INDIAN COUNCIL OF MEDICAL RESEARCH

CONSENSUS DOCUMENT FOR MANAGEMENT OF NEUROENDOCRINE TUMOURS (GEP-NETs)

Prepared as an outcome of ICMR Subcommittee on Neuroendocrine Tumors (GEP-NETs)

Division of Non Communicable Diseases
Indian Council of Medical Research
2019

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Prepared as an outcome of Subcommittee on Neuroendocrine Tumours

Division of Non Communicable Diseases
Indian Council of Medical Research
Ansari Nagar, New Delhi – 110029
2019

Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline. One can use an alternate mode of therapy based on discussions with the patient and institution, national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but will act only as a guidance for clinicians in complex decision –making.

Dr. Balram Bhargava
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus Document for Management of Neuroendocrine Tumours (NETs). The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites. The various subcommittees constituted under Task Force project on Review of Cancer Management Guidelines which worked tirelessly in formulating site-specific guidelines. The purpose of consensus document is to provide clear, consistent, succinct, evidence-based guidance for management of various cancers. I appreciate and acknowledge support extended by each member of the subcommittees for their contribution towards drafting of the document.

Neuroendocrine Tumours require specialized multi-disciplinary care and treatment for better outcome. This document consolidates the modalities of treatment including the diagnosis, risk stratification and treatment. Hope that it would provide guidance to practicing doctors and researchers for the management of patients suffering from Neuroendocrine Tumours and also focusing their research efforts in Indian context.

It is understood that this document represents the current thinking of national experts on the subject based on available evidence. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this Consensus Document for Management of Neuroendocrine Tumours would serve desired purpose.

Balram Bhargava

(Dr. Balram Bhargava)
Secretary, Department of Health Research
and Director-General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer.

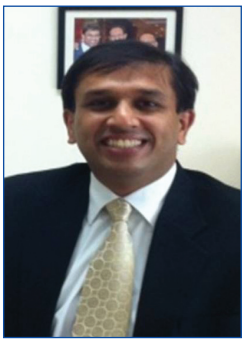
The Task Force on management of cancers has been constituted to plan various research projects. Two sub-committees were constituted initially to review the literature on management practices. Subsequently, it was expanded to include more sub-committees to review the literature related to guidelines for management of various sites of cancer. The selected cancer sites are lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome, Pediatric Lymphoma, Pancreatic Cancers, Hepatocellular Carcinoma and Neuroendocrine Tumours. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The published literature till October 2015 was reviewed while formulating consensus document and accordingly recommendations are made.

Now, that I have spent over a quarter of a century devoting my career to the fight against cancer, I have witnessed how this disease drastically alters the lives of patients and their families. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its co-ordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three year report of PBCR's (2012-2014) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the Consensus Document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson
ICMR Task Force Project

Preface



Neuroendocrine tumours are a rare cancer that originate in the endocrine or hormone-producing cells in pancreas, gastrointestinal tract, testes, ovaries or lungs. This consensus statement covers the gastro-entero-pancreatic neuroendocrine tumours. These cancers are a heterogenous group which show a varied biology ranging from indolent to aggressive. It is important to identify which patients need prompt treatment and those that can undergo watch waiting or observation.

India with a population of 1.2 billion records a low incidence of this cancer but increasing awareness and urbanization is changing this picture and the prevalence has markedly increased in the past decade. This cancer requires specialized multi-disciplinary care and should be ideally treated in centers of excellence for better outcomes. This has been proven worldwide and our nation needs to take steps in the same direction. On this backdrop, the ICMR Guidelines have the potential to go a long way in improving standards of care across India.

I take this opportunity to congratulate the ICMR leadership and the various members and contributors for publishing this excellent resource.

Dr Bhawna Sirohi
Chairperson, Sub-committee Neuroendocrine Cancers
Director, Medical Oncology
Max Healthcare, New Delhi

Prof Shailesh V Shrikhande
Co-chairperson
Deputy Director
Tata Memorial Centre, Mumbai

Preface

Cancer is a leading cause of death worldwide. Globally Cancer of various types effect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

(Dr. R.S. Dhaliwal)
Head, NCD Division

Acknowledgement

The Consensus Document on Management of Neuroendocrine Tumours (NETs) is a concerted outcome of effort made by experts of varied disciplines of oncology across the nation. The Indian Council of Medical Research has constituted various sub committees to formulate the document for management of different cancer sites. The Task Force on Management of Cancers has been constituted to formulate the guidelines for management of cancer sites. The sub-committees were constituted to review to review the literature related to management and treatment practices being adopted nationally and internationally of different cancer sites. The selected cancer sites are that of lung, breast, oesophagus, cervix, uterus, stomach, gallbladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukaemia, ALL, CLL, NHL-high grade, NHL-low grade, HD, MM, MDS, and paediatric lymphoma, pancreatic, hepatocellular & neuroendocrine tumours. All aspects related to treatment were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects.

This document represents a joint effort of large number of individuals and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. GK Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee Dr. Bhawna Sirohi, is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Balram Bhargava, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to benefit the cancer patients.

I would like to thank Dr. R.S. Dhaliwal for his support and coordination in finalizing this document. I would like to acknowledge the assistance provided by administrative staff. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a normal and healthy life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines. The data inputs provided by National Cancer Registry Programme are gratefully acknowledged.

(Dr.Tanvir Kaur)
Programme Officer & Coordinator

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Categories of Evidence and Consensus

Levels of Evidence

Level 1: High quality randomized controlled trials (RCTs) showing (a) a statistically significant difference or (b) no statistically significant difference with narrow confidence intervals; systematic reviews of Level I RCTs

Level 2: Lesser quality RCTs (e.g. <80% follow-up, no blinding, or improper randomization); prospective comparative studies; systematic reviews of Level II studies or of Level I studies with inconsistent results

Level 3: Case control studies; retrospective comparative studies; systematic reviews of Level III studies; retrospective studies

Level 4: Case series

Level 5: Expert opinions

Grading A to C has been done by the sub-committee. Grade A is to be assigned to a treatment or regimen that is easy to administer, has the highest level of evidence, and is cost effective as evaluated by the National Institute for Health and Clinical Excellence or as deemed so by the task force experts on the particular cancer.

On consideration of peripheral oncology centres, regional cancer centres, and tertiary cancer centres in major cities, the set of recommendations can be divided into 2 categories:

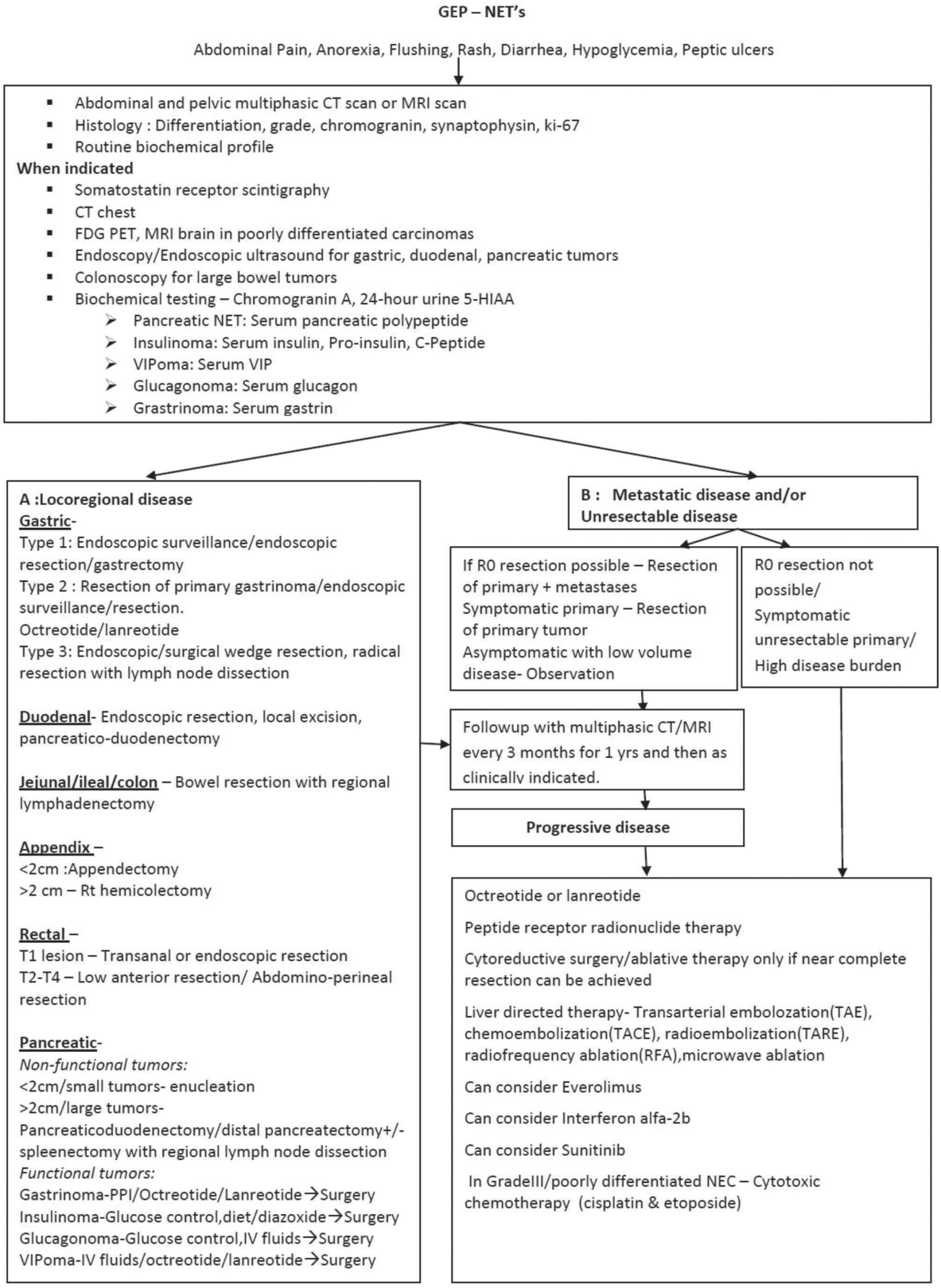
Desirable/Ideal: Tests and treatments that may not be available at all centres but the centres should aspire to have them in the near future.

Essential: Bare minimum that should be offered to all patients by all centres treating patients with cancer.

CONTENTS

CHAPTER

1 ALGORITHMS FOR GEP-NETs



CHAPTER

2 EXECUTIVE SUMMARY

This consensus document may be used as framework for more focused and planned research programmes to carry forward the process. The aim of the Indian Council of Medical Research (ICMR) consensus document is to assist oncologists in making major clinical decisions encountered while managing their patients, while realizing the fact that some patients may require treatment strategies other than those suggested in this consensus document.

- Histological confirmation which includes measurement of the proliferative index (Ki67) is mandatory prior to the commencement of definitive treatment.
- All patients should be staged according to the TNM staging system and risk should be assessed at diagnosis. A baseline contrast-enhanced computed tomography (CECT) scan of the chest, abdomen, and pelvis should be considered.
- Selected cases should be referred to genetics clinics (MEN syndrome)
- Patients should receive multidisciplinary care under the care of a surgical, medical, and radiation oncologist.
- Primary surgery remains the standard of supervision for non-metastatic tumours – insulinoma, VIPoma.
- Patients with advanced NEC should be assessed on an individual basis to determine whether chemotherapy, targeted therapy, PRRT or best supportive care should be provided.
- Preferred regimens for chemotherapy include –Capecitabine-Temozolomide, Cisplatin-Etoposide and for targeted therapy – everolimus and sunitinib.
- Patients should be offered regular surveillance after completion of curative resection or treatment of advanced disease.
- Encourage participation in institutional and ethical review board-approved, registered controlled clinical trials.
- Refer for early palliative care, if indicated.

CHAPTER

3 EPIDEMIOLOGY

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are tumours resulting from the malignant transformation of cells in the diffuse neuroendocrine system that regulates secretion and motility in the gastrointestinal tract (1). The term GEP-NETs is currently the adopted nomenclature for all the NETs of the GI tract and pancreas (2).

The incidence of GEP-NETs seems to be increasing globally. Some of this increased incidence may reflect better detection rates. Similar time-trends are evident in India also. Most of the prevalence and descriptive studies from India are from tertiary referral centers, with lack of population based data.

The broad term GEP-NETs includes tumours in the stomach, small and large intestine, rectum and pancreas. While often considered to be rare, the incidence of this tumour is on the rise (3-5) with a corresponding improvement in survival (6). Thus, understanding the biology and behaviour of these tumours so as to manage them appropriately, is important.

GEP-NETs account for more than 60% of all NETs according to the SEER database (3) and in data from India (7). The most common site GEP-NETs in most databases is the rectum, followed by the small intestine and colon (3, 8). GEP-NETs are more common in men than in women (7) while rectal NETs have the best 5-year survival (4, 8). Pancreatic NETs are more likely to present in a metastatic stage as compared to other GEP-NETs (3, 7). The incidence of GEP-NETs over the last 5 years according to the SEER database is 3.65 / 100,000 (3). The APNET registry is a longitudinal observational registry of patients with GEP-NETs in India, with 6 participating centers. Over 277 patients have been recruited by the APNET registry. Like other geographical regions, there was a slight male predominance in India. The most common site of GEP-NETs was pancreas (44%), followed by duodenum and stomach (each 10%), and rectum (7%). The primary tumour site was unknown in 8% patients. Eleven percent of all tumours were functional, of which the most common were insulinomas (9). Ten percent of the tumours were grade-3 (G3) carcinomas.

In 2008, a study form the Mayo Clinic reported the crude annual incidence of pancreatic NETs per 1,000,000 to be 1.8 in females and 2.6 in males. The study also found that the incidence of the tumours increased with advancing age (10). In contrast to the pancreatic NETs which tend to occur in the 6th-7th decades of life, rectal NETs occur in younger patients, with a peak age of 50 years (3). In Hong Kong, the calculated annual incidence of clinically significant tumours was approximately 0.2 per 100,000 population with an autopsy incidence of 0.1% (11) which is not different from the more recent SEER database (0.27 / 100,000 (3) although considerably lower than Japan (1.27 / 100,000) (5). These reports are not too dissimilar from the incidence of pNETs in Norway or the SEER database which has been estimated to be around 0.23 per 100,000 and 0.18 to 0.24 per 100,000 respectively (4).

Patients with MEN-1 or von Hippel Lindau syndrome may present 15-20 years earlier than patients with sporadic NETs (6). Data from India (7, 12) has indicated that pNETs are not uncommon as a group (NETs) as well as amongst pathological malignant lesions of the pancreas.

CHAPTER

4 DIAGNOSIS, CRITERIA AND INITIAL WORKUP

GEP-NETs are a heterogeneous group of tumours that share a common phenotype, with immunoreactivity for pan-neuroendocrine markers like CgA, synaptophysin, NSE, and CD56. However, GEP-NETs arising in different anatomical sites differ in their biology and clinical presentation. Lung origin may be favored by positive staining for thyroid transcription factor 1 (TTF-1), intestinal or pancreatic origin by CDX2, and pancreatic or rectal origin by IsI1 and PAX8 staining (13, 14).

In a large series of 1260 patients who underwent ^{68}Ga-labeled analogue positron emission tomography/computed tomography (PET/CT) for known or suspected NETs at a tertiary center in North India, 40.3% were found to have GEP-NETs. The most common locsite was the pancreas (33.6%), followed by ileum (19.3%), duodenum (13.4%), and stomach (11.0%). The primary site was unknown in 9.3% patients. MEN-1syndrome was seen in 0.7% of all patients (15).

The APNET registry is a longitudinal observational registry of patients with GEP-NETs in India, with 6 participating centers. Over 277 patients have been recruited into the APNET registry. Similar to other geographical regions, there exists a slight male predominance in India. The most common site of GEP-NETs was pancreas (44%), followed by duodenum and stomach (each 10%), and rectum (7%). The primary tumour site was unknown in 8% patients. Eleven percent of all tumours were functional, of which the most common were insulinomas (9). Ten percent of the tumours were grade-3 (G3) carcinomas.

In another study of 68 patients with metastatic NETs and unknown primary, the small intestine was the most commonly identified primary site by DOTANOC-PET/CT (16).

Evaluation of GEP-NETs should include:

1. Site of origin.
2. Any loco-regional or metastatic spread (stage).
3. Grade of the tumour.
4. Functional status of the tumour and biomarker levels.
5. SSTR expression.
6. Association with known syndromes

Tumour stage

The 5-year survival rate for patients with endocrine pancreatic tumours is estimated to be 60%-100% for localized disease, 40% for regional, and 25% for metastatic, and 80% for all stages (17).

The ENETS and AJCC have proposed a tumour-node-metastasis staging system for the different GEP-NETs (18, 19). The GEP-NETs of the stomach, small intestine, colon/rectum, appendix and pancreas have separate staging systems. Tumour stage, particularly the presence or absence of lymph node or

distant metastasis, has the strongest effect on survival (20). Multiphasic CT or MRI scans are the mainstay of staging GEP-NETs, which appear hyper-vascular. EUS is used to define depth of mural extension and for obtaining tissue samples from deep seated lesions.

Grading of GEP-NETs

IHC estimation of the Ki-67 expression, and mitotic index count are used to grade GEP-NETs as per the WHO classification, into low-grade (G1), intermediate-grade (G2), and high-grade (G3) categories (2). The G1 and G2 NETs usually correspond to well-differentiated tumours on morphology, and the G3 NETs to poorly differentiated neuroendocrine carcinomas (NEC). However, since the emerging evidence suggested that the G3 pancreatic neuroendocrine neoplasms are heterogenous in morphology and biology, the recent WHO 2017 classification has introduced a new category of well-differentiated pancreatic neuroendocrine tumors (WD-pNETs) G3, that show lower response rate to platinum-based chemotherapy while better outcomes compared with poorly differentiated pancreatic neuroendocrine carcinomas (PD-pNECs) G3 (21). These NEC can be of small-, or large-cell type. The most common sites for extra-pulmonary GEP-NEC are esophagus, and rectum or colon. NECs are rarely associated with a hormonal syndrome.

The mitotic rate has traditionally been reported after counting mitosis in at least 40 fields at 40X magnification, in areas of highest mitotic density. While mitotic rates can be calculated on surgical or large biopsy specimens, it may be difficult to report on FNA cytology specimens. For FNA and small biopsy specimens, the Ki-67 index is the preferred method of establishing the proliferative rate. Ki-67 index is reported as the percentage of positive tumour cells in area with highest nuclear labelling. Although the recommendations are to count Ki-67 staining in at least 2000 cells, this is difficult to implement in practice. Overall, the pathologist's impression of the highest Ki-67 index has an acceptable accuracy.

Increasing mitotic rate and Ki-67 index are correlated with worse prognosis and a more aggressive course (22). Although all NETs have the potential to metastasize, the tendency for distant spread is related to a higher proliferative index.

If there is any discordance between the mitotic rate or Ki-67 index, the higher value is used to grade the tumour. There are also concerns about intra-tumoural variability or 'hot-spots' of proliferative activity within any tumour. However, there is now data to suggest that FNA specimens correlate well with the final surgical pathology results, with regards to estimation of the proliferative index (23, 24). However, while the rates of concordance may defer depending on the cellularity of the FNA specimen with a risk of understaging as a G1 tumour based on a hypocellular aspirate (24),

Functional Status

Functional status is based on clinical features of hormone over-secretion, and not by *in-vitro* demonstration of hormonal production by IHC. While the IHC may be positive for multiple hormones on biopsy samples, it is not indicative of functionality. Patients with pancreatic NETs (pNETs) may have symptoms due to secretion of insulin, glucagon, gastrin, and other peptides. Functional NETs can cause significant symptoms even when small, and may be difficult to identify by imaging tests. Biochemical testing is dictated by the clinical symptoms.

Patients with metastatic NET to the liver may have symptoms of episodic flushing and/or diarrhoea (carcinoid syndrome). Carcinoid syndrome is related to the secretion of serotonin, histamine, and tachykinins directly into the systemic circulation, bypassing liver metabolism. Rarely, carcinoid syndrome can develop owing to functioning retroperitoneal metastases.

Biomarker and Hormone Analysis

The sensitivity and specificity of serum CgA for diagnosis of NETs is 73% and 95%, respectively (25). CgA levels are elevated in over 60% of patients with pNETs (26, 27). In patients with G3 NETs, plasma CgA levels are often normal. CgA levels can be falsely elevated in patients receiving PPIs, or those with renal or hepatic failure, hypertension, or chronic gastritis.

Urinary 24-hour 5-HIAA can be estimated in small intestinal NETs (carcinoids). This excretory biomarker is a metabolite of serotonin, and is particularly recommended in patients with suspected carcinoid syndrome. Certain common food items like bananas, eggplant, walnuts, tomatoes etc. should be avoided for at least 48-hours prior to urine collection.

A panel of experts in NETs, based on a Delphic consensus assessment, have concluded that for the future, the most promising strategy for refining and improving the evaluation of therapy would include combinations of imaging and blood-based molecular information provided by transcriptome analysis (28).

Imaging of Midgut Neuroendocrine Tumours

The role of imaging for NETs of pancreas and GI tract is in making the initial diagnosis, to help plan management decisions and for follow up after treatment. The role of the radiologist is to determine the exact site of primary tumour, to assess its resectability, to map the metastatic burden and to find out any complication due to local or metastatic disease. To elucidate this much information there is need of combination of many imaging techniques. Primary NETs are usually small in size and arise in submucosal layer of bowel wall or within pancreas. These may be multiple and may occur at multiple different sites simultaneously (29).

MDCT is the primary imaging modality for localization of the primary mass, staging the disease and assessing its resectability. To improve detection rate of primary tumour it is best to use dual-phase contrast enhanced CT. Nuclear scan techniques such as indium 111 (111 In) octreotide scintigraphy or positron emission tomography (PET) using gallium 68 (30) are complimentary to CT scan and useful when primary tumour is not detected on CT scan. MRI may be considered for patients who are allergic to CT contrast media or in those who have abnormal renal functions. Video capsule endoscopy, double balloon endoscopy and CT enterography are also being used increasingly for evaluation of primary tumour.

Multi-detector Computed Tomography (MDCT)

Contrast enhanced Dual phase CT is used to localize the primary tumour (intraluminal or extraluminal origin), nodal spread or metastases in various organs. The primary tumour in pancreas or intestine shows intense enhancement during early arterial phase. Associated lymph nodal metastases, which are usually larger than the primary tumor, are more readily picked up at CT. Selecting appropriate CT technique is of paramount importance for increasing the sensitivity of detection of endocrine tumours. Iodinated oral contrast should not be administered before CT scan, only intravenous contrast should be given. CT enterography study, using negative oral contrast (mannitol) in a large volume to adequately distend the small bowel and then acquiring the images at arterial as well as portal venous phase improves the detection rates of these tumours. Usually the metastases to liver (similar to the primary lesion) are also hypervascular, show intense enhancement on arterial phase and may become isodense on portal venous phase. The CT protocol should be decided based on clinical indication of the examination.

Magnetic Resonance Imaging (MRI)

MRI is usually employed as a problem solving tool. It is considered for patients with deranged renal functions or having history of allergy to contrast media. Due to decreased spatial resolution of MR as

compared to CT, the sensitivity to detect the small primary tumours is lower. However for detection of liver metastases it is as good as or even better than the CT examination. Intravenous gadolinium based contrast is used to increase conspicuity of the primary lesions and to improve the detectability and numbers of liver metastases. MR enterography using mannitol is also used to distend the lumen for better detection of the primary lesions. Intestinal hypomotility agents can be used to decrease the peristalsis and hence improve the detection of small primary lesions. The lesions of pancreas as well as intestine appear as hypointense on T1WI and hyperintense on T2WI and show intense early arterial enhancement after gadolinium administration (31).The advantages of MRI over CT are lack of ionising radiation and lack of large volume iodinated contrast agents. However prolonged examination time, more expense and lower availability are the disadvantages of MRI.

Functional Imaging

These NETs frequently retain their ability to express the SST receptors. Using the suitable analogues to these surface receptors, functional imaging has got the potential to detect the primary tumour and its metastatic spread. Even the unsuspected distant metastatic sites are also frequently found with the functional imaging thereby modifying the treatment strategy. Indium 111 (111In) is the most commonly used functional imaging with a detection rate of approximately 90 % for primary as well as metastatic disease (32). MIBG scintigraphy is another functional imaging technique which is though having lower sensitivity as compared to In 111, can sometimes detect the lesions which are negative on In 111 scan (29). Functional imaging can also help in prognostication as well as in follow up of patients after treatment with somatostatin analogues (33).

Due to lower proliferative index of the NETs as compared to other solid tumors, standard FDG PET is less useful for imaging of these tumours. Few newer agents have been developed to use with PET for assessment of receptor positive tumours. One such agent is 68 Ga DOTA octreotate having better sensitivity than 111 In octreotide scintigraphy and has the advantage of ability to assess suitability for scintigraphy based therapy (33, 34).

SSTR-based Imaging

Use of SSTR-based imaging in addition to radiological cross-sectional imaging has now become the standard of care for GEP-NETs.

SSTR-based imaging is used for:

1. Defining disease extent, and metastatic sites.
2. Detecting an unknown primary site in patients presenting with metastatic NET.
3. To assess SSTR expression before cold SST analog therapy, or PRRT.

SSTR-based imaging modalities include single photon emission computed tomography (SPECT) with ^{111}In-DTPA-Octreotide (OctreoScan), and PET with ^{68}Ga-labelled SST analogues (DOTA-NOC, DOTA-TOC, and DOTA-TATE). PET images are usually superimposed or fused with CT images for better anatomical localization.

There are minor differences between the different radio-isotope chelates for ^{68}Ga PET. DOTA-TOC, DOTA-TATE, and DOTA-NOC all bind to SSTR2- the predominant receptor type in GEP-NETs, and to SSTR5. However, only DOTA-NOC has additional good affinity for SSTR3. It is not clear whether these differences are clinically relevant.

PET with ^{68}Ga-labelled somatostatin analogues may be superior to OctreoScan. The spatial resolution

of PET is superior to SPECT (0.5cm compared to 1.5cm), and the tissue contrast is also better. These differences are especially important for small tumours, or tumours bearing a low density of SSTR. Besides, PET offers logistical advantages because the more favorable kinetics of the ^{68}Ga-labelled preparations allowing imaging at 30-60 min after injection of the radioisotope. ^{68}Ga is easily eluted from the commercially available ^{68}Ge/^{68}Ga generator. The long half-life of the mother radionuclide ^{68}Ge (270.8 days) makes it possible to use the generator for approximately 9-12 months. Finally, an in-house cyclotron is not needed making the preparation cheaper.

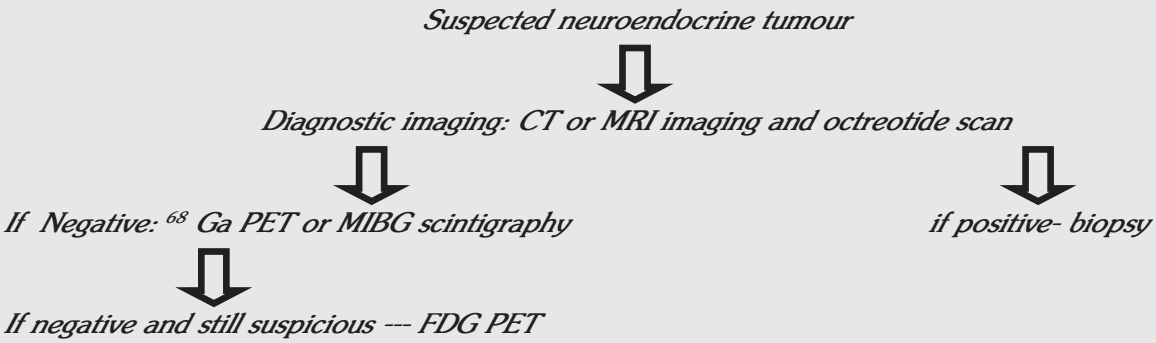
Dual tracer imaging with both ^{18}F-PET and ^{68}Ga DOTA-PET, further refines the treatment options for patients with GEP-NETs.

It is anticipated that the development of imaging modalities to quantify the spatial variation in architecture and function of individual tumours will likely become an essential tool for physicians to make therapeutic decisions in the near future (35).

Imaging modality	Indications	Findings	comments
USG	Screening modality for symptomatic patients For guiding FNAC or biopsy Used for evaluation of liver metastases Post operative/ post procedure for evaluating complications	Well defined hypodense lesions as compared to pancreatic parenchyma, contour bulge	Disadvantage – operator dependent, dependent on availability of good sonographic window, bowel gas frequently hampers the optimal visualization of entire pancreas
Contrast enhanced USG	In research settings or as problem solving tool, not routinely indicated	Increased conspicuity of the lesions few seconds after i.v. administration of the contrast medium, possible use for follow up imaging evaluation	Still used more in research settings only, higher cost is a limitation
Endoscopic USG	Frequently used for evaluation of small or multiple primary tumor sites, particularly when signs and symptoms are there but CT/ MRI fail to pick any lesion	Excellent modality with increasing use in tertiary centres	Significant specialist training is required, limited availability of the trained doctors, FNAC can also be obtained
Computed tomography (CT)	Mainstay of diagnosis, staging and response evaluation CT enterography is useful for increasing the sensitivity to detect smaller jejunal and ileal primary NETs	Tailored protocol for increasing the sensitivity, triple phase CT including the early arterial phase imaging of liver area covering entire pancreas and portal venous phase imaging of the whole abdomen and chest for lymph nodal and metastatic evaluation followed by delayed scan for upper abdomen	Primary imaging modality

MRI	Problem solving tool, useful if CT can not be done due to allergy to contrast media, used to avoid the ionising radiations associated with CT		Expensive, prolonged examination time
Scintigraphic studies (SPECT/ PET CT) using various radiopharmaceuticals	For staging as well as to measure the tumour burden, for prognostication, for therapeutic purposes, for follow up for response evaluation	Combined with CT, scintigraphic studies may be sufficient to provide all required information in most of the metastatic disease cases, many different types of pharmaceutical agents are available with differing sensitivity and specificities, also being actively used for therapeutic purposes	Expensive, radiation exposure, limited availability
Catheter Angiography	Previously used for diagnostic evaluation, now a days with the advent of high quality CT scans, not needed for diagnosis	Used almost always as an initial part of a therapeutic embolization sitting	Bland embolization, embolization with chemotherapeutic agents (chemoembolization), radioembolization , particularly for hepatic metastases

Algorithm for imaging evaluation of midgut neuroendocrine tumours (36)



Syndromes associated with NETs

Most GEP-NETs are sporadic. The main syndromes associated with GEP-NETs are MEN-1 (Wermer syndrome), von Hippel-Lindau disease, tuberous sclerosis, and neurofibromatosis (37, 38).

MEN-2 is characterised by the development of pheochromocytomas, and will not be discussed here.

The MEN-1 syndrome arises due to a germline mutation or inactivation of the MEN-1 gene on chromosome 11, encoding the menin protein. A clinical diagnosis of MEN1 can be made when a patient has two or more MEN1-associated tumours: multi-gland parathyroid hyperplasia causing hyperparathyroidism, pNET, or pituitary adenomas. These patients may also have associated carcinoid tumours of the lung and thymus, adrenal tumours, multiple lipomas, and cutaneous angiomas (39). In addition, type 2 gastric NETs occur frequently in MEN-1 patients with gastrinoma. In a patient suspected to have MEN-1 syndrome, additional investigations such as serum calcium levels, a neck ultrasound, and a parathyroid sestamibi scan are required to rule out parathyroid adenomas.

Gastric NETs

Gastric NETs are being increasingly detected as an incidental findings during endoscopy done for unrelated complaints. The diagnosis is confirmed by endoscopic biopsy. If a NET is suspected during endoscopy, additional biopsies should be taken from the antrum and body of the stomach, to look for mucosal atrophy and parietal cell hyperplasia. Fasting serum gastrin levels are estimated after stopping PPI for at least one week during which time the patient needs to be put on H2 receptor blockers for maintaining acid suppression (40).

Type 1 and 2 gastric NETs have high serum gastrin levels, while type 3 gastric NETs have normal gastrin levels. Type 1 gastric NETs are associated with atrophic gastritis, while type 2 gastric NETs are associated with Zollinger-Ellison syndrome. Estimation of gastric pH is difficult in practice, and is seldom done. A careful endoscopic evaluation and biopsies of the gastric mucosa usually suffice to distinguish between the type 1 and type 2 gastric NETs, both of which are usually multifocal. Type 1 gastric NETs also have low vitamin B12 levels and presence of intrinsic factor (IF) antibodies as markers of atrophic gastritis, usually autoimmune. Endoscopic and EUS evaluation of the duodenal wall and the pancreas (gastrinoma triangle) is indicated to locate the gastrinoma associated with type 2 gastric NETs. Type 3 gastric NETs are usually sporadic and solitary.

Small intestinal NETs

Multi-phasic CECT or MRI of the abdomen and pelvis is recommended for diagnosed or suspected small intestinal NETs (41). The addition of a CT of the chest may also be appropriate in select cases where metastases are suspected. Careful evaluation of the entire small bowel is recommended to detect synchronous lesions.

Most of the small intestinal NETs arise in the distal ileum. They present with intestinal colic or partial bowel obstruction. In a substantial proportion of patients, NETs are discovered after resection for small intestinal obstruction. Tumour infiltration into the mesentery provokes an intense fibrotic reaction that results in kinking of small bowel and ischemia, leading to small intestinal obstruction.

Routine upper endoscopy allows access to the entire duodenum. Antegrade and retrograde enteroscopy (balloon assisted) allow evaluation of almost the entire jejunum and ileum. Capsule endoscopy can evaluate the entire small intestine non-invasively. Caution should be exercised in presence of luminal narrowing because of risk of capsule retention. EUS permits estimation of the size and depth of duodenal lesions, and also the sampling of any suspicious peri-pancreatic lymph nodes.

NETs of the appendix

These are usually incidentally detected in appendicectomy specimens (42). Further management depends on the size and invasive characteristic of the tumour. Tumours <2cm and confined to the appendix are considered cured by simple appendectomy. Larger tumours, and those with positive resection margins or positive nodes require multiphasic CECT or MRI of the abdomen and pelvis, followed by surgical re-exploration.

Rectal NETs

These tumours are usually picked up incidentally at endoscopy of the lower GI tract Once metastases are ruled out on multi-phasic abdominal and pelvic MRI or CECT scans, the treatment depends on the size of the tumour and depth of invasion. This is best done by trans-rectal ultrasound examination. Tumours

<2cm in size without invasion of muscularis propria can be considered for local excision by endoscopy or trans-anal surgery. Tumours 1-2cm in size need surgical resection if the muscularis propria is invaded or lymph node enlargement is present. Tumours >2cm in size need radical surgical resection.

Pancreatic NETs (pNETs)

Of all pNETs, 45%-60% are non-functional, and 40%-55% are functional. The 'non-functioning' pNETs may secrete increased levels of CgA as well as hormones like pancreatic polypeptide (PP) or SST (43). The NCCN NET outcome database revealed that 22% of patients with pNETs had a hormonal syndrome (44). For functional pNETs, hormone analysis should be guided by the clinical symptoms. Personal and family history should be carefully evaluated to rule out an underlying MEN-1 syndrome in all patients with pNETs. pNETS in patients with MEN-1 syndrome are typically multifocal.

Insulinomas secrete insulin, resulting in neuro-glycopenic symptoms. Fasting serum insulin, pro-insulin, C-peptide levels, and concomitant blood sugar levels should be tested. SSTR-based imaging often fails to demonstrate insulinomas; multiphasic CECT scan will often be negative in these tumours because of their very small size when symptomatic. EUS is most useful to localize insulinomas prior to surgery.

Gastrinomas are located in the duodenal wall in around half of cases. These patients present with recurrent or refractory peptic ulcers and dyspepsia, usually with diarrhea. Serum fasting gastrin levels with patient off PPI for >7 days is measured, along with gastric pH, if available. Tumour localization is by multi-phasic CECT scans, SSTR imaging, and endoscopic studies (including EUS).

Glucagonomas are associated with the development of diabetes mellitus, weight loss and cachexia, and/ or migratory necrolytic erythema. Serum glucagon level estimation is often not available, but the tumours are usually easily localized by conventional imaging. Most are large, malignant, calcified, and located in the tail of pancreas

The rare patients with somatostatinomas also have diabetes mellitus and/or diarrhoea/ steatorrhoea due to excess SST secretion.

VIPomas are characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome) due to excess secretion of vasoactive intestinal polypeptide (VIP). Serum electrolytes and VIP levels, if available are measured. Multiphasic CECT or MRI scans, and SSTR based imaging are used to localize these tumours which tend to be metastatic at presentation.

NET of unknown primary

Localising studies include multiphasic CECT or MRI scans, SSTR-based imaging, upper endoscopy, colonoscopy, EUS, and small bowel evaluation. Radionuclide bone scan is recommended with bone metastasis are suspected. Small intestinal NETs may be small and difficult to localize.

CHAPTER

5 STAGING AND PROGNOSTIC CRITERIA

In 2006 and 2007, the ENETS proposed a staging scheme, similar to most other types of epithelial neoplasms, for NETs of the digestive tract that was accompanied by a histologic grading system that could be applied to all disease stages (45, 46). In 2010, the WHO endorsed staging NETS using the TNM-based system.

The 7th edition of the AJCC staging manual, which reflects a modification based on the proposal by ENETS (45), includes a separate TNM staging systems for NETs of the Stomach, Duodenum/Small bowel, Colon/Rectum, Appendix and Pancreas.

Notable differences between the ENETS proposal and AJCC manual include the following:

- The ENETS proposal stages poorly differentiated NEC in the same way as well differentiated NETs while AJCC stages poorly differentiated NECs as adenocarcinomas.
- AJCC applies the adenocarcinoma staging scheme to all pancreatic neoplasms (including both well differentiated NETs and poorly differentiated NEC). Furthermore, the T stage definitions differed between the AJCC and ENETS systems.

It is unclear which staging system provides better separation of the prognostically different groups. At least one analysis using a large International cohort study concluded that for pNETs, the ENETS staging system provided superior prognostic stratification (47).

The prognostic validity of both, the TNM stage and proliferative rate using this new system, in GEP NETs is supported by several studies (22, 48-55). For example, in one series of 425 patients with a pNETs, 5-yr survival rates for low-, intermediate-, and high-grade tumours were 75, 62, and 7%, respectively (53). Using the AJCC classification, 5-yr overall survival rates for stage I, II, III, and IV tumours were 92, 84, 81, and 57%, respectively. However, others noted no significant difference in outcomes between stage I and II midgut (jejunal and ileocecal) NETs (5-yr overall survival – 100% for both), and heterogeneous outcomes in patients with stage IIIB (node positive) disease depending on whether disease was resected (5-yr overall survival 95%) or unresectable (5-yr overall survival 78%) (54).

Neither the ENETS nor the AJCC staging systems acknowledge a distinction between resected and microscopically involved versus large and unresectable mesenteric lymph nodes.

NETs of unknown primary, especially the well differentiated variety, often present initially with liver metastases, and most of these include GEP-NETs. NETs of unknown primary are, by definition, metastatic disease and therefore considered stage IV in all TNM staging systems. For this reason, the histological grade is particularly important and may be the only prognostic marker available for this group of tumours.

Staging

AJCC classifies GEP NETs according to the (T), node (N), metastasis (M). The AJCC introduced its first

TNM staging system for the classification of neuroendocrine tumours in its 7th edition of the AJCC Cancer Staging Manual (19).

*Please refer to **Appendix** for:*

a) Site specific staging

b) Grading & Histological Classification

c) Nomenclature

d) Pathological reporting of GEP-NETs

Table 1: ENETS/WHO Nomenclature and classification for digestive system neuroendocrine tumours

Differentiation	Grade	Mitotic count*	Ki-67 index¶	Traditional	ENETS, WHO
Well-differentiated	Low grade (G1)	<2 per 10 HPF	<3%	Carcinoid, islet cell, pancreatic (neuro) endocrine tumour	Neuroendocrine tumour, Grade 1
	Intermediate grade (G2)	2 to 20 per 10 HPF	3 to 20%	Carcinoid, atypical carcinoid , islet cell, pancreatic (neuro) endocrine tumour	Neuroendocrine tumour, Grade 2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, Grade 3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, Grade 3, large cell

* Counted in 10 high power fields (HPF). 10 HPF = 2 mm^2, at least 40 fields (at 400x magnification) evaluated in areas of highest mitotic density. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th edition. ¶ Ki-67 index as assessed by MIB1 antibody staining: percent positive after count of 2000 cells in area of highest nuclear labeling. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th edition. The term "atypical carcinoid" only applies to intermediate-grade NETs of the lung.

Table 2. WHO 2017 classification for pancreatic neuroendocrine neoplasms (56)

	Mitotic index	Ki67 index
Well differentiated NENs		
Neuroendocrine tumor (NET) G1 Neuroendocrine tumor (NET) G2 Neuroendocrine tumor (NET) G3	<2/10 HPF 2-20/10 HPF >20/10 HPF	<3% 3-20% >20%
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3 Small cell type Large cell type	>20/20 HPF	>20%
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)		

Prognostic Criteria

Tumour stage and grade are the most important prognostic indicators. Apart from the tumour stage and grade, the margin status (positive or negative) and the presence of vascular or perineural invasion should be included in the pathology report since some studies have suggested that these factors may also have prognostic significance (57, 58).

While elevated levels of CgA have been associated with poorer prognosis, this may not always hold true. The molecular basis of neuroendocrine tumours remains poorly understood, and additional molecular predictors of outcome remain investigational.

A recent study found that over expression of mTOR, or its downstream targets was associated with shorter overall survival in 195 NET tissue samples which included 15% pNETs and 85% of other GI carcinoids (59). Small bowel carcinoid tumours have been found to have recurrent mutations in the CDK inhibitor, CDKN1B (p27) (60), and loss of CDKN1B expression has been reported to be an adverse prognostic factor in GEP-NETs (61).

Circulating tumour cells (CTCs) have also been studied as possible prognostic markers, based on the idea that tumour cells in the blood would be indicative of more disseminated disease. A recent study found that the presence of 1 CTC in 7.5 mL of blood was independently associated with worse PFS and overall survival in patients with varyingly pre-treated metastatic NETs from various primary sites (62).

More research is required, however, before these and other new molecular assays are routinely used in practice. A multinational consensus meeting of experts concluded that, to date, no single currently available biomarker is sufficient as a diagnostic, prognostic, or predictive marker in patients with NETs (62).

CHAPTER

6 MULTIDISCIPLINARY TREATMENT FOR EARLY DISEASE

A multidisciplinary team approach remains at the core of treating all cancers—such treatment relies upon an effective interdisciplinary network including surgical, medical, and radiation oncologists; gastroenterologists; pathologists; radiologists (for interventional and nuclear medicine); nurse specialists, and palliative care physicians.

All new patients should be discussed at a tumour board or interdisciplinary team meeting, and the treatment strategy should be confirmed based on a complete work-up of the patient. In most patients with localised disease, resection will be the treatment of choice.

Surgical Principles for the management of GEP NETs

- Prior to surgery, all symptoms of hormonal excess must be treated. Octreotide or lanreotide can be considered for symptom control in most pNETs, although, caution is advised in patients with an insulinoma as the medication can worsen hypoglycaemia, resulting in fatal complications. For insulinomas, adequate glycaemic control should be achieved with diet, diazoxide and / or Everolimus. Gastrin hypersecretion in patients with gastrinomas can be controlled with proton pump inhibitors. Patients with glucagonoma need good glycaemic control.
- Resection should include complete removal of the tumour with negative margins.
- A thorough exploration of synchronous primary tumours should be performed as incidence of synchronous tumours is 15–30 %.
- Cholecystectomy is recommended when performing surgery for advanced NETs in patients anticipated to receive long-term octreotide therapy, as these patients are at higher risk of developing biliary symptoms and cholecystitis.
- In patients with functional carcinoid tumours, Octreotide therapy should be administered parenterally prior to induction of anaesthesia to prevent carcinoid crisis and be discontinued the next day after assessment.
- All patients who might require a splenectomy should preoperatively receive the trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C).

Pancreatic NETs

Patients with localized pNETs should be considered for surgical resection (40). Exceptions to surgery include patients with other life-limiting comorbidities or high surgical risk, particularly if the tumour is small and indolent. While studies have suggested that patients with incidentally detected tumours <1 cm in size may be safely observed in some selected cases, depending on the site of the tumour (63). Other studies, including an analysis of the SEER database, suggest that some small tumours (measuring <2 cm in size in these studies) can pursue a more aggressive course (64). Surgery must be considered in all functional tumours irrespective of their size and in tumours >1cm even if they are non-functional.

The various surgical options available for pNETs include:

1) Pancreas-parenchyma sparing surgeries: preferred in benign, functional or non functional tumours.

Enucleation (with / without a Roux-en-Y pancreaticojejunostomy)

Criteria:

a. Tumour < 2cm in size (65),

b. Located 2-3mm away from the main pancreatic duct (66, 67),

c. Solitary lesion in any part of the pancreas

Central pancreatectomy

Criteria:

a) Lesions in the neck and / or body (68).

b) Located in close proximity to the main pancreatic duct

c) Sufficient proximal remnant for a safe closure and and distal remnant for anastomosis to the jejunum

2) Radical surgeries – preferred in high grade, malignant lesions as well as benign lesions that are larger (2cm) or multiple

Pancreatoduodenectomy (PD)

Criteria:

a) Tumours located in the head and uncinate process (69)

b) In non-metastatic tumours involving the superior mesenteric or portal vein over a short segment in surgically fit patients (the actual benefit of such a surgery needs to be better defined (70))

Distal pancreatectomy (with / without spleen preservation)

Criteria:

a) Tumours located in the body and tail of pancreas

In terms of a comparison between laparoscopic and open, it must be clearly appreciated that these are not antagonistic techniques but rather be regarded as complementary performed for the right indication. Laparoscopic procedures such as enucleation and distal pancreatic resections are feasible for benign pNETs (71) but should be attempted only by trained pancreatic laparoscopic surgeons. A reasonable experience in performing laparoscopic ultrasonography is mandatory when performing laparoscopic

resections (72). Open surgery, too, must be performed only by surgeons trained to do so and is the preferred approach for malignant (or lesions of indeterminate malignant potential) as well as larger lesions especially those in the head of pancreas and uncinate process.

Role of Lymphadenectomy

While an extended lymphadenectomy is not indicated in pNETs, a regional lymphadenectomy must be performed in all patients with gastrinomas and in those patients with non-gastrinoma lesions 15 mm (73). Additionally, in patients undergoing enculeation of the lesion, peripancreatic lymph nodes (especially those adjacent to the hepatic artery and within the porta hepatis) must be sampled (74).

Extended resections (incl. vascular and contiguous involved organs)

While the feasibility of vascular resections (arterial and venous) is undisputed (69, 75-82), the actual benefit of aggressive surgery in terms of reducing local and distant recurrence rates is not completely understood (83). There is no clear evidence on this aspect owing to the conflicting reports in literature on benefits (83). Additionally, the generally low incidence of the disease precludes the conduct of well designed randomised controlled trials (84) to truly test the hypothesis of the benefit of vascular resections.

While a recent review (85) examining the role of only resection of the primary tumour in patients with unresectable metastatic liver disease indicates a potential benefit of such surgeries, the inherent bias of surgical resection being performed in patients with a better performance status and less advanced disease in the cohorts analysed cannot be undermined – precluding any firm conclusions being drawn from this analysis.

Additional precautions during surgery

Surgery for Gastrinoma (86)

The treatment approach for gastrinoma usually depends on the results of preoperative localization studies and on findings during exploratory laparotomy. In patients with occult gastrinoma (ie, no primary tumour or metastasis seen on imaging), either observation or exploratory surgery, is recommended. Should the lesions not be identified in the pancreas on exploration, the entire area included in the "Gastrinoma triangle" of Stabile (bounded by the junction of common and cystic ducts superiorly, the second and third portions of duodenum inferiorly and head and neck of pancreas medially) must be carefully examined. If despite this the lesion cannot be isolated, a duodenotomy must be performed to rule out duodenal gastrinomas (87). An intraoperative ultrasound with local resection or enucleation of tumours and periduodenal node dissection must be performed. Gastrinomas in the distal pancreas are treated with a distal pancreatectomy. The role of routine splenectomy in such cases is debated. Given that gastrinomas have the potential to involve regional lymph nodes, routine splenectomy is advised to enable an adequate lymphadenectomy. However, there is no firm evidence to support splenectomy in all cases. Another option is to use the "Warshaw technique" which, with resection of splenic vessels but preservation of the spleen, can achieve lymph node retrieval comparable to distal pancreatectomy with en-bloc splenectomy.

Surgery for Insulinoma

All insulinomas should be resected regardless of size because of the disabling side-effect i.e. hypoglycaemia. Sporadic tumours are usually solitary, whereas familial tumours are multiple. Enucleation is the primary treatment for exophytic or peripheral insulinomas, as they are primarily benign. If enucleation is not possible due to invasion or the location of the tumour within the pancreas, then PD for tumours in the head of the pancreas or median pancreatectomy for small body tumours or distal pancreatectomy with preservation of the spleen for smaller tumours in the tail may be considered. Distal pancreatectomy can

be performed laparoscopically. While open surgery is recommended for multiple lesions (88) and lesions in the head and uncinate process of pancreas (89), laparoscopy could be considered for solitary, smaller lesions in the body and tail (71, 90). A recent meta-analysis reported that laparoscopic procedures are safe for patients with insulinomas and may be associated with shorter hospital stays (91).

Glucagonomas

Most glucagonomas are malignant and calcified and located in the tail of the pancreas, with regional node involvement. The recommended treatment is distal pancreatectomy with splenectomy and resection of the peripancreatic lymph nodes. For tumours in the pancreatic head, PD with resection of the peripancreatic lymph nodes is recommended. Small (<2 cm) peripheral glucagonomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumours of the head or distal pancreas. Glucagonomas are known to be associated with hypercoagulable state in 10-33% of patients. Therefore, perioperative anticoagulation should be considered in view of the risk of venous thromboembolism.

Gastric NETs

Three types of gastric NETs are recognized: ***type 1*** (associated with chronic atrophic gastritis or high gastric pH); ***type 2*** (associated with antrum-sparing type A Zollinger-Ellison syndrome); and ***type 3*** (sporadic, unifocal, no association with either atrophic gastritis or Zollinger-Ellison syndrome) (92). *Refer to Appendix for more detail.*

Type 1 gastric NETs pursue an indolent course, with a rate of metastases of <5%. Annual endoscopic surveillance and endoscopic resection of prominent tumours is recommended for patients with locoregional type 1 gastric neuroendocrine tumours. Antrectomy can be considered if gastric tumours are increasing significantly in size or number.

In general, for locoregional type 2 gastric NETs, the primary gastrinoma must be resected. If the primary tumour is not resected, endoscopic surveillance and endoscopic resection of prominent gastric carcinoid tumours should be considered and/or octreotide or lanreotide can be given.

Patients with non-metastatic gastric NETs and normal serum gastrin levels (type 3) often have more aggressive tumours and are usually treated with radical resection of the tumour with regional lymphadenectomy. For early stage, smaller tumours, endoscopic or wedge resection can be considered if there is no evidence of lymphadenopathy on EUS (93). Although, endoscopic resection has been considered for small (<1 cm), superficial, low-grade tumours, surgery remains the cornerstone of treatment (94).

Summary of surgical recommendations

Primary tumour – extent of resection

Desirable/ Essential -

Type 1 < 1cm – endoscopic surveillance

Type 1 ≥ 1cm – endoscopic resection (EMR /ESMD) or surgical resection

Type 2 < 1cm and no duodenal or pancreatic NET – endoscopic surveillance

Type 2 < 1cm and duodenal or pancreatic NET – resect the pancreatic / duodenal tumour

Type 2 ≥ 1cm – endoscopic resection (EMR /ESMD) or surgical resection

Type 3 – Resection (Preferably surgery) unless tumour <1cm and facilities for advanced endoscopic resection are available

Lymphadenectomy

Essential / Desirable – Standard lymphadenectomy (if gastrectomy being performed)

Duodenum, Small Intestine, and Colonic NETs

For small localized lesions arising in the duodenum, endoscopic resection is recommended, if feasible. Transduodenal local excision with or without lymph node sampling and PD are other options for primary treatment of non-metastatic duodenal NETs. Tumours of the distal duodenum can be managed by pancreas-sparing duodenal resections (95). If endoscopic resection was performed, follow-up upper GI endoscopy should be performed, as appropriate.

For patients presenting with tumours in the jejunum, ileum, or colon, surgical resection(s) of the bowel with regional lymphadenectomy is recommended. Careful examination of the entire bowel should be performed during surgery as synchronous lesions may be present.

Summary of the Surgical Recommendations

Duodenal NET

Primary tumour - Extent of resection

Tumour <1cm

Desirable / Ideal – EMR /ESMD

Essential – Surgical resection (wedge resection)

Tumour ≥ 1cm

Desirable / Ideal / Essential – Surgical resection (wedge resection / PD)

Lymphadenectomy

Tumour ≥ 1cm

Desirable / Ideal / Essential – Standard lymphadenectomy

Small intestinal NET

Primary tumour - Extent of resection

Desirable / Ideal / Essential – Surgical resection (wedge resection)

Lymphadenectomy

Desirable / Ideal / Essential – Standard lymphadenectomy

Small intestinal NET

Primary tumour - Extent of resection

Desirable / Ideal / Essential – Surgical resection (standard colectomy)

Lymphadenectomy

Desirable / Ideal / Essential – Standard lymphadenectomy

NETs of the Appendix

Most commonly, appendiceal NETs are incidental finding, during appendectomy performed for appendicitis (42). These tumours mostly have well-differentiated histology. For most appendiceal tumours ≤ 2 cm and confined to the appendix, the chance of metastasis are uncommon and a simple appendectomy is sufficient.

However, some controversy exists regarding the management of appendiceal NETs measuring < 2 cm with more aggressive histologic features. A population-based study analyzing the SEER database found evidence that lymph node metastases can develop in some patients with appendiceal neuroendocrine tumours 2 cm or smaller (96). Some surgeons thus advise more aggressive treatment for 1- to 2-cm tumours with poor prognostic features, such as lymphovascular or mesoappendiceal invasion and / or atypical histologic features. In a retrospective case series that included 79 patients with appendiceal carcinoid tumours, small-vessel invasion was a risk factor for metastases in patients with tumours < 2 cm (97). Patients with an incomplete resection or tumours > 2 cm are at risk for locoregional or distant metastases. A complete staging with abdominal/pelvic CT or MRI scans should be performed in these patients. If no distant disease is identified, they should undergo re-exploration with a right hemicolectomy.

A small proportion of appendiceal NETs may also contain evidence of adenocarcinoma also termed as "adenocarcinoid" or "goblet cell carcinoid" tumours. Management of these tumours proceeds on the same lines as adenocarcinomas of the colon.

Summary of surgical recommendations

Primary tumour – extent of resection

Desirable/ Essential -

Well-differentiated appendiceal NET <2 cm - appendicectomy

Tumours measuring 1–2 cm but with positive or unclear margins or with deep mesoappendiceal invasion, higher proliferation rate (G2) and/or vascular invasion - right-sided hemicolectomy (98)

Tumours >2 cm - right-sided hemicolectomy

Lymphadenectomy

Essential / Desirable – Standard lymphadenectomy

Rectal NETs

The treatment of rectal NETs is based on the size of the primary tumour. If the lesion is ≤ 2 cm or confined to rectal mucosa (T1), endoscopic or transanal excision is recommended. Given the higher risk of invasion with larger tumours, examination under anaesthesia and/or EUS before the procedure should be considered for all tumours irrespective of the size (99). In a recent retrospective review of patients with well-differentiated rectal NETs of 11 to 19 mm (n= 87), incidence of metastasis was 66% (100).

Tumours > 2 cm, invasion of the muscularis propria, or associated lymph node metastases should be treated with low anterior resection or, an abdominoperineal resection depending on the location of the lesion in rectum (101).

Rectal NET

Primary tumour - Extent of resection

T1; Tumour <1cm

Desirable / Ideal – Endoscopic / transanal excision

Essential – Surgical resection

T2 – 4; Tumour ≥ 1cm

Desirable / Ideal / Essential – Surgical resection (AR / APR)

Lymphadenectomy

Tumour ≥ 1cm

Desirable / Ideal / Essential – Standard lymphadenectomy

Surgery for metastatic / recurrent disease in GEP-NETs

The most common sites of metastases from intestinal NETs include regional/mesenteric lymph nodes, liver, and bones. In some cases, patients with limited hepatic metastases or other sites of disease can undergo complete resection of the primary tumour and metastases with curative intent (102). As per the ENETS 'Consensus guidelines', the minimal requirements for resection of liver metastases with curative intent resection (103) includes a resectable primary tumour along with the following:

a. Resectable well-differentiated liver disease with acceptable morbidity and <5% mortality
b. Absence of right heart insufficiency
c. Absence of extra-abdominal metastases
d. Absence of diffuse peritoneal carcinomatosis

A recent meta-analysis reported 5-year overall survival rates ranging from 41% to 100% in patients undergoing hepatic resection (104).

Non-curative debulking surgery can also be considered in select cases, especially if the patient is symptomatic either from tumour bulk or hormone production and if at least 90% of the tumour volume is resectable (105). Planned cytoreductive, incomplete (R2) resection of advanced disease in patients with asymptomatic or non-functional disease is controversial. However, it is not uncommon for patients with small bowel primary tumours to experience symptoms of intermittent abdominal pain from episodic bowel obstruction or bowel ischaemia related to the primary tumour and surrounding fibrosis. Palliative small bowel resection is recommended in these patients.

Resection of recurrent locoregional disease, isolated distant metastases, or a previously unresectable tumour that has regressed should be considered for selected patients with adequate performance status.

Liver Transplantation for metastatic GEP-NETs

Several series have now reported the results of liver transplantation for liver limited disease in carcinoids (106-108). However majority of patients undergoing liver transplantation ultimately develop recurrence. Considering the high rate of recurrence and the risks associated with transplantation, liver transplantation is still investigational and not part of routine care at the present time.

Resectable primary with unresectable / untransplantable liver metastases (where the liver is the only distant site of metastases)

In this subgroup of patients, resection of the primary tumour must be considered so long as it can be resected without any additional morbidity to the patient. For the liver disease, the choice of liver-directed

therapies includes transarterial embolisation and chemoembolisation (TAE and TACE), radiofrequency ablation (RFA), cryoablation, alcohol ablation, radioembolisation with Yttrium-90 microspheres.

Summary of recommendations

In the case of metastatic GEP-NETs, the plan of management should be made by a multidisciplinary team after a thorough evaluation of the primary tumour and burden of metastatic disease (109). Factors that need to be considered in decision –making include:

a) Symptoms and resectability of the primary tumour

b) Resectability of the metastases (at last 90% debulking should be achievable)

c) General condition of the patient – to withstand the therapy

CHAPTER 7

MULTIDISCIPLINARY TREATMENT FOR GEP NETS (INCLUDING METASTATIC DISEASE)

Prognosis for GEP NEC is poor for all stages of disease with median survival of 38 months for localized disease, 16 months for regional disease, and 5 months for metastatic disease, from the time of diagnosis (110-113). Long-term relapse-free survival is possible among patients with localized disease who are treated with multimodality therapy.

General approach:

Unfortunately, most patients will present with metastatic disease not amenable to resection. In these cases, curative treatment is not possible, but many patients will benefit in terms of both quality of life and survival from the use of systemic chemotherapy and supportive measures. Evidence suggests that greater benefit is achieved if patients are treated early, before becoming symptomatic.

Data to support the current treatment of GEP NEC is based on retrospective reports and the parallel recommendations for small cell carcinomas of the lung. GEP NECs are responsive to systemic chemotherapy and platinum-based chemotherapy represents the backbone of treatment for advanced-stage GEP NEC especially if the Ki67 is more than 55%. (64, 111, 114-117).

Adjuvant Therapy

Adjuvant or neoadjuvant chemoradiation is reasonable if the risk of local recurrence is thought to be higher than average, depending upon the anatomic location of the tumour (eg, rectum). However, distant recurrences are far more frequent than local recurrences.

Chemotherapy or Chemoradiotherapy can be used for locally advanced disease (T3-T4 and/or lymph node involvement), using a platinum agent and etoposide. This treatment can be considered definitive or neoadjuvant, depending on whether surgical resection is possible after the therapy (118).

The RADIANT-3 randomised controlled trial investigated the role of everolimus 10 mg/day (n = 207) or placebo (n = 203) in patients with advanced, progressive, low- or intermediate-grade pancreatic NETs (119). Everolimus was associated with a survival benefit of 6.3 months resulting in a median OS of 44 months (the longest OS reported in a phase III study for this population). Prognostic factors associated with a poor outcome included elevated baseline CgA, NSE, placental growth factor, and soluble vascular endothelial growth factor receptor 1 levels..

Metastatic Disease

Metastatic GEP NEC is responsive to systemic platinum-based chemotherapy, but almost all patients relapse and die of their disease.

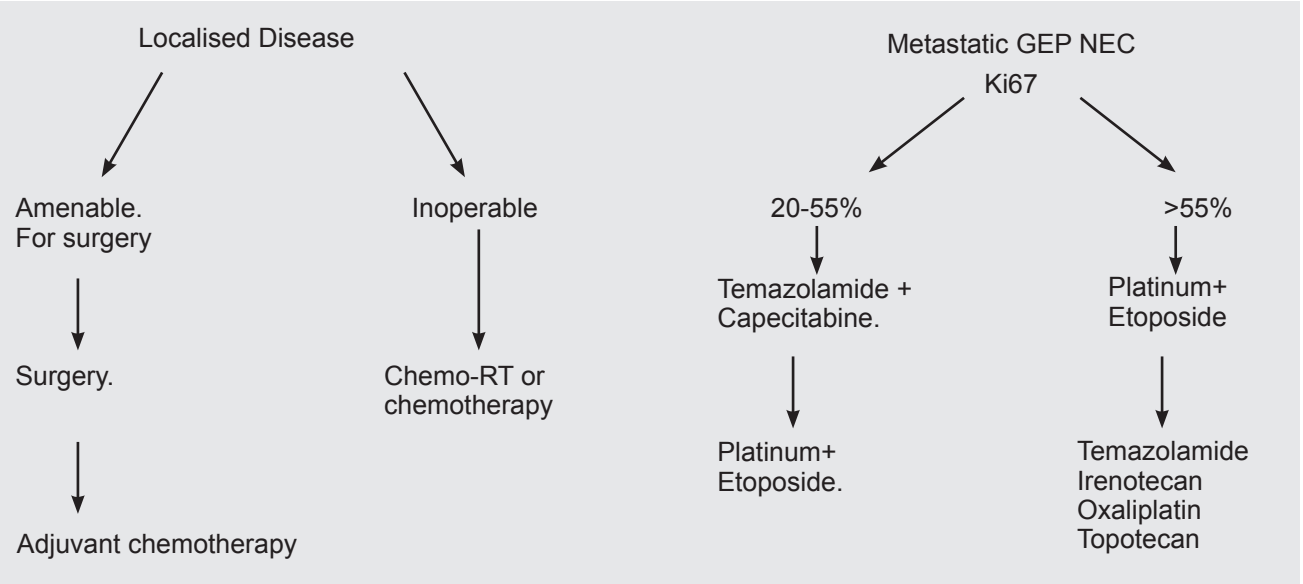
Craniospinal irradiation — Data on extrapulmonary poorly differentiated NECs suggest a low frequency of central nervous metastases (116), and prophylactic cranial irradiation PCI is not generally recommended, as it is for SCLC.

The initial treatment of metastatic GEP NEC is with a two-drug platinum-based regimen, generally cisplatin or carboplatin plus etoposide (120) as they have demonstrated objective response rates of 42-67%, median duration of response 8-9 months and a median survival 15-19 months (121, 122). An acceptable alternative is irinotecan plus cisplatin (123). Ironically, while patients with Ki-67 >55% demonstrated better response rates (42% vs 17%), they were noted to have a poorer overall survival (10 vs 14 months) as compared to patients with a Ki-67 index of <55% (124).

Relapsed or progressive disease

There is little data on second-line therapy (and no studies comparing chemotherapy versus best supportive care), and no standard regimen has been established. Patients who progress more than three months after discontinuation of first-line treatment may still be platinum-sensitive.

No standard cytotoxic chemotherapy regimen has been established beyond first-line treatment in platinum-refractory cases; however, several retrospective studies suggest that GEP NEC patients can benefit from further lines of chemotherapy after failure of platinum / etoposide treatment (111, 125-129). Temozolomide, irinotecan,Oxaliplatin and Topotecan have been tried in small cohorts of patients – Temozolomide is commonly used in the second-line setting, although reported clinical results are discrepant (125, 126, 128, 130-132). Capecitabine and Temozolomide in combination have shown to produce response rates up to 33% as well as disease stabilization rates of 71% in poorly differentiated endocrine carcinoma patients who failed on first-line chemotherapy (126). It was noted that a Ki-67 index <60% was predictive of response to treatment and survival (133).



Hormone therapy / SST analogues

SST analogues have been used to provide symptomatic relief to patients with NETs. In a recent review, Modlin et al. (134) analysed 15 studies using slow-release formulations of sandostatin and its long acting analogues such octreotide and Lanreotide, viz. Sandostatin LAR and Somatuline SR / Autogel. They noted that symptomatic relief was encountered in 74.2% and 67.5% patients and a biochemical response in 51.4% and 39% of patients receiving Sandostatin LAR and Somatuline SR / Autogel. The results of a recently concluded phase III trial (the CLARINET study [Controlled study of Lanreotide Antiproliferative Response In Neuro-Endocrine Tumors]) which enrolled patients with non-functional midgut and pancreatic GEP-NETs who were allocated to receive lanreotide Autogel (120 mg/28 days) versus placebo (135).

Octreotide LAR (PROMID trial (136)) was found not only to effect symptomatic and biochemical responses, but more importantly stabilize tumour disease as evidenced by lengthening of the time to tumour progression. In another study, patients with a proliferative index <10% displayed a better response to Octreotide LAR as compared to those with a higher index (137).

Promising results have been noted in early phase trials using a novel pan SST receptor analogue, Pasireotide (SOM230) (138). Studies are underway combining the use of SST analogues with newer agents.

In addition to the above two therapies, newer therapies have shown encouraging results. These therapies have been recently reviewed (139, 140) and hence only salient aspects will be discussed here.

Peptide receptor radionuclide therapy (PRRT)

PRRT is radionuclide (Lutetium-177 / ^{177}Lu or Yttrium-90)-labelled SST analogues treatment has been developed to managing metastatic, unresectable pancreatic NETs that express SST receptor 2. The rationale for this therapy involves receptor localisation and internalisation of the analogue (140) to permit the targeted delivery of radiation directly to the tumour cell. One of the most promising PRRTs is ^{177}Lu-DOTATATEThis has been tested in patients with inoperable or metastasized pancreatic NETs (141, 142). Complete and partial tumour remission occurred in 2% and 28% of patients (142). Complications encountered with the use of PRRT include nausea and vomiting, haematological, myelodysplastic, renal and hepatic toxicities (139, 142) and is contraindicated in in patients with poor renal function (139). Overall, however, this therapy has the advantage of being very well tolerated delivered in a convenient schedule of 3 monthly cycles. Despite this, ^{177}Lu-DOTATATE compares favourably with the limited number of alternative therapeutic approaches (143). The benefit of this therapy remains investigational at the current time. The recently published NETTER trial (144) has demonstrated treatment benefit with ^{177}Lu-Dotatate, documentingin markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors. Also, preliminary evidence of an overall survival benefit was seen in an interim analysis in this study.

CHAPTER

8 SUPPORTIVE CARE

WHO definition : "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" . This is aimed at the comfort of the patient in all possible scenarios. Patients should receive physical, psychological, spiritual and social support if feasible. Quality of life should be the main focus of care. Care to be offered for each suffering by a multi professional team in the hospital, home or hospice – the choice of patient and family in concurrence with treating physician.

Goals:

- Relief from suffering
- Treatment of pain and other distressing symptoms
- Psychological and spiritual care
- Support system to help the patient live as actively as possible
- Support system to sustain and rehabilitate the patients family

Aims:

- Provides relief From pain, shortness of breath, nausea and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor to postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible
- Offers a support system to help the family cope
- Uses a team approach to address needs of patients and their families
- Will improve quality of life
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy.

PHYSICAL
Pain , Nausea and vomiting, Constipation, Dysponea, Bowel Obstruction
Fungating wounds

SOCIAL
Financial, education, job, social environment eg neighbours

HOLISTIC SUFFERING

PSYCHOLOGICAL
-Stage of Grief
(Denial, anger, bargaining, depression, acceptance)
-Helpless, hopeless, lack of self worth, despair
-Family collusion

SPIRITUAL
-Why me?
-Meaning of disease
-What is next?

Psychological care

Psychological care and emotional support are extremely essential part of palliative care. It offers a support system to help patients live as actively as possible until death and help the family cope during the patient's illness and in their own environment.

Principle guidelines for psychological care in palliative care are:

- At time of initial consultation assess- Psychological wellbeing, reactions to current losses, support system and coping of patients and caregivers Privacy and confidentiality should be maintained at all times.
- Assessment will include mood, feelings, concerns, family relationship, social support, impact of illness on day to day life and work.
- Patient and caregivers both should be evaluated during assessment
- All staff are directly responsible for patient care and should offer general emotional support based on skilled communication, effective information provision, genuineness and respect
- Psychological support should be provided through intimate care and positive communication skills during the difficult situations
- Need based interventions should be planned for e.g. from self help to specialized psychological interventions for patients
- Patients and caregivers with significant level of psychological distress and premorbid psychiatric issues should be referred to specialist psychiatric services promptly
- Psychological needs and problems of the staff caring for patients should be explicitly assessed and adequately met to improve quality of care.

Social care :

On-going Psycho Social Assessment is fundamental need in palliation to assess emotional, social, economic status of patients and families to help them sustain in advanced phase of the cancer.

Interventions:

- Facilitating respite care (if feasible): counselling, telephonic help and providing material and emergency aid such as free medicines, monthly ration, education fees of dependents, fulfilling last wishes of children and providing stay and food while patient is on short duration medical interventions like radiotherapy.
- Advocacy and referral networks: address economic and existential concerns of families when patient is a primary income source in his family; link families with local resources and various schemes of government
- Empowering and educating families: helping them combat fear of contagion, stigma and isolation.
- Community Outreach: Creating awareness amongst Medical and Paramedical health professionals at grass root level.

CHAPTER 9

FOLLOW-UP AND SURVIVORSHIP

Follow-up schedule after surgery / chemotherapy

Year	Time from start of chemotherapy (months)	Clinical examination	Elevated tumour marker levels, CgA or 24 hour urine 5-HIAA	CT CAP	Discharge
0	0	✓	✓	✓	
1	3	✓	✓		
	6	✓	✓		
	9	✓	✓		
	12	✓	✓	✓	
2	18	✓	✓		
	24	✓	✓	✓	
3	30	✓	✓		
	36	✓	✓	✓	
4	48	✓	✓		
5	60	✓	✓		✓

Advanced NEC

- Following completion of chemotherapy or PRRT, review every 3 months (may be extended if the patient is stable)
- Measure the serum chromogranin A / urine 5-HIAA level (whichever is elevated at diagnosis) at each clinic visit
- No routine imaging is indicated, unless symptom driven
- Consider CT / Octreoscan if signs/symptoms suggest disease progression or increasing tumour marker levels
- Ensure that all patients receive palliative care support if possible (desirable)
- If no further treatment can be offered following evidence of disease progression, the patient should be discharged from the clinic with adequate psychological/palliative support, if possible.

CHAPTER

10 PALLIATIVE CARE

Palliative care is aimed at providing comfort to the patient in all possible scenarios. Patients should receive physical, psychological, spiritual, and social support, if feasible. Quality of life should be the main focus of care. Care should be offered for each type of suffering by a multidisciplinary professional team in the hospital, home, or hospice, depending on the choice of the patient and family in concurrence with the treating physician.

CHAPTER

11 RESEARCH AVENUES

Service

National Neuroendocrine Cancer Registry

Survival outcomes – 1-year and 5-year survival data

Education

- Training and credentialing of surgeons, pathologists, radiologists, medical oncologists, and radiation oncologists in site-specific areas
- Interventional radiology training

CHAPTER

12 APPENDIX

A. Pathology reporting of gastroentero-pancreatic neuroendocrine tumours (GEP-NETs)

Pathology report should include essential, reproducible and uniform information that provides correct diagnosis and allows accurate decision-making by a multidisciplinary team.

The essential components that form the core data items of a pathology report of GEP-NETs include:

Macroscopic data:

1. Site of tumour
2. Tumour size
3. Tumour multi-centricity
4. Tumour perforation
5. For rectal NETs tumours, additionally-
   a) Relationship to the peritoneal reflection
   b) Distance from dentate line
6. Distance of tumour from resection margins-longitudinal cut-end margins and circumferential resection margins (CRM)

Microscopic data:

1. Histologic type

   -include immunohistochemistry for neuroendocrine markers (if performed)
2. Grade (specify grading system used)
3. Mitotic rate (per 10 high-power fields (HPF) or $2mm^2$, counted in 50 HPFs in the most mitotically active regions)
4. Extent of invasion/ microscopic tumour extension
5. Presence of vascular emboli
6. Presence of perineural invasion
7. Resection margins (longitudinal cut-end margins and CRM)
8. Lymph node- includes total number examined and total metastatic nodes
9. Pathologic TNM staging, UICC/AJC TNM 7^{th} edition

10. Ki-67 labeling index

11. Background abnormalities or proliferative changes in the adjacent non-neoplastic tissues

Brief Notes

Nomenclature

A unified term of 'gastroentero-pancreatic neuroendocrine tumours (GEP-NETs)' has replaced the previous terminology of carcinoid tumours for all NETs of GIT, including those of the pancreas. This has been due to concerns of undermining of NETs malignant potential by the usage of carcinoid term.

In general, NETs are stratified into well-differentiated and poorly-differentiated categories. Differentiation and grading, predominantly convey similar information, however, harbour subtle conceptual differences. While differentiation refers to the extent to which a tumour resembles its non-neoplastic counterparts, grading reflects the inherent biologic aggressiveness of the tumour. With the new WHO 2017 classification, the term 'tumour' is used to describe well differentiated tumours (that include grade 1, grade 2 and grade 3) while poorly differentiated morphology, with either small cell or large cell morphology are applied with the term 'carcinoma' for pancreatic NET (56).

Nomenclature can be also based on the functionality of tumour that results in a clinical syndrome, such as insulinoma, gastrinoma, glucagonoma.

Tumour size

Tumour size should be recorded in all three dimensions. This is best measured after serial slicing of the tumour. If multiple tumours are present, dimensions of all tumours should be recorded.

Tumour multicentricity

Presence of solitary or multiple tumours should be recorded. Multiple tumours may, albeit not always, signify an underlying syndrome.

Tumour perforation

Tumour perforation is defined as a macroscopically visible defect through the tumour. Notably, perforation of the proximal intestine as a secondary outcome of a distal obstructing tumour is not regarded as tumour perforation

Histological type

Histologic types include either a pure NET or a mixed adeno-neuroendocrine carcinoma (MANEC).

Histologic type is classified as:

1. Well-differentiated NET (grade 1)
2. Well-differentiated NET (grade 2)
3. Poorly differentiated NEC (includes small cell carcinoma and large cell neuroendocrine carcinoma) (grade 3)
4. Mixed adenoneuroendocrine carcinomas (MANEC): includes tumours consisting of both adenocarcinoma and neuroendocrine carcinoma components, with each component accounting for at least 30% of the tumour.
5. Goblet cell carcinoid: is an appendiceal neoplasm (distinct from MANEC) composed of glands with cells containing intra-cytoplasmic mucin and scattered neuroendocrine cells. These tumours can

infrequently transform to a higher grade carcinoma wherein they are referred to as carcinoma ex-goblet cell carcinoid. The presence of higher grade carcinoma in the form of poorly differentiated adenocarcinoma, signet ring cell adenocarcinoma or undifferentiated carcinoma in a goblet cell carcinoid should be looked for and documented when identified.

IHC of Neuroendocrine lineage markers: Commonly used IHC markers to identify NETs include:

1. Synaptophysin (as a small vesicle antigen),
2. CgA (as a component of neurosecretory granules)
3. CD56 (neural cell adhesion molecule [N-CAM])
4. Protein gene product (PGP-9.5)
5. NSE

IHC for confirming diagnosis

IHC may not be required in resected specimens if histology is typical. However, it is very useful in most biopsy specimens to confirm the neuroendocrine nature of the tumour cells. In well differentiated NETs, role of IHC markers is adjunctive and helps to reinforce histologic diagnosis. In poorly differentiated NETs, IHC is essential to confirm neuroendocrine lineage of tumour cells and exclude other differential diagnoses.

A minimum of two IHC markers is recommended to confirm neuroendocrine lineage.

Adequate quality assurance must be ensured and optimal controls must be employed when interpreting IHC results.

IHC of specific hormones

Using IHC, a large assortment of peptide hormones (somatostatin, gastrin, insulin, serotonin, pancreatic polypeptide, vasoactive intestinal peptide etc.) can be detected in the tumour cells, although their expression can be very variable and is dependent on the cell type, site of origin and grade/ differentiation of the tumour. These can be performed to confirm the source of a clinical symptomatology. However, IHC expression and tumoural hormone secretion need not go hand in hand; there may be IHC expression without secretion or vice versa. High-grade tumours may be devoid of immunoreactivity for any peptide hormone. Although IHC for specific hormones may provide additional prognostic information, its benefit beyond that provided by the WHO grading and staging is not clear. Maintaining panels of multiple NET hormones and their quality assurance has not been found to be cost effective. Therefore, routine use is not justified or recommended although it may be performed if clinically essential, for instance to determine the relevant tumour causing a clinical syndrome.

IHC for site of primary tumour

In the metastatic setting, IHC can give clues to the site of primary tumour. CDX-2 for intestinal, PDX1 or Islet-1 for pancreatic, TTF-1 (thyroid transcription factor 1) for lung/thyroid can be of use in metastatic lesions (145).

IHC for grading

Immunohistochemistry for Ki-67 (MIB-1) is mandatory to grade the tumour according to the WHO 2010 classification. IHC for Ki67 (MIB1), a cell cycle proliferation antigen, is detectable as nuclear stain and is routinely used for assessing tumour grade (see **Grading** section).

IHC for prognostication

A number of markers (CK19, CD99 etc.) have been investigated, however currently, these are utilised in a research setting and are not recommended for routine use.

Organ specific NETs

Gastric NETs differ from other NETs and are divided into several subtypes, depending on the etiology and background pathology (Table 1) (146-148). Typing of gastric NETs has important implications in prognosis and treatment of these tumours.

Table 1. Gastric NET classification (146-148)

Features	Type 1	Type 2	Type 3	Type 4
Proportion	80%	5-10%	15-20%	Rare
Associated condition	CAG	ZES/MEN1	Sporadic	Sporadic
Site	Fundus/body	Fundus/body	Anywhere	Anywhere
Plasma gastrin levels	Elevated	Elevated	Normal	Normal
Tumour multiplicity	Multiple	Multiple	Solitary	Solitary
Tumour size	<1-2 cm	<1-2 cm	2-5 cm	2-5 cm
Histology	Well differentiated	Well differentiated	Well differentiated	Poorly differentiated
Grade	G1	G1	G2	G3
Background pathology	Atrophy; ECL hyperplasia/ dysplasia	Hyperplasia of parietal and chief cells; ECL hyperplasia/ dysplasia	None	None
Prognosis	Good	Good (but metastasis in 10-20%)	Poor	Very poor

Abbreviations: CAG- Chronic atrophic gastritis; ZES- Zollinger Ellison syndrome; MEN1- Multiple endocrine neoplasia type-1, G1-grade 1; G2-grade 2; G3-grade 3; ECL- Enterochromaffin-like cell

Regarding duodenal NETs, occurrence as sporadic or in a background of a syndrome, MEN1, NF1 etc., should be recorded. Duodenal somatostatinomas are typically glandular and may be mistaken for an adenocarcinoma. Psammoma bodies in somatostatinomas, when present, are a useful clue to their neuroendocrine nature. IHC should be used to distinguish NET from adenocarcinoma in such cases.

Most small intestinal NETs arise in the distal ileum and about 25-40% are multiple; latter feature is associated with worse prognosis.

Grading

Grade of a tumour refers to its biologic aggressiveness. is a reliable measure of tumours aggressiveness. According to WHO 2010 classification, grading is based on the tumour proliferative rate which in turn is assessed by evaluating the mitotic count and Ki-67 index in histologic material (2). The WHO system has adopted the grading system provided by the European Neuroendocrine Tumour Society (ENETS) (45, 46). Grade 1 (G1) and grade 2 (G2) NETs are generally well-differentiated and show diffuse and strong positivity for neuroendocrine IHC markers. Focal necrosis in a well differentiated tumour maybe a clue to a higher grade - G2, which however has to be confirmed by the mitotic count and Ki-67 staining. Grade

3 (G3) indicates a poorly differentiated neuroendocrine carcinoma. Notably, term 'carcinoma' is used for G3 tumours in contrast to G1-2 tumours in the WHO grading system. G3 tumours display reduced or absent staining for CgA while synaptophysin reactivity is maintained. High mitosis, necrosis and high Ki-67 labeling are typical for G3 tumours.

In the pathology report, the mitotic count and/or Ki-67 and the grade should be mentioned. The grading system applied should also be specified in parenthesis.

In WHO 2017 (56) grading, the G3 pancreatic tumors are labelled as WD NET and PD NEC, based on the histological differentiation and it has prognostic significance.

Table 4. G3 NETs vs G3 NECs.

G3 NET	G3 NEC
MEN1,DAX, ATRX mutations	P53, RB1 mutations
Recognisable as NETs	Small cell or Large cell type
Often evolve from a recognisable lower grade component	No lower grade component
Usually Ki67 < 40 to 55%, Mitotic count < 20/10HPF	Usually Ki67>55%

Mitotic index is defined per 10 HPF. For the evaluation of mitotic count in 10 HPF or 2 mm^2 (based on each HPF being 0.2 mm^2), scanning of at least 50 fields (at 40 magnification) in the areas with the highest mitotic density is required, in accordance with the WHO classification (2).

Ki-67 index is calculated as the percentage of Ki-67 positive tumour cells in the areas of the highest density of Ki-67 positive cells, also referred to as "hot spots." Eyeballed estimate for hot spots is adequate. To evaluate the Ki-67 index, 2000 tumour cells are counted in the hotspot areas (2). In some cases, Ki-67 staining on different and multiple slices is useful for accurate Ki-67 index evaluation.

For Ki-67 index, evaluation is best done on primary tumour. In cases where primary tumour tissue is not available, metastatic tumour can be assessed. The Ki-67 index may be evaluated for metastases too, depending on local policy; however there is not enough evidence to indicate that this is mandatory if primary tumour is available. .

When the amount of tumour tissue is limited (biopsy material or metastatic site), it may not be possible to give an accurate mitotic count. In these cases, Ki-67 index provides a more accurate reflection of tumours proliferative rate than mitotic count.

In case, there is discordance between Ki-67 index and mitotic count on the resection specimen, the worst of the two indices should be incorporated for grading.

Pathologic Staging

The TNM staging (7th edition) for NET is done in accordance with the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC); this incorporates input from the primary tumour (T), lymphnode involvement (N), and distant metastasis (M) (19). The pT stage differs with site of tumour and is based on the tumour size and extent of local invasion; pN is staged after evaluating adequate number of removed lymph node for metastasis, and pM implies microscopic confirmation of distant lesions

Well differentiated neoplasms are staged separately by site; while large cell/ small cell neuroendocrine carcinomas and pancreatic NET are staged as carcinomas of the same site in the TNM 7th edition (19).

American Joint Committee on Cancer/TNM 7th edition (19): T staging for NET

Stomach

Primary Tumour (T)

- **TX** Primary tumour cannot be assessed
- **T0** No evidence of primary tumour
- **Tis** Carcinoma in situ/dysplasia (tumour size less than 0.5 mm), confined to mucosa
- **T1** Tumour invades lamina propria or submucosa and 1 cm or less in size
- **T2** Tumour invades muscularis propria or more than 1 cm in size
- **T3** Tumour penetrates subserosa
- **T4** Tumour invades visceral peritoneum (serosal) or other organs or adjacent structures

Duodenum/Ampulla/Jejunum/Ileum

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 or less* (small intestinal tumours); tumour 1 cm or less (ampullary tumours)
- **T2** Tumour invades muscularis propria or size > 1 cm (small intestinal tumours); tumour > 1 cm (ampullary tumours)
- **T3** Tumour invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumours) or invades pancreas or retroperitoneum (ampullary or duodenal tumours) or into non-peritonealized tissues
- **T4** Tumour invades visceral peritoneum (serosa) or invades other organs For any T, add (m) for multiple tumours

* Note: Tumour limited to ampulla of Vater for ampullary gangliocytic paraganglioma

Colon or Rectum

Primary Tumour (T)

- **TX** Primary tumour cannot be assessed
- **T0** No evidence of primary tumour
- **T1** Tumour invades lamina propria or submucosa and size 2 cm or less
- **T1a** Tumour size less than 1 cm in greatest dimension
- **T1b** Tumour size 1–2 cm in greatest dimension
- **T2** Tumour invades muscularis propria or size more than 2 cm with invasion of lamina propria or submucosa
- **T3** Tumour invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues

- **T4** Tumour invades peritoneum or other organs For any T, add (m) for multiple tumours

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

Appendiceal Carcinoid

Primary Tumour (T)

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

Note: Tumour that is adherent to other organs or structures, grossly, is classified cT4. However, if no tumour is present in the adhesion, microscopically, the classification should be classified pT1-3 depending on the anatomical depth of wall invasion.

*Penetration of the mesoappendix does not seem to be as important a prognostic factor as the size of the primary tumour and is not separately categorized.

ANATOMIC STAGE/PROGNOSTIC GROUPS

- **Stage I** T1 N0 M0
- **Stage II** T2, T3 N0 M0
- **Stage III** T4 N0 M0, Any T N1 M0
- **Stage IV** Any T Any N M1
- **pTNM Pathologic Classification**. The pT, pN, and pM categories correspond to the T, N, and M categories except that pM0 does not exist as a category.
- **pN0**. Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Pancreatic

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 or less in greatest dimension
- **T2** Tumour limited to the pancreas, more than 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)

* This also includes the "PanInIII" classification.

ANATOMIC STAGE/PROGNOSTIC GROUPS

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

Lymph nodes (N) (the same for all primary sites)

pNX- Regional lymph node status cannot be assessed

pN0- No regional lymph node metastasis

pN1- Regional lymph node metastasis*

* N1 indicates the presence of any single or multiple metastases in any lymph node group. Data on the prognostic significance of individual metastatic lymph nodes is lacking, hence is not incorporated in the TNM 7.

All of the lymph nodes dissected must be examined histologically. Serial sections, IHC or molecular techniques are not recommended for routine use on nodes negative on light microscopy.

Distant Metastases (M)

- **M0** No distant metastases
- **M1** Distant metastasis

TNM Descriptors

Prefixes and suffixes are used to identify the setting of TNM staging. Prefixes used include:

- "y"- cases in which classification is performed during or following initial multimodality therapy (ie,

neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy).

- "r"- indicates a recurrent tumour when staged after a documented disease-free interval
- "a"- designates the stage determined at autopsy
- Suffix used is:
- "m" -indicates the presence of multiple primary tumours in a single site and is recorded in parentheses: pT(m)NM.

Resection Margins

Complete resection is a strong determinant of overall survival and prognosis. Tumours are classified as R0 when margins are completely free of tumour microscopically, R1 when margins are involved microscopically but free macroscopically, and R2 when margins are involved macroscopically.

For luminal tumours, margins include: doughnuts (when submitted for evaluation), longitudinal cut-ends and CRM (in low rectal tumours located at or beneath the peritoneal fold). The CRM corresponds to the adventitial soft tissue margin closest to the deepest penetration of tumour and is a surgical margin created by sharp or blunt dissection. Assessment of CRM is necessary for any segment of GIT which is not encased (completely or incompletely) by peritoneum. The distance between the tumour and CRM should be recorded. The CRM is considered as positive if tumour is located 1 mm or less from the non-peritonealized surface.

For enucleation procedures, the outer surface/periphery of the resection specimen should be inked. Distance of the tumour to the outer surface/margin is measured and 'radial' sections i.e. sections perpendicular to the outer inked surface/margin are taken for examination microscopically.

For partial pancreatectomy/ PD specimens, closest distance of the tumour to pancreatic parenchymal resection margin and to the CRMs (anterior, posterior, SMA and SMV margins) is evaluated. (For detailed evaluation, please refer to section grossing of pancreatic resection specimens).

For endoscopic resection specimens, margins include mucosal margins and the deep margin/base of resection. Distances from margins should be recorded. Margins should be marked by ink (different colored inks, if more than one margin is included in a single section) and appropriately recorded in the macroscopic description.

Background abnormalities

The presence of relevant pathological abnormalities in the background tissue should be recorded, for instance- intestinal metaplasia, gastric mucosal atrophy, ECL hyperplasia, microadenoma and synchronous tumours(s).

Sampling

The following sections of tissue are recommended as a minimum sampling:

1) 4 sections, at least, of the tumour to document:

- the deepest tumour penetration into or through the organ wall
- involvement of serosa
- involvement of any adjacent organs

- vascular or perineural invasion
- mitotic rate and Ki-67 index

2) One section each to show the closest distance of tumour to:-
   - proximal and distal margins
   - CRM (wherever applicable)
   - Mucosal margins or base (in endoscopic resections)
   - Capsule/outer surface (enucleation specimens)
3) Section of the adjacent mucosa/parenchyma
4) Sections of all lymph nodes (dissected and separately sent)

A. Patient Preparation and Procedure and doasging

[a] SST analogue withdrawal: A 4 weeks withdrawal for long-acting SST analogues (LAR formulations) and of at least 24 h for short-acting preparations are advised before PRRT to minimize competitive inhibition by the cold formulations and maximize radiopharmaceutical targeting. In a highly symptomatic patient (carcinoid syndrome), a long-acting release formulation is substituted by a short-acting formulation 1 month prior to therapy (149).

[b] Renal protection by Amino acid based protocols

Renal uptake of radiolabelled SST analogues has been attributed to the receptor-mediated endocytic renal transporter system involving megalin-mediated cubilin-dependent endocytosis across the proximal epithelium. This Megalin-cubulin pathway based proximal tubular reabsorption of the radiopeptide leads to renal irradiation and potential nephrotoxicity. This is more pronounced in 90Y based PRRT owing to its harder beta energy (there is a report of creatinine clearance loss of about 3.8 % per year for 177Lu-DOTATATE and 7.3 % per year for 90Y-DOTATOC) (149).

To counteract this, positively charged amino acids (l-lysine and/or l-arginine; 25 g of each amino acid in 2 litres of normal saline), are coinfused to competitively inhibit the proximal tubular reabsorption of the radiopeptide. In many settings, where pharmaceutical grade combination of both amino acids is not available, mixed amino acid infusion is used for nephroprotection with good results (149).

While several protocols of amino acid co-infusion have been used (such as single day to 3 day protocols with varying combinations including addition of plasma expander Gelofusine, a succinylated bovine gelatin molecule), the single day protocol has been most adopted for its easy adaptability in a busy setting.

[c] Antiemetic regimen:

Hyperemesis consequent to metabolic acidosis due to amino acid infusion is a frequent occurrence during PRRT procedure (149). Traditional antiemetics such as 5-HT3 antagonist (ondansetron) alongwith a corticosteroid (e.g. dexamethasone) manages this well. In patients with sever hyperemesis, addition of oral Aprepitant, an NK1 antagonist has been very effective in controlling the condition.

[d] Radiopharmaceutical administration and regimen: Using the other hand, the radiopharmaceutical is administered over 20 to 30 min via an indwelling catheter to ensure safe intravenous administration; special care needs to be taken to prevent paravascular infiltration (149).

How many cycles; What dose?

^{177}Lu-DOTATATE / ^{177}Lu-DOTATOC

Standard fixed dose regimen constitutes administered activity of 5.55–7.4 GBq (150–200 mCi) each cycle; total number of cycles: three to five; time interval between cycles: 6–12 weeks (most Indian settings use 12 weeks except for Neoadjuvant setting where the cycles are administered more frequently) (149).

^{90}Y-DOTATATE / ^{90}Y-DOTATOC

Typically, 2.78–4.44 GBq (75–120 mCi) are administered every cycle for 2-4 such cycles at an interval of 6–12 weeks (149).

Tandem therapy of 177Lu-DOTATATE in combination with Y-90 DOTATOC

While these have been used on trial basis in a few centres, there is need for further data before can be recommended.

A trial from Italy (150) reported 26 patients with metastatic NET were treated with four therapeutic cycles of alternating [(177)Lu]DOTA-TATE (5.55 GBq) and [(90)Y]DOTA-TATE (2.6 GBq). induced objective responses in 42.3 % of patients with metastatic NET with a median progression-free survival longer than 24 months.

In another study from Poland (151), fifty patients with disseminated NET were included prospectively and divided into two groups: group A (n = 25) was treated with 90Y-DOTATATE, whereas group B (n = 25) received the 1:1 90Y/177Lu-DOTATATE. Overall survival was significantly higher in group B (p = 0.027). Median event-free survival time in group A was 21.4 months and in group B 29.4 month. However, these initial results in a couple of reports need further exploration in the future.

[e] Radiation Protection Instructions during Discharge from Isolation Ward

While discharging the patients (typically next day in Indian setting), the standard radiation protection measures are advised to the patients are asked to avoid contaminating other persons using the same toilet facilities. Some important instructions are: (i) double toilet flush after urination, (ii) washing handsafter urination, (iii) if contaminated with urine, washing with abundant cold water without scrubbing , (iv) avoidance of soiling underclothing or areas around toilet bowls for 1 week following therapy, (v) washing/discarding the contaminated clothing, (vi) instruction regarding gloves and protective clothing for persons caring for catheterized patients. These are particularly important in the first 2 days when high levels of activity excretion in the urine are of particular concern (149).

Side effects

One of the strong points of 177Lu-DOTATATE PRRT is extremely well-tolerability and excellent safety record. Acute side effects such as nausea, headache and rarely vomiting due to metabolic acidosis induced by the amino acid co-administration are easily managed with standard antiemetics as mentioned before. The delayed side effects include renal toxicity (mainly noticed with 90Y-based PRRT) and bone marrow toxicity (2–3 % of cycles with 177Lu-DOTATATE; 10–13 % of treatment cycles with 90Y-DOTATOC) (152-154).

CHAPTER

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CHAPTER

14 ABBREVIATIONS

AAR	Age-adjusted incidence rate
AJCC	American Joint Cancer Committee
APNETS Society	Asia-Pacific Neuroendocrine Tumour
ASA	American Society of Anaesthesiologists
BD	Twice daily
BMI	Body mass index
BSC	Best supportive care
CAPOX	Capecitabine and oxaliplatin
CDK	cyclin-dependent kinase
CECT	Contrast-enhanced computed tomography
CF	Cisplatin and 5-FU
CgA	Chromogranin A
CI	Confidence interval
CRT	Chemoradiotherapy
CT	Computed tomography
CTV	Clinical target volume
DOTA-NOC	1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid - 1-Nal3-octreotide
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMR	Endoscopic mucosal resection
ENETS	European Neuroendocrine Tumour Society
EUS	Endoscopic ultrasonography
5-FU	5-Fluorouracil
FDG	Fluoro-deoxyglucose glucose
FNA	Fine needle aspiration
GEP-NET	Gastroenteropancreatic neuroendocrine tumours
GI	Gastrointestinal
Gy	Gray
GOO	Gastric outlet obstruction
5-HIAA	5-hydroxy-indole acetic acid
HPF	High-power field
ICMR	Indian Council of Medical Research
IHC	Immunohisotchemistry
IV	Intravenous
LVEF	Left ventricular ejection fraction
MDCT	Multi-detector computed tomography
MEN	Multiple endocrine neoplasia
MRI	Magnetic resonance imaging
mTOR	mammalian target of Rapamycin
MUGA	Multi-gated acquisition scan
NACT	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NET	Neuroendorcine tumour
NEC	Neuroendocrine Cancer
NSE	Neuron specific enolase
OD	Once daily
PD	Pancreatoduodenectomy
PET	Positron emission tomography
PFS	Progression-free survival
pNET	Pancreatic neuroendocrine tumour
PO	Per oral
PPI	Proton pump inhibitor
PRRT	Peptide radionuclide receptor therapy
PS	Performance status
QDS	Four times a day
RR	Relative risk
SC	Subcutaneous
SEER	Surveillance, Epidemiology, and End Results Program
SPECT	Single photon emission computed tomography
SST	Somatostatin
SSTR	Somatostatin receptor
TDS	Thrice daily
ULN	Upper limit of normal range
VIP	Vasoactive intestinal peptide
WHO	World Health Organization

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