



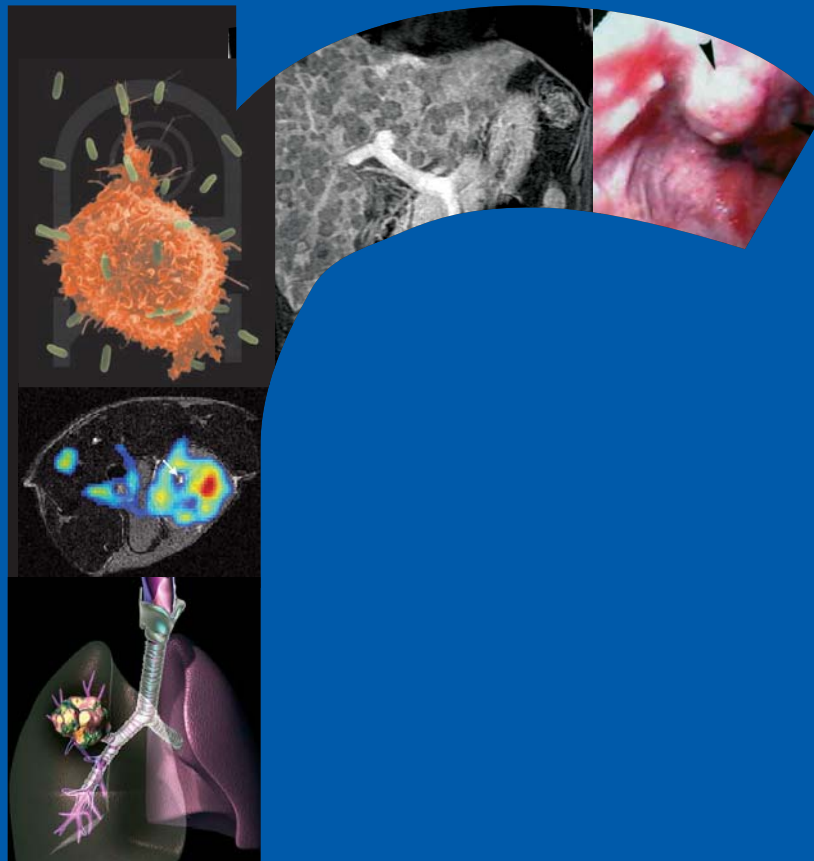
ISSN 0973-9653

CANCER NEWS

VOL 5

NO 6

FEBRUARY 2012



**RAJIV GANDHI CANCER INSTITUTE AND
RESEARCH CENTRE**

Website: www.rgci.org

From the Desk of Director Research

Pancreatic cancer, a “silent disease”, is notoriously difficult to diagnose in its early stages, when it is a protean disease that can be difficult to distinguish from other much more common disorders. It is the most lethal type of digestive cancer with a 5-year survival rate of 5%, making it one of the 4 or 5 most common causes of cancer mortality in developed countries. Although infrequent, it has a very poor prognosis and incidence varies greatly across regions, which suggests that lifestyle factors, such as diet, and environmental factors, like vitamin D exposure, play a role. Because pancreatic cancer is strongly age-dependent, increasing population longevity and ageing will lead to an increase of the global burden of pancreatic cancer in the coming decades. Smoking is the most common known risk factor, causing 20-25% of all pancreatic tumors. Many factors associated with the metabolic syndrome, including overweight and obesity, impaired glucose tolerance, and long-standing diabetes also increase the risk, while atopic allergy and use of metformin as a treatment for diabetes have been associated with a reduced risk of pancreatic cancer. A family history of pancreatic cancer is associated with an increased risk of pancreatic cancer and it is estimated that 5-10% of patients with pancreatic cancer have an underlying germline disorder.

Pancreatic cancer is a disease caused by the accumulation of genetic alterations in specific genes. Elucidation of the human genome sequence, in conjunction with technical advances in the ability to perform whole exon sequencing, have provided new insight into the mutational spectra characteristic of this lethal tumour type. Although there has been progress made in chemotherapeutic strategies against pancreatic cancer, the overall survival has not significantly improved in the last decade. Recently, development of chemotherapy in combination with molecular targeted therapies hold great promise in pancreatic cancer treatment, especially in patients with metastatic disease. Growing bodies of preclinical and clinical evidences indicate that the combination of conventional modalities with specific molecular targeted therapy increase the efficacy of the monotherapy without an increase in toxicity.

We need to improve our knowledge on pancreatic cancer cells, relationships between tumoral, endothelial and stromal cells, and pancreatic cancer patients. Perhaps it is more important to target our therapy by identifying those patients who are most likely to derive benefit and achieve meaningful responses. This is particularly crucial in a disease, such as pancreatic cancer, that has such a short life expectancy that the “window” for any given treatment may be quite small. Consequently, further studies should include the development of more predictive assays and improved exploitation of surrogate biomarkers of response.

The present issue of Cancer News includes regular articles under the section “Special Feature”, “Perspective”, “Research & Development”, “New Technology”, “Clinical Trials”, “Watch Out” and “Globe Scan”.

The Institute gratefully acknowledges the intellectual support from Dr P Jagannath, Chairman, Department of Surgical Oncology, Lilavati Hospital, Mumbai for providing the “Guest Article” on ‘Update on Neuroendocrine Tumors’.

Dr D C Doval

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Printed and Published by: Rajiv Gandhi Cancer Institute & Research Centre,
Sector - 5, Rohini, Delhi - 110 085
Printed at: Sagar Printers & Publishers, 1880 Udaichand Marg, Kotla Mubarakpur, New Delhi - 03

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SPECIAL FEATURE

NEUROENDOCRINE TUMORS OF PANCREAS – AN OVERVIEW

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) comprise a group of rare neoplasms arising from the neuroendocrine system of the gut (Fig 1). The annual incidence is estimated at 1–4 in 100,000, showing a trend of a higher incidence over recent decades. GEP-NETs are classified as “functional” (F-NETs) or “nonfunctional” (NF-NETs) based on the presence or absence, respectively, of a specific clinical syndrome associated with hormone oversecretion. Hormone secretion, however, does not uniformly result in a clinical syndrome, for example, as in the case of pancreatic polypeptide (PP) secretion. GEP-NETs may have benign, uncertain, or malignant behavior. Furthermore, they may arise sporadically or be associated with genetic syndromes, for example, multiple endocrine neoplasia type 1 (MEN-1). Pancreatic neuroendocrine tumors (PNETs) are a subgroup of GEP-NETs and are rare pancreatic neoplasms, compared to common exocrine counterparts. It is estimated that 3% of primary pancreatic neoplasms are PNETs. The overall prognosis and long-term survival for PNET patients is far better than for patients with exocrine pancreatic cancer. The overall 5-year survival rate is 30% in NF-PNETs to 97% in insulinoma.

Origin

The true cell or cells of origin of PNETs are not fully understood. It is hypothesized that these arise from neuroendocrine stem cells located in pancreatic ductules from which pancreatic islet cells arise. Each pancreatic

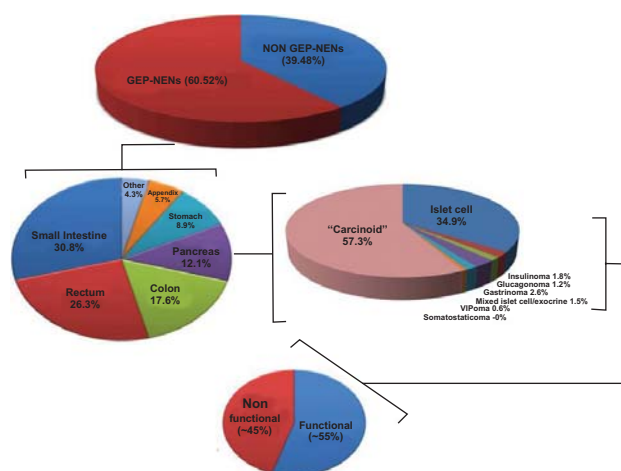


Fig 1: Distribution of various neuroendocrine tumors

endocrine cell type could give rise to a PNET. Additionally, PNETs may rarely produce nonpancreatic hormones ectopically. Hormone producing PNETs (Table 1) can be divided into: (a) common types, that is, insulinoma (17%) and gastrinoma (15%), and (b) rare functional tumors, VIPoma (2%), glucagonoma (1%), carcinoids (serotonin, 1%), somatostatinoma (1%), and exceedingly rare neoplasms like PPoma, ACTHoma, GRFoma, calcitonin producing tumors, and others.

Classification and Prognosis

WHO introduced a histological classification system for GEP-NETs (including PNETs) in 2000. TNM staging when applied to PNETs, also provides survival discrimination by stage for surgical and nonsurgical patients. Nonetheless, the factors associated with long-term survival after resection of PNETs remain controversial. In a recently conducted multivariate analysis of long-term survival on the largest cohort of patients (3,851) after PNET resection reported to date, it was found that factors adversely affecting survival were age (>55 years),

Table 1: Summary of PNET Characteristics

Tumor (Secreted Product)	Clinical Presentation	Pancreatic Localization (%)	Malignancy (%)
Insulinoma (insulin)	Whipple's triad ^a	>97	<10
Gastrinoma (gastrin)	Zollinger-Ellison syndrome ^b	25-60	60-90
VIPoma (vasoactive intestinal polypeptide)	Verner-Morrison syndrome ^c	>90	40-70
Glucagonoma (glucagon)	Glucagonoma syndrome ^d	>95	50-80
Somatostatinoma (somatostatin)	Somatostatinoma Syndrome ^e	55	>70
GRFoma (growth hormone releasing factor)	Acromegaly	30	>60
ACTHoma (ACTH)	Ectopic Cushing syndrome	4-16	>95
Carcinoid (serotonin/?)	Carcinoid syndrome ^f	1.4 to 7.9	60-80
PTH-related peptide-producing NET (PTHrP)	Hypercalcemic symptoms	Rare	84
Calcitonin-producing NET	Hypocalcemic symptoms	Rare	>80
Well-differentiated NF-PNETs (e.g., PP or none)	Mass effect (jaundice, hemorrhage, etc.)	100	60
Poorly differentiated PNETs	Mass effect/syndromes reported	Rare	100

^a Hypoglycemic symptoms, low blood glucose levels, reversible upon glucose intake; ^b Diarrhea, hypergastrinemia, gastric acid hypersecretion, peptic ulcer diathesis; ^c WDHA syndrome: water diarrhea, hypokalemia, achlorhydria; ^d 4D syndrome; necrolytic migrating erythematous dermatitis, diabetes, deep vein thrombosis, depression; ^e (Questionable) elevated somatostatin serum levels, diabetes, hypochlorhydria, cholelithiasis, dia/steatorrhea, anemia, weight loss; ^f Flushing, diarrhea, cardiac valvular disease, bronchospasms.

Abbreviations: ACTH, adrenocorticotropic hormone; GRF, growth hormone releasing factor; NF, nonfunctional; PNET, pancreatic neuroendocrine tumor; PP, pancreatic polypeptide; PHT, parathyroid hormone; PTHrP, PTH-related peptide; VIP, vasoactive intestinal polypeptide.

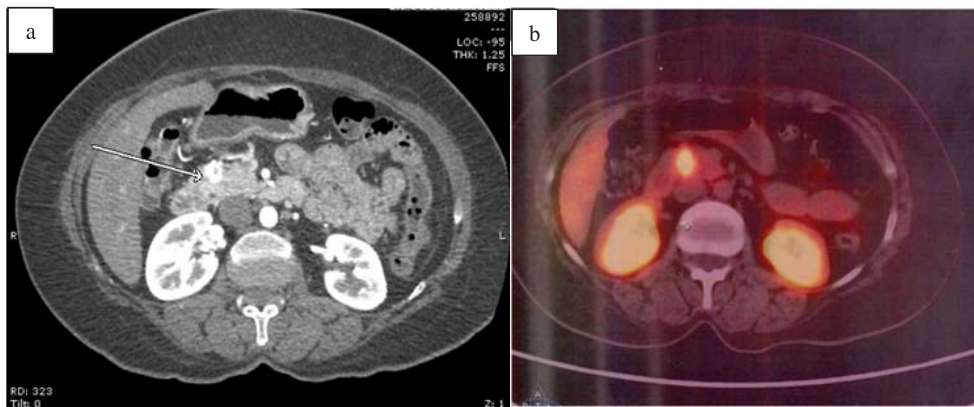


Fig 2: (a)-Well enhancing lesion in arterial phase seen in head of pancreas ; (b)- Same lesion is seen as metabolically active on DOTATOC scan

NFPNET, poor tumor differentiation, distant metastases, and surgical procedure (pancreatico-duodenectomy).

Presentation

Typical clinical presentation of both functional & non functional PNETs is summarized in Table 1. Nonfunctioning PETs and PPomas do not cause a clinical syndrome. Jaundice, poorly localized upper abdominal pain or dyspepsia may occur when nonfunctioning PET enlarges to enormous size.

Diagnosis with Imaging

CT-MRI: The current practice is to obtain high-quality multidetector (multislice) CT scan or contrast enhanced MRI (Fig 2a). CT / MR criteria to determine a tumor's resectability is based on the relationship of the pancreatic tumor (of exocrine or endocrine origin) to the SMA and celiac axis. Encasement (greater than 180-degree involvement of the vessel by tumor) of the celiac axis or the SMA or occlusion of the superior mesenteric-portal venous confluence without the technical option of venous reconstruction are considered criteria for a tumor's unresectability.

Endoscopic ultrasound (EUS): It is currently considered the most sensitive modality for identifying small PNETs and is thus used for preoperative tumor localization in patients with MEN-1, in which multifocal disease is common and of course EUS guided FNA can be done.

PET Scan-DOTATOC-Octreoscan: Recent studies show that Somatostatin receptor scintigraphy (SRS) or Octreoscan is the most sensitive method to localize the PNET primary and extent at one time including liver, bone, and lymph node metastases. The use of SRS changes management in 19% to 47% of PNETs.

PET scanning using [18F]fluorodeoxyglucose for non-functioning islet cell tumors is insensitive because of their low proliferative rate generally. However, recent PET studies using 11 C-labeled DOPA or 5-hydroxytryptophan show it to be more sensitive than SRS or

computed tomography scans for localizing the extent of pancreatic NE tumors or carcinoid tumors.

Serum Tumor Markers

Several circulating tumor markers are very useful for follow-up but isolated elevation of marker levels is generally not sufficient for diagnosis without tissue confirmation. These markers are Chromogranin A (CgA), Neuron specific enolase, Pancreatic Polypeptide (PP) etc. Chromogranin levels are elevated in 60-100% cases of either functional or non-functional PNETs. Sensitivity & specificity of Serum chromogranin in detecting PNETs ranges from 70% to 100%. PP is another nonspecific biochemical marker. PP has a sensitivity of 54% in functioning tumors & 57% in non-functioning tumors. Its specificity is 81%. But when combined with CgA, the sensitivity increases to 96% for gastroenteropancreatic NETs, 95% for nonfunctioning tumors, and 94% for pancreatic tumors.

Pathology

WHO has classified PNETs based on their differentiation, size, vascular invasion and proliferation index (Table 2). Adequate tissue sampling is critical in differentiating various subtypes of pancreatic NET. This classification is important from management point of view. Poorly differentiated PNETs are generally highly aggressive malignancies where treatment with platinum based regimen is generally indicated, according to small cell carcinoma guidelines.

Management of Functional Tumors

Insulinoma: These are the most common functioning neuroendocrine tumors of the pancreas. These can occur anywhere in the pancreas and are seldom malignant.

The uncontrolled secretion of insulin results in hypoglycemia, manifested by neuroglycopenic symptoms, such as blurred vision, confusion, and abnormal behavior, which may progress to loss of consciousness and seizure. The diagnosis of insulinoma syndrome is established by

Table 2: WHO Classification of PNETs

WHO Classification	Well-Differentiated Neuroendocrine Tumor	Well-Differentiated Neuroendocrine Carcinoma	Poorly-Differentiated Neuroendocrine Carcinoma
Biological behavior	Benign/ uncertain behavior	Low malignancy	High malignancy
Metastases	-	+	+
Ki-67/ MIB-1 index (%)	<2	2-20	>20
Pathological differentiation	Well- differentiated	Well- differentiated	Poorly- differentiated
Vascular invasion	+/-	+	+
Size (diameter)	<2 cm	>2 cm	Any size

supervised fasting of the patient, to include a laboratory work-up and observation. Serum levels of plasma glucose, C-peptide, proinsulin, insulin, and sulfonylurea are measured at intervals of 6 to 8 hours and at the point when symptoms develop. Patients with insulinoma have an insulin level greater than 3 mcIU/mL (usually greater than 6 mcIU/mL) when blood glucose is less than 40 to 45 mg/dL with an insulin-to-glucose ratio of 0.3 or less, reflecting the inappropriate secretion of insulin at the time of hypoglycemia.

Once the biochemical diagnosis is established, localization studies performed as part of the preoperative evaluation include upper GI endoscopy with EUS of the pancreas and duodenum and multidetector CT. MDCT can localize ~60% of insulinomas. If CT is normal, 2nd test is EUS. If even EUS is not able to localize, get regionalization of an insulinoma done by selective arterial calcium stimulation and hepatic veins sampling. Calcium is used as a secretagogue for insulin and is injected into the gastroduodenal artery, SMA, and splenic artery; a serum sample for insulin measurement is obtained from the right hepatic vein (Imamura-Doppman procedure). By all these investigations ~90% of insulinomas can be localized. Rest can be localized at the time of surgery by intra-operative ultrasound. Octreoscan is not very useful in insulinomas as compared to other PNETs, as these are not very consistent in octreotide avidity.

Preoperatively blood glucose level should be maintained by diet and/or diazoxide. Surgical resection (enucleation) is usually curative as most are small (<2cm), solitary & benign. If enucleation is not possible due to the location of the tumor within the pancreas, segmental resection of the pancreas, distal pancreatectomy, or pancreaticoduodenectomy may be necessary.

Gastrinoma: Most patients have a long history of ulcer disease, abdominal pain, diarrhea, severe gastroesophageal reflux, and prolonged use of acid-suppressive medication and/or a history of gastric or duodenal surgery. A serum gastrin level of 1,000 pg/mL or greater and a gastric pH of 2 or less secures the diagnosis of ZES. Serum gastrin

level should be done while fasting and patient should be off proton pump inhibitors for at least 1 week. More than 60% gastrinomas are malignant. 90% of gastrinomas are located in triangle of Stable & Passaro which is bounded by cystic duct, D2-D3 junction and junction of neck & body of pancreas. Once the diagnosis is established biochemically, tumor localization studies should be performed which include upper GI endoscopy with EUS of the pancreatic head and duodenum, multidetector CT, and somatostatin receptor scintigraphy. With the improvements in imaging studies and EUS, gastrinomas are usually successfully localized. Duodenal gastrinomas can be locally resected by either duodenotomy or segmental duodenectomy with periduodenal lymph node dissection. Rarely pancreaticoduodenectomy is needed if the tumour is infiltrating the pancreas. For pancreatic gastrinomas, the operation is based on the anatomy of the tumor and may consist of enucleation or pancreaticoduodenectomy.

NFPNET & Other Rare FPNET: From management point of view, all the rare FPNETs are treated as NFPNETs. In these, one should first establish the diagnosis with FNA (EUS-guided FNA of the pancreas or ultrasound-guided FNA of the liver if metastases are present). Resect localized, nonmetastatic disease confined to the pancreas if a gross complete resection can be performed. If radiographically occult liver metastases are found at the time of the operation, remove them if possible. If the liver metastases are of small volume but diffuse, the primary tumor is usually removed due to the potential for major morbidity from the primary, which is a possibility because of the relatively long anticipated survival of the patient. In the setting of known metastatic disease or a large, borderline resectable primary tumor, first initiate cytotoxic chemotherapy.

The degree to which surgery is applied to the primary pancreatic tumor is based on the presence and/or extent of distant disease and the presence or absence of symptoms (bleeding, obstruction) from the primary tumor. For example, resection of an asymptomatic primary in the distal pancreas has a limited role, if any, in the presence of unresectable extrapancreatic metastatic disease.

When dealing with a resectable primary tumor and resectable liver metastases, it is usually best to remove the pancreatic tumor first; if that procedure goes well, then consider resecting the liver under the same induction anesthesia. However, a two-stage procedure is often used.

(Dr Shamim Akhtar, Sr Resident; Dr Shivendra Singh, Sr Consultant & Chief GI Oncosurgery & Liver Transplantation)

GUEST ARTICLE

UPDATE ON NEUROENDOCRINE TUMORS

Steve Jobs was diagnosed in 1995 with a pancreatic mass. He thought he will have only six months and then after the biopsy, the doctors told him that he had an unusual tumor-Neuroendocrine tumor which has better prognosis. He survived for six very productive years with path breaking products like iPod and iPad.

Neuroendocrine tumors are unusual tumors which are so named as they arise from Neuroendocrine cells distributed throughout the body particularly in gastrointestinal tract. In the GI tract they produce specific peptides which produce specific syndromes. The tumors arising from Neuroendocrine cells are called Neuroendocrine Tumors (NETs). As the endocrine cells are distributed largely in stomach, pancreas, small and large intestines the term Gastro Enteropancreatic (GEP) tumors is used to specify the location in gut. *It is important to recognise these tumors as they have better prognosis.*

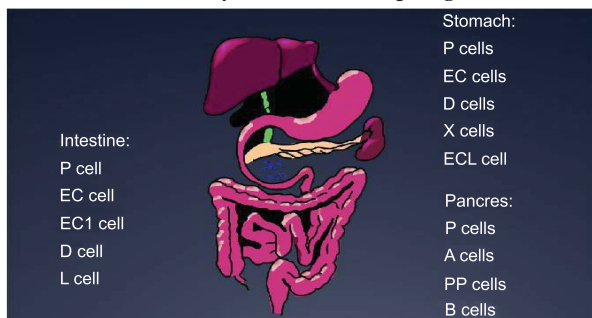


Fig: Distribution of Endocrine Cell Types

GEP-NET can be functioning – producing peptides or non-functioning which do not produce bioactive peptides. Various syndromes are described in Table 1.

Clinical Features

Most tumors are characterized by a slow progression, patients are often younger and the overall 5-year survival ranges from 60-80% in most cases of well differentiated tumors. While small functioning tumors, such as insulinoma,

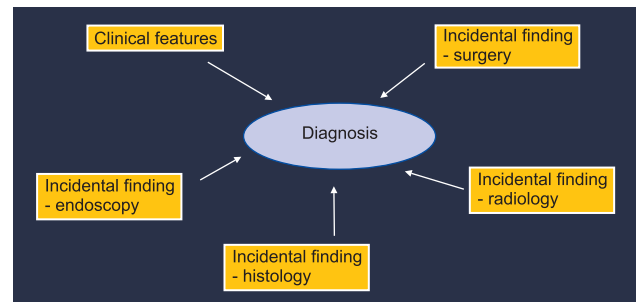


Fig: Pathways to Diagnosis

gastrinoma etc are recognized earlier due to clinical symptoms related to hormonal overproduction, the non-functioning tumors are usually large, remain undiagnosed till very late and often have liver metastases at presentation.

Diagnosis

The diagnosis is made as Incidental mass on imaging; Typical hormonal syndrome; Surgical finding; Endoscopic lesion; Histological surprise.

Biochemical evaluation of Serum Chromogranin A (CgA) (found in about 60%-80% of both functioning and non-functioning GEP-NENs) is an important marker for diagnosis and follow-up. Specific hormone evaluation establishes diagnosis for functional NENs while establishing non-functioning NENs may be a clinical challenge with high reliability on imaging and tissue diagnosis.

Standard imaging has an important role in localizing the primary tumor, identifying sites of metastatic disease and assessing response to treatment. While MDCT scan is by far the most common investigation modality with sensitivity reaching as high as 94%, MRI examination may be complementary for characterisation of liver metastases from NENs. An endoscopic ultrasound (EUS) has an important role in the preoperative assessment of the pancreas where a small functioning tumor or the possibility of multiple tumors is suspected.

Functional imaging modalities, such as somatostatin receptor scintigraphy (SRS, Octreoscan®) allows a better staging of the disease, visualization of occult tumor, and evaluation of eligibility for somatostatin analogue (SSA) treatment. Due to a low metabolic activity of GEP-NENs,

Table 1: Nonfunctional and Functional Syndromes in GEP-NET Tumors

Tumor/ Syndrome	Symptom	Secretory Product	Malignancy
Non-functional	Non-specific, incidental	Chromogranin A, PP, α/β -HCG, Calcitonin	60-80%
Carcinoid-syndrome	Flush diarrhea bronchial obstruction	Serotonin	100%
Insulinoma	Hypoglycemia	Insulin Proinsulin	5-10%
Gastrinoma/ ZES	Ulcers, diarrhea	Gastrin	60-80%
VIPoma	Excessive diarrhea	Vasoactive Intestinal Peptide	40-75%
Glucagonoma	Necrolytic migratory erythema, D. mellitus	Glucagon	50-80%
Somatostatinoma	D mellitus steatorrhea cholelithiasis	Somatostatin	50%
GHRHoma	Acromegaly	GHRH	100%
CRHoma, ACTHoma	Cushing-syndrome	CRH, ACTH	90-100%

FDG-PET scan has not been a very sensitive test for these tumors except for tumors with high proliferative activity and low differentiation. DOTATOC-PET scan (68Ga-DOTA-octreotide-PET) a combination of PET-CT with 68Ga (gallium) linked to a SSA²⁹ has proved to be very sensitive for detection of NENs with a great impact on patient management.

Histopathological evaluation and immunohistochemistry (IHC) is the cornerstone of diagnosis for NENs. The tissues for sampling should preferably be a True-Cut Biopsy either from the liver lesions or from the primary area if accessible or from surgical specimens. Specific IHC tests viz synaptophysin and CgA are diagnostic of NENs. IHC expression of a protein Ki67 helps prognostication of the tumors and discriminates well-differentiated forms from poorly-differentiated carcinomas. Proliferative index directly correlates with aggressive behaviour of NENs.

Treatment

Most patients receive a combination of treatment modalities.

Surgery: Surgery is potentially curative and is recommended for both functioning and non-functioning tumours. Conventional contraindications to surgical resections such as superior mesenteric vein invasion and nodal or distant metastases, should be redefined in patients with advanced pancreatic NETs. Surgery can be combined with Local ablation/Chemoembolization and Radioembolization.

Current Systemic Treatment Options for Patients with Advanced NETs: Somatostatin analogues; Interferon-alfa; Chemotherapy; Peptide receptor-targeted therapy; Molecular-targeted therapies.

Functional tumors with symptoms of hormone hypersecretion are managed with twice/thrice daily subcutaneous injections of somatostatin analogues (Octreotide). Long acting somatostatin analogues administered once in 3-4 weeks (Sandostatin LAR[®]) are costlier but have shown significant improvement in the quality of life of patients and have as good or better efficacy compared with short acting octreotide and especially so in mid-gut tumors.

Patients with NENs often maintain a good quality of life for a long period despite having metastases, nevertheless aggressive surgery wherever possible either as curative or palliative option should be considered strongly even in presence of liver metastases. Conventional contraindications to surgical resections, such as superior mesenteric vein invasion and nodal or distant metastases, should be redefined in patients with advanced pancreatic NENs. Other modalities, such as chemoembolization, radiofrequency ablation and recently available radioembolization, can be simultaneously considered for metastatic liver disease.

Tumor differentiation is a critical part in deciding the medical line of treatment. SSA form an integral part of treatment of well differentiated NENs. Streptozotocin and recently combination chemotherapy with 5 FU and oral temozolomide are used as second line treatment for inoperable or metastatic well differentiated (G1-G2) foregut NENs. Cisplatin and Etoposide based chemotherapy are advocated for G3 tumors poorly differentiated NENs/anaplastic carcinomas. Midgut NENs are less responsive to chemotherapy. mTOR inhibitor Everolimus, or RAD001 (Afinitor[®], Novartis), is a new oral, once-daily drug that holds promise in pre-clinical studies with promising anti-tumor activities, high response and progression free survival rates.

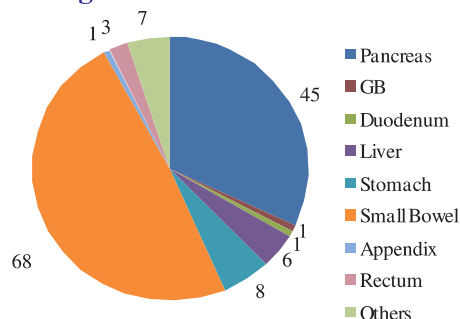
Patients with inoperable or metastatic GEP NENs and a positive nuclear medicine imaging are considered for peptide receptor radiotherapy (PRRT), an approach that uses somatostatin analogues tagged with radioactive molecules (usually ⁹⁰Yttrium, ¹⁷⁷Luututium or ¹¹¹Indium) targeted against somatostatin receptors. Renal toxicity and bone marrow toxicity may be the limiting factors for this form of treatment.

Factors Influencing the Therapeutic Decision: Type of NET; TNM stage and grade; extent of liver involvement; functioning vs non-functioning tumor; patient's performance status; availability of different therapeutic modalities.

Summary

A precise pathology is crucial in the management of NENs. A multidisciplinary team management is necessary for patients. Surgical intervention is the key step in NEN management, even when non-curative however treatments need to be individualized rather than a blanket protocol based on the patients symptomatology and sequential evaluation.

Organ-wise distribution of NETs



APNET Registry (www.apnetregistry.com): We have initiated Asia Pacific NET registry for these rare tumors and have more than 150 tumors diagnosed and treated by all current modalities.

(Dr P Jagannath, Chairman, Dept of Surgical Oncology, Lilavati Hospital, Mumbai)

PERSPECTIVE

PATHOLOGY OF PANCREATIC NEURO-
ENDOCRINE TUMORS

Definition

“Pancreatic Neuroendocrine Tumors” or simply “Pancreatic Endocrine Tumors” (PNET/PET) are sporadic/inherited, functional/non-functional tumors of pancreas, arising or differentiating towards islet cells of pancreas or less commonly towards diverse endocrine cell types of diffuse endocrine system not seen in pancreas, e.g. gastrin secreting cells. The PNETs account for less than 5% of all pancreatic tumors.

Epidemiology

The incidence of PNET is ~1-1.5/100,000. However, the prevalence is higher because many survive the disease longer than other tumor types. The median age has been reported between 51-58 years in different studies. While some studies have revealed a male predominance, no gender bias has been noted in others. Most tumors are sporadic but 15% are associated with multiple endocrine neoplasia type 1 (MEN1), Von Hippel Lindau syndrome and Neurofibromatosis 1.

Pathophysiology

PNET are solid or cystic tumors with no preferred location in pancreas. These tumors are separated into functional & non-functional types. The former secrete hormones, producing characteristic clinical syndrome. Occasionally, the functional tumors may secrete ectopic hormone, e.g. ACTH or Growth Hormone Releasing Hormone producing Cushing Syndrome or Gigantism. The functional tumors are often designated by suffixing “oma” to the hormone type produced; like insulin producing tumors draw the appellation of Insulinoma and so on. The non-functional tumors either do not secrete hormones or do so without producing syndromic features. The peptides demonstrated on immunohistochemistry do not make a tumor functional unless syndromic symptoms are in attendance. In terms of frequency of occurrence, the non-functional tumors are >insulinoma>gastrinoma>glucagonoma>VIPoma>somatostatinoma. Among the functional variants, insulinomas make up 42%, gastrinomas 24%, glucagonomas 14%, VIPomas 10%, somatostatinomas 6%, and the remaining ectopic and multiple hormone-producing neoplasms are rare.

Molecular Basis of PNET

Molecular pathogenesis of PNETs is incompletely understood. The sporadic tumors have shown a great heterogeneity in terms of genetic alterations. Bulkier and nastier tumors have greater number of alterations underlining their genomic instability and tumor progression. del 1, del 11q and +9q appear as early events being nearly universal; -3p, -6pq & -10pq and +5q, +12q, +18q & +20q seem associated with malignant outcome. Additionally, gains on 4 & 7 and losses on 21q are linked to metastasis.

Inherited PNETs occur in 80-100% of patients with MEN1, 10-20% of patients with von-Hippel-Lindau syndrome and 10% with neurofibromatosis (NF1).

Pathology & Biologic Behaviour

PNET have been classified into three grades as per WHO 2010 scheme:

Grade 1 – Well Differentiated NE **Tumor**

Grade 2 – Well Differentiated NE **Carcinoma**

Grade 3 – Poorly Differentiated NE Carcinoma (Small Cell type, Large Cell Neuroendocrine Carcinoma)

Some tumors are definitely malignant at presentation as demonstrated by (a) identifiable metastasis and (b) by malignant histology corresponding to small cell carcinoma or large cell neuroendocrine carcinoma. Many, however, are well differentiated and organ confined. This latter group requires separation into Well Differentiated NE Tumor and Well Differentiated NE Carcinoma for prediction of their biological behaviour. It is often also seen that some tumors with uncanny resemblance to well differentiated PNET and unlike Small Cell Carcinoma have high mitotic activity or MIB1 labelling and shall necessarily be classified as Grade 3 tumors (Fig1). Mitotic count & proliferation surrogate of MIB1 labelling has been recommended by WHO as tools for this division of categories as shown in the Table 1 below. It will be worthwhile noting that these features are heterogeneously expressed in various areas of a tumor and small biopsies may erroneously grade a tumor lower than it actually is and larger samples of tumor are therefore preferable for grading.

While proliferation indices have been recommended by WHO, a variety of other features have been identified as indicator of biologic behaviour of which *necrosis*, *vascular invasion*, and *confinement to organ of origin* are important and should be included in the final pathology report.

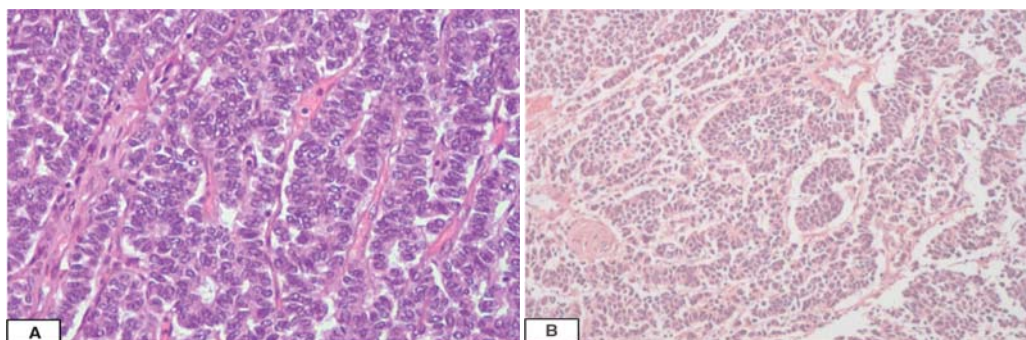


Fig. 1: “A”; H&E X 100x Trabecular pattern of well differentiated PNET. Note thin fibrous strands with fine vasculature. “B”; A similar growth pattern as “A” but higher power examination showed apoptosis and mitosis. The MIB1 labelling was > 50%

Grade	WHO 2010
Low (Grade 1)	< 2 mitoses/10 HPF & MIB1 Index of $\leq 2\%$
Intermediate (Grade 2)	2- 20 mitoses/10 HPF or MIB1 Index 3-20%
High (Grade 3)	> 20 mitoses/10 HPF or MIB1 Index of >20%

Table 1: Classification of Neuroendocrine Tumors of Pancreas, based on mitotic activity and MIB 1 labelling

All said, the natural history of PNET is poorly understood. Stage, like in other cancers, may be an important prognostic marker. The AJCC recommends TNM staging like any other pancreatic carcinoma primarily to collect data which may overtime yield potential prognostic factors of relevance.

To summarise, the biologic behaviour of PNET is capricious, at least for lower grade tumors. A pathologist should make all efforts to include following points in his report on PNET:

- Site and diagnosis.
- Differentiation viz. Well/poorly differentiated
- Mitoses/MIB1 labeling index and grade of tumor for well differentiated PNET.
- Other less well congealed prognostic factors as necrosis, vascular & perineural invasion and organ confinement.
- Stage though not validated is recommended.
- Non-NET component like adenocarcinoma etc.
- Margins of resection.
- Upregulated expression of CD44 and CK19 immunoreactivity has been shown to be associated with aggressive behaviour and can be included as site specific factors.

Clinical Presentation

Most tumors are identified incidentally by imaging especially the non-functioning ones. These tend to be

large and approximately 70% are more than 5 cm and of advanced stage at diagnosis. In our practice, liver metastasis is often noted and various studies have estimated the incidence of liver metastasis at 60-80%.

Symptomatic patients may present with anyone of the following common hormonal syndromes:

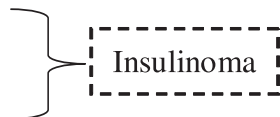
- Insulinoma, which is the most common secretory PNET to produce symptoms and causes hypoglycaemic attacks. It presents early and approximately 90% are benign.
- Zollinger-Ellison syndrome (gastrinoma) results from excessive gastrin, BAO/MAO secretion. It produces multiple site Peptic Ulcer Disease and can also cause diarrhea. 60 – 80 % behave as malignant tumors.
- Glucagonoma leading to mild diabetes mellitus (DM) with erythematous ulcerating dermatitis.
- Verner-Morrison syndrome (VIPoma) characterised by watery diarrhea, hypokalemia, achlorhydria also known by acronym of WDHA syndrome.
- Somatostatinoma syndrome causing diarrhea, cholelithiasis and DM.

Role of Laboratory in Management of PNET

In addition to establishing a diagnosis of Neuroendocrine tumor through correct interpretation of needle aspirate and biopsy material, the Laboratory has a major role to play in diagnosis and management of PNET. The functional tumors produce their own

hormones which are assayed for diagnosis as well as for monitoring therapeutic response. In addition, electrolytes are often disturbed and their measurement is necessary for appropriate corrections. The tests often useful in PNET are listed below:

- i) Electrolyte Panel
- ii) Glucose, Plasma or Serum
- iii) Insulin, Fasting
- iv) Proinsulin
- v) C-Peptide, Serum or Plasma
- vi) Gastrin
- vii) Glucagon
- viii) Vasoactive Intestinal Peptide
- ix) Somatostatin
- x) Chromogranin A (CgA): It is a helpful marker in diagnosis, establishing metastatic disease as well as for monitoring PNET. Levels >1,000 indicate poor prognosis. Reduction of CgA by 80% or more after cytoreductive surgery predicts symptoms and disease control. May be elevated due to PPI therapy or impaired renal function. Results obtained with different assay methods or kits cannot be used interchangeably.



Conclusion

Pancreatic endocrine tumors (PNETs) continue to be difficult lesions to diagnose and prognosticate, both for surgical pathologist and clinical medicine specialist. These neoplasms can be graded into 1 of 3 tiers, based on histologic characteristics in likeness to epithelial neuroendocrine tumors in other anatomic sites. However, Grade 1 tumors are by far the most common and are the most difficult to prognosticate. The WHO 2010 criteria along with other alluded in the text above can be useful in this evaluation.

Key Points

- 1) Pancreatic NETs are rare but increasingly diagnosed at small size as incidentalomas on MRI and EUS
- 2) Grading is necessary to forecast behavior. WHO 2010 criteria are easy to apply and are based upon proliferative indices.
- 3) Histopathology report should be comprehensive and shall include features mentioned.
- 4) CgA is the best circulating marker to assist in diagnosis, establish metastasis and conclude on effectiveness of surgery.

(Dr Anurag Mehta, Director Laboratory Services)

PANCREATIC CANCER: NOTABLE ADVANCES 2011

SUNITINIB, EVEROLIMUS APPROVED FOR RARE TYPE OF PANCREATIC CANCER

The FDA approved two drugs in May 2011 for the treatment of advanced pancreatic neuroendocrine tumors that cannot be surgically removed or that have spread to other parts of the body. Both were shown to more than double the time it took for cancer to progress compared to treatment with a placebo. The approval of these two new drugs increases treatment options for the disease, which previously consisted of only interferon and chemotherapy. It also highlights how the marriage of preclinical and clinical discovery can transform the way to treat a disease. Such successful studies offer reason for optimism that a growing understanding of tumor biology, and gradually improving ability to selectively inhibit key targets, will lead to additional novel targeted therapies that make an impact in other difficult-to-treat malignancies, gastrointestinal and otherwise.

- Everolimus (Afinitor®) targets an important signaling molecule in tumor cells called mTOR. Its approval was based on a clinical trial of 410 patients with metastatic or locally advanced disease who received either everolimus or placebo. Patients treated with everolimus lived more than twice as long—a median of 11 months without the cancer worsening—compared to a median of 5 months in patients who received placebo.
- Sunitinib (Sutent®) inhibits the vascular endothelial growth factor (VEGF) receptor, which is involved in the development of cancer growth-fueling blood vessels. The drug's approval was based on data from a randomized study of 171 patients with metastatic or locally advanced pancreatic neuroendocrine tumors that received sunitinib or a placebo. Patients treated with sunitinib lived more than twice as long without their disease progressing (median 11 months) compared to those who received placebo (5 months).

Fact

Each year, the incidence of pancreatic cancer has been increasing by 0.8% in men and 1% in women since 1998.

(ASCO, Clinical Cancer Advances, 2011)

IN FOCUS

ROLE OF RADIOLOGY IN PNET

Introduction

Neuroendocrine tumors (NETs) are a rare but diverse group of malignancies that arise in a wide range of organ systems. NETs of pancreas account for about 2% of pancreatic neoplasms. Incidence is about 1 in 100,000 and they are usually divided into functioning and non-functioning tumors. Because they result in clinical symptoms, functioning tumors are usually small at diagnosis. These are named according to the hormones they produce, usually one of three types: insulinomas, gastrinomas, and glucagonoma. Non-functional tumors are discovered late when they are large enough to cause symptoms from local infiltration or metastasis.

Insulinomas constitute about 50% of all endocrine tumors and are more common in females. Usually solitary and less than 2cm in size, they present with Whipple's triad comprising of starvation attack, hypoglycemia (fasting glucose < 50mg/dl) and relief by IV dextrose.

Gastrinomas comprise about 20% of endocrine tumors and have a predilection for males. They occur in the gastrinoma triangle, are usually less than 1cm in size, less vascularized than insulinoma and can be multiple. It presents with Zollinger-Ellison syndrome.

Glucagonomas are usually large at presentation and cause necrolytic migratory erythema characteristically.

Non-functional islet cell tumors histologically resemble other NETs but do not secrete significant biologically active substances. Most of these tumors, however, secrete Chromogranin A which can be detected in the serum and thus confirm the diagnosis.

Although diagnostic procedures have improved dramatically, NETs frequently present with liver metastasis at the time of diagnosis. The treatment of patients with liver metastases is complex, and there are often several factors that must be taken into account. Curative surgery should always be considered but may not be possible due to the diffuse nature of the disease. NETs are relatively slow-growing tumors and patients can survive for several years with current treatment modalities. Radiology has played an increasingly important role in diagnosis and management, including embolization, radionuclide therapy, and ablative techniques.

Diagnosis

Due to the small size, NETs are difficult to detect and multimodality imaging along with clinical features and biochemical parameters are used for diagnosis. Various imaging modalities like Ultrasound, including Endoscopic Ultrasound, CT scan, MRI, Radioisotope Imaging, Digital Subtraction Angiography and venous sampling are used to detect these tumors. Imaging not only makes the diagnosis but also guides biopsy procedures, localizes the tumor preoperatively and intra-operatively.

Primary tumor is seen as a round or ovoid markedly enhancing nodule with no vascular encasement or duct obstruction usually in pancreatic body or tail. Tumor larger than 3cm in size or showing calcification suggests possibility of malignancy. For the evaluation of liver metastases, the use of triple-phase multi-detector CT and contrast enhanced MRI is suggested to establish a baseline, which can help assess disease extent and allow post treatment comparison. The arterial anatomy of the liver and portal vein patency can also be determined. Liver metastases have low signal intensity on T1-weighted MR images and high signal intensity on T2-weighted images. T2-weighted imaging may pick up metastasis without contrast administration.

The radio-pharmaceuticals used for imaging functioning neuroendocrine tumors are either similar in molecular structure to the hormones that the tumors synthesize or incorporated into various metabolic and cellular processes of the tumor cells. Somatostatin analog called Octreotide (Sandostatin) labeled with Indium-111 is the most common radioisotope in NETs imaging. Radio-iodinated derivatives of guanethidine, I-131 Metaiodo-benzylguanidine (MIBG) and I-123 MIBG are also used. The newer Ga-68 DOTA-NOC and FDG/fluoride PET-CT scans are better and are now replacing Octreotide scans for staging. These receptor based scans become less effective in dedifferentiated tumors which lose Somatostatin Receptor (SSTR) expression. However, a dedifferentiating and aggressive tumor will increase its metabolic rate and glucose consumption, thereby facilitating detection with FDG-PET. Non-functioning tumors are usually large at presentation with solid, cystic components and no uptake of Octreotide due to absence of SSTR activity. But they show highly accurate and preferred FDG-PET activity due to high proliferation rate.

Ultrasound and CT scans are the preferred modalities for guided biopsies from primary tumor or metastatic deposits. Very small tumors are better targeted using

Endoscopic Ultrasound (EUS) guidance. In extreme situations, one may resort to laparoscopic biopsy for establishing the tissue diagnosis.

Intervention

Primary tumors are usually tackled by surgery. Curative surgery for hepatic metastases should always be considered as the first treatment option. Unfortunately, less than 20% of patients present with surgically manageable disease. Most patients present with extensive bilobar disease or bulky tumor that requires alternative therapy. Symptomatic residual disease can be treated initially with a trial of Octreotide therapy. Nonprogressive asymptomatic disease may be simply observed initially. Refractory, unresectable, or recurrent disease with hepatic predominance is the domain of the interventional radiologist.

Local treatment strategies, such as embolization, chemoembolization, and targeted radionuclide therapy, are increasingly being used. Local ablative techniques, such as radiofrequency ablation (RFA), cryotherapy, and percutaneous ethanol injection (PEI), are also important alternatives. Careful patient selection is needed, as is tailoring of the treatment to the therapeutic goal in a given patient. This goal may be palliation of hormonal symptoms, reduction of tumor bulk, or even conversion to resectable status. Performance status and extent of hepatic disease involvement should also be evaluated.

Trans catheter arterial chemoembolization (TACE): The liver has a dual vascular supply that lends itself to the use of hepatic transcatheter arterial embolization (TAE). The hepatic artery is the primary supplier of hyper-vascular liver metastases. Embolization induces ischemia of tumor cells, thereby reducing hormone output and causing liquefaction. TACE has been developed based on the principle that ischemia of tumor cells increases sensitivity to chemotherapeutic substances. Regional delivery of chemotherapy leads to increased intratumoral drug concentration and exposure time that result from reduced blood flow with embolization.

It is generally accepted that embolization of the entire liver at a single treatment session should not be attempted. In the majority of patients, one hepatic lobe is embolized per session—usually the lobe with the greatest tumor burden. Indeed, tumor burden is the only predictor of tumor response. It has been shown that patients with more than 75% of the liver involved by metastatic disease generally have worse outcomes. Factors that do not contribute to treatment outcome include site of

primary tumor, tumor differentiation, previous treatment, and size of liver metastases. An unresected primary tumor or the presence of extra-hepatic metastasis should not limit the use of either technique.

Portal vein embolization is another interventional technique used for NETs. It is usually selected for use in patients who are candidates for extended hepatectomy to increase the volume of potential liver remnant. Interventional radiology is also useful in the management of complications of NETs, such as hemorrhage and pseudo-aneurysm formation.

Ablative techniques rely on the principle that decreasing the volume of viable tumor or preventing new growth may lead to longer survival. If local ablation can decrease hormone production, significant symptomatic relief can be obtained. RF ablation is the most commonly used ablative technique in metastatic NETs. This technique involves converting RF waves into heat. A high-frequency alternating current is passed from an uninsulated electrode into surrounding tissues. This results in friction heating between tumor particles surrounding the electrodes and produces cellular destruction. Percutaneous, open or laparoscopic approaches are used. Like embolization techniques, RF ablation is associated with the release of hormones during the procedure. Therefore, it is important to consider prophylactic treatment with Octreotide. Major complications, such as hemorrhage or abscess formation, are rare.

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs is now becoming established treatment modality for NETs. Patients with inoperable NETs, progressive disease or symptoms that are not controlled with medication will benefit with survival benefit of several years and markedly improved quality of life. The tumor needs to be SSTR positive as determined with Octreotide scan. Octreotide labeled with Indium 111-DTPA, Yttrium-90-DOTA or Lutetium 177-DOTA-TATE (Lu-TATE) have been used alone or in combination.

Conclusion

Interventional radiology is becoming increasingly important in the management of pancreatic neuroendocrine tumors with further development in future in targeted therapies.

(Dr S Avinash Rao, Sr Consultant; Dr A K Chaturvedi, Director; Dr Ankur Sharma, DNB Student; Department of Radiology)

RESEARCH & DEVELOPMENT

Circulating miR-18a in Pancreatic Cancer

Researchers at Kyoto Prefectural University of Medicine, Japan, have hypothesised that miR-18a in the plasma is a potential biomarker in patients with pancreatic cancer. miR-18a is located in the miR-17-92 cluster and reported to be highly expressed in pancreatic cancer tissues. The study evaluated the plasma miR-18a assay using quantitative RT-PCR by comparing plasma results obtained from 36 patients with pancreatic cancer and from 30 healthy volunteers. The results showed that expression of miR-18a was significantly higher in pancreatic cancer tissues ($P=0.012$) and pancreatic cancer cell lines ($P=0.015$) than in normal tissues and fibroblasts. Plasma concentrations of miR-18a were significantly higher in pancreatic cancer patients than in controls ($P<0.0001$). Plasma levels of miR-18a were significantly lower in postoperative samples than in pre-operative samples ($P=0.0077$). Circulating miR-18a might provide new complementary tumor markers for pancreatic cancer.

(Br J Cancer, Nov 22, 2011)

NACT in Locally Advanced Pancreatic Cancer

According to a study conducted at Harvard Radiation Oncology Program, USA, neoadjuvant chemotherapy (NACT) before chemoradiation therapy (CRT) may improve outcomes for patients with locally advanced pancreatic cancer. Seventy consecutive patients with unresectable ($n=46$) or borderline resectable ($n=24$) locally advanced pancreatic cancer were treated with CRT from 2005 to 2009. Patients typically received 50.4 grays in 28 fractions (91%) with concurrent 5-fluorouracil (84%) or capecitabine (14%). Forty patients received CRT alone, and 30 patients received NACT before CRT for a median of 4 months, typically gemcitabine (93%). All patients without progression after NACT were offered CRT. The median follow-up of the patients was 14.2 months (range, 3-57 months). On multivariate analysis, receipt of NACT and surgical resection were associated with increased overall survival (OS). The present study has shown that gemcitabine-based neoadjuvant chemotherapy confers a significant OS advantage by allowing the selection of patients who will derive greatest benefit from CRT.

(Cancer, Oct 21, 2011)

Survival Impact of Malignant PNET

The low incidence of malignant “functional” (F) or “nonfunctional” (NF) neuroendocrine islet cell tumors (ICTs) of the pancreas represents a challenge to precise post-therapeutic survival prediction. Researchers have examined the survival impact of malignant pancreatic ICT morphologic subtypes. A pancreatic ICT data set was created from a US-based population database from 1980-2004. Prognostic factors with survival impact and relationships between surgical therapy and overall survival (OS) were analyzed. There were 2,350 individuals with malignant ICTs. There was no difference in resection rates between FICTs and NFICTs (23% vs 20%, $P=ns$). Median OS was 30 months, with group differences ranging from NE carcinomas (21) to VIPomas (96; $P<0.0001$). Median OS of resected versus unresected FICTs was 172 versus 37 months, while that of NFICTs was 113 versus 18 months ($P<0.0001$). When controlled for other established prognostic parameters, histopathologic subtype assignment of pancreatic ICTs affects survival prediction and resection is associated with superior survival for all tumor types.

(J Surg Oncol, Oct 17, 2011)

Type 2 Diabetes Drugs and Pancreatic Cancer

A team of investigators at Larry L. Hillblom Islet Research Center, UCLA have shown that two newer drugs used to treat Type 2 diabetes could be linked to a significantly increased risk of developing pancreatitis and pancreatic cancer, and one could also be linked to an increased risk of thyroid cancer. The US Food and Drug Administration's (FDA) database for adverse events reported between 2004 and 2009 among patients using the drugs sitagliptin and exenatide was examined. They found a six-fold increase in the odds ratio for reported cases of pancreatitis with these drugs, compared with four other diabetes therapies they used as controls. They also found that patients who took the two drugs were more likely to have developed pancreatic cancer than those who were treated with the other therapies. The FDA data did not indicate links between the two diabetes drugs and any other form of cancer. The researchers caution that the FDA's adverse events database is not the ideal mechanism to compare adverse event rates between drugs and stressed that randomized, controlled clinical trials remain the gold standard for such assessment.

(Science Daily, Sep 17, 2011)

NEW TECHNOLOGY

Future Diagnostic Tool for Pancreatic Cancer

A team of scientists from four Boston-area Institutions and Physical Sciences, Inc. has demonstrated that optical coherence tomography (OCT) can reliably distinguish between pancreatic cysts that are low-risk and high-risk for becoming malignant. Researchers used the technique to examine surgically removed pancreatic tissue samples from patients with cystic lesions. By identifying unique features of the high-risk cysts that appeared in the OCT scans, the team developed a set of visual criteria to differentiate between high and low risk cysts. They compared OCT diagnosis to those obtained by examining thin slices of the pancreatic tissue under a microscope. Results showed that OCT allowed clinicians to reliably differentiate between low-risk and high-risk cysts with a success rate close to that achieved by microscope-assisted examinations of slices of the same samples. They recently received FDA approval for testing this technology in human patients by using an OCT probe which is small enough to be inserted into the pancreas through a biopsy needle, guided into suspect masses in the pancreas by endoscopic ultrasound imaging.

(Science Daily, Aug 17, 2011)

New Drug Combination of Pancreatic Cancer

Researchers from Virginia G Piper Cancer Centre have shown that upon using Nab-Paclitaxel (Abraxane®)-an albumin bound form of Paclitaxel, about half of the patients showed reduction in tumor size measured by CT scan and about 50% lived at least a year compared to the average survival of 6 months. Scientists found that in pancreatic cancer, an albumin-binding protein called secreted protein acidic and rich in cysteine (SPARC) was present at high levels in cells within the pancreatic tumor microenvironment. It was hypothesized that the albumin formulation of nab-paclitaxel may be taken up by tumor cells with high SPARC expression. Based on these findings, this study was conducted in which 67 patients were treated and showed impressive results. Following completion of a safety and dose finding phase, 44 patients were treated in the phase II group. About half the patients showed reductions in tumor size and about 50% lived at least a year. The results of this study need to be confirmed in a large population.

(J Clin Oncol, Dec 1, 2011)

miRInform™ Pancreas Pancreatic Cancer Assay

Scientists from Asuragen, Inc. have evaluated the use of microRNA-based test, miRInform™ Pancreas for the diagnosis of pancreatic ductal adenocarcinoma (PDAC) in fine needle aspirates. Currently, gastroenterologists use endoscopic ultrasound guided fine needle aspiration (EUS-FNA) to obtain tissue for diagnosis of pancreatic carcinoma. According to the data, the addition of a miRNA-based molecular test may enhance the diagnostic accuracy of FNA cytology on indeterminate and suspicious specimens. Asuragen developed and validated miRInform™ Pancreas, which interrogates the expression of seven proprietary miRNAs, in a large multi-center collaboration involving seven sites and 186 subjects. When used in conjunction with conventional FNA cytology, miRInform™ Pancreas allows diagnosis of PDAC with 92.5% accuracy, as compared to 80.2% for FNA cytology alone. Furthermore, a primary benefit of the miRNA panel is its ability to characterize samples with indeterminate or suspicious FNA cytology with an overall accuracy of approximately 77%. This landmark study has clearly shown how molecular analysis can have a central role in the evaluation of indeterminate cytology specimens in pancreatic mass lesions.

(Asuragen Inc, Nov 3, 2011)

SBRT for Pancreatic Cancer

A study conducted at the University Hospitals-Case Medical Center, USA have shown that Stereotactic Body Radiation Therapy (SBRT) is safe and could be beneficial in the treatment of pancreatic primary malignancy with acceptable rate of adverse events. SBRT has emerged as a potential treatment option for local tumor control of primary malignancies of the pancreas. Twenty consecutive patients receiving SBRT for unresectable pancreatic adenocarcinomas and a neuroendocrine tumor were considered for this study. Prior to SBRT, cylindrical solid gold fiducial markers were placed within or around the tumor endoscopically, surgically, or percutaneously under CT guidance to allow for tracking of tumor during therapy. Mean radiation dose was 25 Gray delivered over 1-3 fractions. Chemotherapy was given to 68% of patients in various schedules/ timing. The mean total gross tumor volume reduction at 3 and 6 months after SBRT were 21% and 38%, respectively. The results showed SBRT as a safe and likely effective local treatment modality for pancreatic primary malignancy with acceptable rate of adverse events.

(J Surg Res, Sep 5, 2011)

CLINICAL TRIALS

Comparison of MDCT and EUS

A team of scientists at the Izmir Atatürk Training of Research Hospital performed study to compare Multidetector CT (MDCT) and Endoscopic Ultrasonography (EUS) for differentiating benign and malignant lesions, to determine local and vascular invasion in pancreatic cancer and applied these techniques for deciding resectability of tumor. The study was conducted from June 2009 to June 2010. A total of 56 patients were recruited but analysis was done for 51 patients as patients with common bile duct tumor, gall bladder tumor and papillary tumor (n=2) were excluded from the study. Results showed that for diagnosis of resectability MDCT alone demonstrated definite role in 6 (14%) of 43 patients and EUS alone demonstrated role in 4 (9%) of 43 patients. When both EUS and MDCT were used together, accurate decision for resectability was accomplished in 27 patients. To achieve better decision in terms of correct resectability/ unresectability, EUS should also be used with MDCT.

(Hepatogastroenterology, Dec 2011)

FOLFIRI for Pancreatic Endocrine Carcinoma

Results from prospective multicenter phase II study in progressive metastatic well differentiated pancreatic endocrine adenocarcinoma showed that the FOLFIRI regimen can be used as first line chemotherapy. Pancreatic endocrine carcinomas are heterogeneous and rare disease and its response towards standard chemotherapy regimen is unsatisfactory. Twenty patients with progressive non-resectable metastatic well differentiated pancreatic endocrine carcinoma were recruited in a prospective multicentre phase II trial and received chemotherapy with FOLFIRI schedule (irinotecan 180mg/m²) infusion combined with simplified (LV5FU2) every 14 days. The median number of administered cycles was 12, the 6 month non-progression rate was 80% and overall survival at 24 months was 65%. Median progression-free survival was 9.1 months. The study showed that FOLFIRI was well tolerated by patients as first line of chemotherapy and achieved stabilization in most patients. In future, it could be used as alternative therapy for advanced endocrine carcinomas of the pancreas.

(Dig Liver Dis, Nov 2011)

Gemcitabine Versus Gemcitabine Plus Radiotherapy

Researchers from Indiana University Melvin and Bren Simon Cancer Center conducted a trial on 74 patients with localized unresectable adenocarcinoma of the pancreas to assess the role of radiation therapy with concurrent gemcitabine compared to gemcitabine alone. The patients were randomly assigned to receive gemcitabine alone [at 1000 mg/m²/wk ; Arm A : 37 patients were enrolled in this group]; and gemcitabine (600 mg/m²/week plus radiotherapy 1.8 Gy/Fraction and total 50.4 Gy ; Arm B: 34 patients were enrolled in this group). Results showed that patients in Arm B had greater incidence of grades 4 and 5 toxicities (41% vs 9%) but grades 3 and 4 toxicities were similar in both the arms. The overall survival was 9.2 months and 11.1 months for Arms A and B respectively. Through this trial it was concluded that overall survival was improved with the addition of radiation therapy to gemcitabine.

(J Clin Oncol, Nov 1, 2011)

Neoadjuvant Therapy in Pancreatic Adenocarcinoma

Neoadjuvant treatment shows some activity in patients with gastrointestinal malignancies, but no phase III trials have been completed to examine the role of neoadjuvant treatment in pancreatic cancer. Researchers from ULCA School of Public Health have done meta-analysis of best available phase II trials. These trials were identified using MEDLINE search and the Cochrane Central Register of Controlled Trials from 1960 to July 2010. A total of 14 phase II clinical trials were included in the study and analysis was done for 536 patients. These patients were divided into 2 groups: patients with initially resectable tumors (group A) and patients with borderline/unresectable tumors (group B). Primary end points were rate of resection and survival. According to the results of the study after the treatment with neoadjuvant therapy resectability was 65.8% (95% CI, 55.4-75.6%) compared with 31.6% in group B (95% CI, 14.0-52.5%). A partial response of 31.8 (95% CI, 24.2-39.8%) was found in patients with borderline/unresectable tumors (group B) and 9.5% in group A (P=0.003). Median survival in resected patients was 23 months for group A and 22 months for group B. Nearly one-third of tumors that were not operable were able to be ultimately resected after treatment. It was concluded that patients with locally advanced disease of pancreas may get benefit from neoadjuvant treatment.

(Surgery, Sep 2011)

WATCH-OUT

Anti-IGF-I Receptor Antibody

Rajeeva Singh et al of Immunogen Inc. , USA, were awarded patent no. 8,034,904 on 11th October 2011 by USPTO for their invention entitled “Anti-IGF-I receptor antibody”. Insulin-like growth factor-I receptor (IGF-I receptor) is a transmembrane heterotetrameric protein, which has two extracellular alpha chains and two membrane-spanning beta chains in a disulfide-linked .beta.-.alpha.-.alpha.-.beta. configuration. The IGF-I receptor has been implicated in promoting growth, transformation and survival of tumor cells. Many types of tumors are known to express higher than normal levels of IGF-I receptor, including breast cancer, colon cancer, ovarian carcinoma, synovial sarcoma and pancreatic cancer. The present invention relates to antibodies that bind to human insulin-like growth factor-I receptor (IGF-I receptor) and more particularly, anti-IGF-I receptor antibodies that inhibit the cellular functions of the IGF-I receptor.

(www.patents.com, Dec 12, 2011)

C12ORF48 as Target Gene

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer deaths in the western world and prostate cancer (PC) is the most common malignancy in males and the second leading cause of cancer-related deaths in the United States and Europe. Yusuke Nakamura et al of Oncotherapy Sciences Inc. Kanagawa, Japan, have filed an application no. 20110263679 titled “C12ORF48 As a Target Gene for Cancer Therapy and Diagnosis” in USPTO which was published on 27th October 2011. Through microarray analysis and RT-PCR, the present invention relates to the discovery that C12ORF48 is over-expressed in several cancer cells. The functional knockdown of endogenous C12ORF48 by siRNA in cancer cell lines results in drastic suppression of cancer cell growth, suggesting its essential role in maintaining viability of cancer cells. The present invention further provides methods of screening for therapeutic agents useful in the treatment of C12ORF48 associated disease, such as pancreatic cancer and prostate cancer, as well as methods of inhibiting the cell growth and treating or alleviating one or more disease symptoms.

(www.freepatentsonline.com, Nov 15, 2011)

Cyclic Peptide Antitumor Agents

Inventors Richard B Silverman et al of Northwestern University, USA, have been awarded US patent No. 8058244 B2 on 15th November 2011 for their invention entitled “Cyclic Peptide Antitumor Agents”. Sansalvamide A, produced by a marine fungus, is a cyclic depsipeptide with cytotoxic activity against several cancer cell lines. A study of the mechanism of action of this natural product showed it to be an inhibitor of topoisomerase I. Many cancers like pancreatic cancers do not respond well to chemotherapy. Sansalvamide A is a cyclic depsipeptide with lipophilic properties affording it protease resistance and membrane permeability, allowing for greater oral bioavailability. It is an object of the present invention to provide compounds and/or methods for their preparation and use as antitumor agents, thereby overcoming various deficiencies and shortcomings of the prior art. The search for an effective antitumor agent, for pancreatic and other cancer disease states, remains an on-going concern.

(www.ip.com, Dec 10, 2011)

Pancreatic Cancer Markers

Pancreatic cancer continues to have a high mortality rate due to the horrible prognosis and lack of effective treatments. It is highly resistant to both chemo- and radiation therapies. Currently, the molecular basis for these characteristics of pancreatic cancer is unknown. Thus there is a need for improved methods for the early diagnosis and treatment in form of serum biomarkers for pancreatic cancer. David M Lubman et al have filed an application no. 20110236993, published on 29th September 2011, in USPTO for patenting the invention titled “Pancreatic Cancer Markers”. The present invention provides methods and compositions for the identification of protein glycosylation patterns associated with pancreatic cancer. In some embodiments, the present invention provides a method of diagnosing pancreatic cancer in a subject, comprising detecting the presence of a cancer marker (e.g., Alpha-1- α glycoprotein or amyloid). In fact, 85% of patients initially present with advanced, non-resectable disease, highlighting the importance of identifying early detection biomarkers. In addition, in a subset of patients, it may be difficult to distinguish chronic pancreatitis and pancreatic cancers. A serum biomarker test is expected to improve the efficiency of the diagnosis, where the blood contains the unique secretome of the tumor cells.

(www.freshpatents.com, Nov 29, 2011)

GLOBE SCAN

Metabolite Detection in Pancreatic Cancer

Identification of metabolic features of pancreatic carcinoma by in vivo proton magnetic resonance (MR) spectroscopy at 3 Tesla was sought. Forty healthy volunteers and 40 patients with pancreatic carcinoma confirmed by histopathology underwent T2-weighted imaging. Respiration-triggered (1)HMR spectroscopy was used to detect metabolites in normal pancreas and cancerous tissue. Unsuppressed water at 4.7 ppm was used as an internal reference to determine metabolite concentrations. Each ratio among the different peak areas was statistically evaluated between normal pancreas and pancreatic carcinoma. The following five groups of spectra were detected: unsaturated fatty acids (-CH=CH-) at 5.4 ppm; residual water at 4.7 ppm; choline metabolites at 3.2 ppm; unsaturated fatty acids (-CH₂-CH=CH-) or a combination of N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG), glutamine, glutamate, macromolecules and unsaturated fatty acids (-CH₂-CH=CH-) at 2.0 ppm and lipids at 1.3 ppm. Thus, compared with normal pancreas, pancreatic carcinoma has a higher ratio of fatty acids (-CH=CH-) to lipids and lower ratios of lipids to unsuppressed water and choline to unsuppressed water.

(China: *Radiol Med*, Nov 17, 2011)

Circulating Dendritic Cells

Pancreatic cancer is a malignant neoplasm with a poor prognosis that might be associated with defective immune function. In a study, authors aimed to clarify the role of circulating myeloid dendritic cells (cmDCs) and lymphoid (cl)DCs in patients with unresectable pancreatic cancer. The study covered the period from January 2001 to December 2009, and involved 104 patients with unresectable pancreatic cancer. The number of cmDCs and clDCs using flow cytometry before and after chemotherapy, chemoradiotherapy and immunochemotherapy were measured. The percentage of the cmDC subset in the unresectable pancreatic cancer patients was significantly lower than in healthy volunteers ($p=0.006$). The patients with a high percentage ($\geq 0.23\%$) of cmDC subset survived longer than patients with a low percentage ($<0.23\%$) ($p=0.0030$). The percentage of cmDC subset was significantly increased after immunochemotherapy ($p=0.0055$). The results indicate that a

high level of cmDCs is associated with better survival rate and is an independent favorable prognostic factor in patients with unresectable pancreatic cancer. It is likely that immunochemotherapy increases the number of cmDCs.

(Japan: *Anticancer Research*, Nov 31, 2011)

Partial Pancreatic Resection

Pancreatic resection for cancer may produce pancreatic exocrine insufficiency (PEI), which is poorly understood. This study examined the coefficient of fat absorption (CFA), symptoms, quality of life (QoL) and the accuracy of faecal elastase-1 (FE-1) measurement to predict PEI. Forty patients were analysed following resection for pancreatic malignancy. CFA and FE-1 levels were uncorrelated. Overall, QoL increased at 6 ($p=0.0212$) and 12 ($p<0.0001$) months after surgery, mainly driven by physical, role and social functioning, and by appetite. Importantly, however, Body Mass Index (BMI) and symptoms were unaffected by PEI, which suggests a subclinical presentation; such patients had attributes indicating poorer QoL (notably insomnia, $p=0.0012$). PEI was common and sustained following resection and not associated with significant symptoms. These patients had a tendency toward poorer QoL. FE-1 is a poor surrogate for diagnosing impaired fat absorption. Postoperative pancreatic enzyme replacement should be considered more routinely.

(UK: *Pancreatolgy*, Nov 15, 2011)

Curcumin Analog Inhibits Tumor

The histone methyltransferase EZH2 is a central epigenetic regulator of cell survival, proliferation and cancer stem cell (CSC) function. EZH2 expression is increased in various human cancers, including highly aggressive pancreatic cancers (PC), but the mechanisms underlying for its biological effects are not yet well understood. EZH2 function in PC using CDF, a novel analog of the turmeric spice component curcumin that has anti-oxidant properties was probed. CDF decreased PC cell survival, clonogenicity, formation of pancreatospheres, invasive cell migration and CSC function in human PC cells. These effects were associated with decreased expression of EZH2 and increased expression of a panel of tumor suppressive microRNAs (miRNAs). Taken together, the results indicated that CDF inhibited PC tumor growth and aggressiveness by targeting an EZH2-miRNA regulatory circuit for epigenetically controlled gene expression.

(USA: *Cancer Research*, Nov 22, 2011)

CANCER CONTROL

Anticancer Activity of Green Tea

Researchers at University of California, USA, have reported new molecular targets of green tea extract (GTE) which provide the evidence on anticancer activity of green tea in pancreatic cancer. The scientists exposed GTE to a human pancreatic adenocarcinoma cell line, i.e., HPAF-II cells, to identify the cellular targets of green tea action and performed 2-dimensional gel electrophoresis of cell lysates. Thirty-two proteins were found with significant altered expression levels which are involved in drug resistance, gene regulation, motility, detoxification and metabolism of cancer cells. GTE was found to inhibit the molecular chaperons heat-shock protein 90 (Hsp90), its mitochondrial localized homologue Hsp75 (tumor necrosis factor receptor-associated protein 1 or TRAP 1) and heat-shock protein 27 (Hsp27) concomitantly. The study also showed that GTE inhibited Akt activation, levels of mutant p53 protein and induced apoptosis along with the growth suppression of cells.

(*Proteomics*, Oct 5, 2011)

Cigarette Smoking and Pancreatic Cancer

A research team at Instituto di Ricerche Farmacologiche "Mario Negri", Italy, has analyzed the data from 12 case-control studies within the International Pancreatic Cancer Case-Control Consortium (PanC4). The analysis included 6507 cases of pancreatic cancer and 12890 control subjects to assess the dose response relationship between cigarette smoking and cancer of pancreas and to examine the effects of temporal variables. When compared with never smokers, the odds ratio (OR) was 1.2 for former smokers and 2.2 for current cigarette smokers with a significant increasing risk with increasing number of smoking cigarettes among current smokers (OR = 3.4 for ≥ 35 cigarettes per day). The risk increased with respect to duration of cigarette smoking up to 40 years of smoking. The study concludes that current cigarette smoking is related to a two-fold increased risk of pancreatic cancer which further increases with the number of cigarettes smoked and duration of smoking. Also the risk is found to decrease with increasing time since cigarette smoking cessation reaches the level of never smokers after around 20 years of quitting.

(*Annals of Oncology*, Nov 21, 2011)

Salivary Bacteria Might Signal Pancreatic Cancer

According to a study conducted at David School of Medicine in University of California, Los Angeles, particular types of mouth bacteria are associated with pancreatic cancer and pancreatitis. The initial analysis found significant differences between the bacterial colonies in the saliva of cancer patients (n=10) when compared with those of healthy controls (n=10). It was found that 31 bacterial species were higher and 25 species were fewer in the spit samples of patients with pancreatic cancer than in control subjects. Further, the samples of saliva from 28 patients with pancreatic cancer, 27 with chronic pancreatitis and 28 healthy people were checked to validate the candidate marker bacteria and verify the findings with real-time polymerase chain reaction. Among the six validated candidate bacteria, two- *Neisseria elongata* and *Streptococcus mitis* - were found less often in the mouth of cancer patients than those of their healthy peers, whereas the levels of another species- *Granulicatella adjacens* were significantly higher. The study suggests that the levels of certain bacteria can be used as non-invasive biomarkers with the promise of earlier detection of pancreatic cancer.

(*Medscape Medical News*, Oct 14, 2011)

The Pancreatic Cancer Cohort Consortium

The Pancreatic Cancer Cohort Consortium was formed in 2006 within the framework of National Cancer Institute-Sponsored Cohort Consortium. It consists of more than a dozen prospective epidemiologic cohort studies whose investigators work together to improve the understanding of the etiology of pancreatic cancer through joint or pooled analysis of data. The Pancreatic Cancer Cohort Consortium was formed with initial purpose of conducting a genome-wide association study, PanScan. PanScan involves the identification of genetic factors, environmental exposures and gene-environment interaction which lead to the development of pancreatic cancer. The research also seeks to the development of methods of surveillance and diagnosis for early detection of the disease. PanScan investigators have conducted two genome-wide association studies, PanScan I and PanScan II, which led to the discovery of four novel regions in genome associated with the risk for pancreatic adenocarcinoma. In addition, various other genetic and epidemiologic studies have been planned or published.

(*National Cancer Institute*, Oct 21, 2011)

GUIDELINES AND NEW THERAPIES

2011 ASCO Guidelines

Date	Guidelines
February 22, 2011	American Society of Clinical Oncology Clinical Practice Guideline Update on the Role of Bone Modifying Agents in Metastatic Breast Cancer
April 11, 2011	American Society of Clinical Oncology Provisional Clinical Opinion: Epidermal Growth Factor Receptor(EGFR) Mutation Testing for Patients with Advanced Non-Small Cell Lung Cancer Considering First-Line EGFR Tyrosine-Kinase Inhibitor (TKI) Therapy
July 25, 2011	American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Chemotherapy Sensitivity and Resistance Assays
September 6, 2011	American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small Cell Lung Cancer
September 6, 2011	American Society of Clinical Oncology Endorsement of the Cancer Care Ontario Practice Guideline on Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Invasive Breast Cancer
September 26, 2011	Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

FDA Approvals of Anticancer Agents, September 2010-September 2011

Generic Name	Trade Name	Indications	Date of Approval
Denosumab	Xgeva	Prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors	November 18, 2010
Ipilimumab	Yervoy	For the treatment of unresectable or metastatic melanoma	March 25, 2011
Vandetanib	Vandetanib	For the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced, or metastatic disease	April 6, 2011
Abiraterone Acetate	Zytiga	Use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel	April 28, 2011
Vemurafenib	Zelboraf	Treatment of patients with unresectable or metastatic melanoma with the BRAFV600E mutation as detected by an FDA-approved test	August 17, 2011
Brentuximab Vedotin	Adcetris	Accelerated approval for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates and the treatment of patients with systemic anaplastic large cell lymphoma (ALCL) after failure of at least one prior multi-agent chemotherapy regimen	August 19, 2011
Crizotinib	Xalkori	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA approved test, Vysis ALK Break-Apart FISH Probe Kit	August 26, 2011

(American Society of Clinical Oncology, Clinical Cancer Advances, 2011)



INTERNATIONAL PROSTATE CANCER SYMPOSIUM & FIRST NATIONAL CONFERENCE ON MEN'S HEALTH (THEME: PROSTATE)

**11th International Conference of
Rajiv Gandhi Cancer Institute & Research Centre, Delhi, India**

VENUE:

**6th April 2012 - Auditorium: PGIMER & Dr. RML Hospital, New Delhi
7th & 8th April 2012 - Sovereign Hall, Le Meridien, New Delhi**

INTERNATIONAL FACULTY

Ajay Nehra, USA
Ashok Hemal, USA
Ashish Kamat, USA
Andrew Vickers, USA
Bernd J. Krause, USA

Chandan Guha, USA
Deborah Kuban, USA
David Macleod, USA
Fritz H. Schröder, USA
Hui Meng Tan, Malaysia

John Davis, USA
James Eastham, USA
Monique Roobol, USA
Pramod Sogani, USA
Robert Stein, USA

Ridwan Shabsigh, USA
Shiv Srivastava, USA
Shigeo Horie, Japan
Siegfried Meryn, Austria
Vikram S Dogra, USA

TENTATIVE SCIENTIFIC PROGRAM

- Is single port minimally invasive surgery the future in Uro Oncology
- Single Port Robotic Radical Prostatectomy (Live Demonstration)
- Status of Robotic Radical Prostatectomy in India
- Robotic Radical Prostatectomy (Live Demonstration)
- Da Vinci Robotic System in Oncology Centre in India
- Screening of Carcinoma Prostate (Panel Discussion)
- Molecular basis of Carcinoma Prostate
- Pathology of Prostate Cancer
- Evolution of Radiation Techniques in Management of Carcinoma Prostate
- Treatment options in Carcinoma Prostate (Panel Discussion)
- Advances in Imaging of Carcinoma Prostate
- Hormone Therapy - past, present & future
- Hormone Therapy with Radiation in Carcinoma Prostate
- Hormone Therapy with Radical Prostatectomy
- Advances in Hormone Refractory Carcinoma Prostate
- Bone health (Bisphosphonates and RANK ligand Inhibitors) in Carcinoma Prostate
- Ablative therapy in Prostate Cancer
- Role of Radiation in Palliation of Carcinoma Prostate

Symposium: Why men die earlier and suffer more

- Statistics on men
- Hypogonadism
- MHSI Oration: Diabetes and Indian men
- Panel discussion: New strategies in the management of ED and LUTS

- Guest Lecture: Micropenis and its management
- Cardiovascular diseases in men
- Debate: Testosterone supplementation in elderly men is dangerous
- Psychiatric afflictions in men

Lectures: The evolution of men's health as a specialty, Lessons from the European Men's Health Study

- Where the world is going on men's health
- Symposium: Spreading the word on men's health

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