-octreotide, 90Y-DOTA-octreotide, 90Y-DOTATOC and MAURITIUS

**Interventional radiologist**

***Role:***

* Embolization- Transcatheter arterial embolization (TAE) alone or in combination with transcatheter arterial chemoembolization (TACE),
* Radionuclide therapy Therapeutic radiopeptides delivered arterially,
* Ablative techniques- radiofrequency ablation. Hepatic cryotherapy and percutaneous ethanol injection

**Other key roles in the MDT for NET**

* Oncology psychiatrists and social workers – They help by recognizing and managing the cognitive side-effects of cancer and treatment
* Clinical psychologists help people cope with emotional and personal problems
* Nutritionist/ Dietician– Help with diet and nutrition during treatment
* Palliative care provider – Helps to improve quality of life
* Occupational therapists – Offer practical and psychological support

**Patient communication**

Communication between multidisciplinary team and patients is most important. In cancer management, communication skills are a key to achieving the important goals which include

* Establishing trust and rapport
* Gathering information from the patient and the patient’s family
* Breaking bad news
* Giving information about the illness
* Addressing patient’s emotions
* Eliciting patient’s concerns.

**Benefits of the MDT approach in NET**

MDT approach in NET ensures that

* Patients receive timely treatment and care from appropriately skilled professionals
* Every patient benefits from an individualized, coordinated and treatment plan
  + There is continuity of care
* There is improved coordination of care
  + There is effective communication occurs between primary, secondary and tertiary care
  + Adherence to established guidelines is monitored
  + Reliable data are collected and used for the future benefit of patient management, for audit and for research
  + Patients are well informed and supported

All these factors result in improved outcomes outcomes including quality of life and survival.

**FUTURE PERSPECTIVES** [112]

The future will see a new era in NET therapy, based on

* Clinical trials signaling a shift beyond symptom control to improvement in progression-free survival.
* Customized treatment based on patient and disease factors
* Biomarkers and molecular imaging for prediction of response
* Personalized treatment based on molecular genetics and tumour biology

Molecular targeted therapy will be the treatment of the future and will include the increasing use of targeted agents, PRRTs, combination of cytotoxics with targeted agents and combination of targeted agents.

**KEY POINTS**

* A multidisciplinary team of physicians is essential for the successful treatment of neuroendocrine tumours.
* All patients with NET should be evaluated by a multidisciplinary team
* The evidence supports changes in clinical management by multiple disciplines, including medicine, surgery, pathology, radiology, medical oncology and nuclear imaging
* The core team comprises of a gastroenterologist, endocrinologist, pathologist, radiologist, onco-surgeon, medical oncologist, interventional radiologist and nuclear medicine specialist
* The role of the surgeon is most importantly complete surgical resection with minimal surgical morbidity.
* The gastroenterologist is involved in the early detection of NET is carried out endoscopic ultrasound (EUS), he is also concerned with prognostic considerations and guiding how the patient should be managed
* Endocrinologist has expertise in the treatment of hormone secreting tumours
* The medical oncologist contributes to the interpretation of patient-specific [prognostic](http://www.gistthefactsinfo.com/health-care-professional/resources/glossary.jsp#Prognostic) factors, monitoring for disease recurrence, and progression.
* The pathologist contributes to the diagnosis – biopsy report, disseminating report results, need for sufficient tissue samples or additional tests.
* The radiologist is involved in the diagnosis – Imaging- abdominal/pelvic CT with contrast, , EUS, FNA, Follow up imaging, PET
* Interventional radiologist performs transcatheter arterial embolization transcatheter arterial chemoembolization; radiofrequency ablation
* Nuclear medicine specialist performs octreoscan, administers tumour-targeted radioactive treatment using radiolabeled somatostatin analogues
* Consultations between all the core team members is important to ensure optimal care of patients with NETs
* The benefits of multidisciplinary disease management of patients include reducing recurrent disease, optimizing timing of surgery, prolonging survival for the patient and enhancing response to therapies

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**GLOSSARY**

ACP, Acid Phosphatase

AJCC American Joint Committee on Cancer

BNP, brain natriuretic peptide

CEA, carcino embryonic antigen

CgA - chromogranin A

DTPA - diethylene triamine pentaacetic acid

ENETS - European Neuroendocrine Tumour Society

EUS - endoscopic ultrasound

FDG - fluorodeoxyglucose

GPCA - gastric parietal cell autoantibody

GI - Gastrointestinal;

HCG- human chorionic gonadotrophin

5HIAA -5-hydroxyindoleacetic acid

5HTP - 5-hydroxytryptophan

Men-1 - multiple endocrine neoplasia 1

MIBG - meta iodobenzylguanidine

NET - neuriendocrine tumours

NF - neurofibromatosis

PET - positron emission tomography

PP - pancreatic polypeptide;

PTH - parathyroid hormone;

SSRS - [Somatostatin receptor scintigraphy](http://www.google.co.in/url?sa=t&rct=j&q=ssrs%20somatostatin%20receptor%20scintigraphy&source=web&cd=1&sqi=2&ved=0CCgQFjAA&url=http%3A%2F%2Fwww.ncbi.nlm.nih.gov%2Fpubmed%2F19500849&ei=lpkzT9GWCY-JrAeczZWkDA&usg=AFQjCNFRLAffWh0tVhFzCLtPUS0g3Hb6CQ)

SSTR - somatostatin receptors

TNM - Tumour, node, metastasis

VHL - Von Hippel Lindau