INDIAN COUNCIL OF MEDICAL RESEARCH

CONSENSUS DOCUMENT FOR MANAGEMENT OF PANCREATIC CANCER

Prepared as an outcome of ICMR Subcommittee on Pancreatic Cancer

ICMR

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Division of Non Communicable Diseases
Indian Council of Medical Research
2019

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

Foreword

I am glad to write this foreword for Consensus Document for Management of Pancreatic Cancers. 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.

Pancreatic Cancers 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 Pancreatic Cancers 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 Pancreatic Cancers would serve desired purpose.

(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

Pancreatic Cancer remains an aggressive cancer with a dismal long term prognosis. Radical pancreatic surgery, currently the only option for cure, is feasible in only 40% patients since the vast majority present to the clinician in advanced stages of the disease. Fortunately, the past 2 decades have not only seen tremendous refinements in surgical technique with improved short and long term outcomes, but the molecular understanding has progressed enormously. Simultaneously, medical and radiation oncology has witnessed excellent progress that has clearly resulted in a paradigm shift in the management of pancreatic cancer. It is no surprise that Pancreatic Cancer in 2019 is treated in a multi-disciplinary fashion with superior outcomes.

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.

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

Prof Shailesh V Shrikhande
Chairperson, Sub-committee Pancreatic Cancers
Professor & Head, Division of Cancer Surgery
Chief, Gastrointestinal and Hepato-Pancreato-Biliary Service
Deputy Director. Tata Memorial Hospital, Mumbai

Dr Bhawna Sirohi
Co- Chairperson
Director, Medical Oncology
Max Healthcare, New Delhi

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.
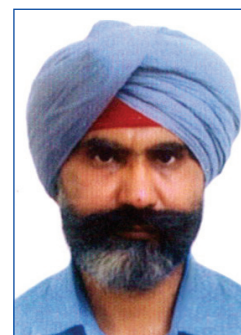
The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document 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 Pancreatic Cancer 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. 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 benefits 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

1 ALGORITHM FOR PANCREATIC CANCER

PANCREATIC CANCER (Adenocarcinoma)

Upper Abdominal Pain, Anorexia, Unexplained weight loss, Obstructive Jaundice

- Triphasic thin sliced (Pancreas protocol) CT abdomen and pelvis Or Contrast-enhanced MRI + CT Thorax
- Liver function tests / Coagulation profile / Pretreatment S. CA 19-9 levels (after normalization of liver functions)

Optional Procedures
- ERCP & temporary stenting (plastic / short metal) ± Biopsy / Brush biopsy / Bile cytology (Symptomatic jaundice / asymptomatic jaundice with S. Bilirubin higher than 20 mg% (prior to surgery) / prior to neoadjuvant chemoradiotherapy in borderline resectable tumors)
- EUS ± FNAC (Borderline resectable tumors, No clear mass on radiology, Pancreatitis, locally advanced non-metastatic tumors)
- Laparoscopy ± biopsy/ Peritoneal washings (Borderline resectable /Locally advanced large tumor, tumor with suspected metastatic nodes, high CA 19-9 (in absence of obstructive jaundice), Repeated EUS guided FNAC's are –ve in borderline or locally advanced or metastatic cases for planning non surgical treatment.

A :Resectable (Stage-1)
Periampullary / head mass - PPPD
D1 tumor - Classical Whipple
Body & tail - Distal pancreatectomy ± Splenectomy, median pancraetectomy
Locally advanced inoperable at surgery
Biopsy confirmation
Biliary/ Gastric bypass – (endoscopic or surgical),
if indicated
See B

B: Borderline (Stage-2)/ Locally advanced (Stage-3)
Confirm tissue diagnosis
NACT/RT in good PS patient (Trial)
Re- staging (To see Table A)
Resectable
PPPD/ Classical Whipple/ Distal pancreatosplenectomy
Not resectable at surgery/ Disease progression
Second line chemo±Targetted Therapy(To see Table B)
Metastatic
See C

C : Metastatic (Stage-4)/ Inoperable cases /Poor PS/ASA4
Confirm tissue Diagnosis of metastases

Locally Inoperable / ASA 4
Chemotherapy 3 to 4 # F/B CTRT F/B 3 to 4 # chemotherapy
Palliative Chemoradiotherapy
Metastatic
Palliative Chemotherapy +Targeted therapy(To see Table B)
Palliation
Biliary and gastric bypass
ERCP & Metal Stenting/Duodenal stenting / PEG (Non surgical candidate with Jaundice / GOO)
Pain management (EUS Guided or intraoperative Celiac block or RT if not earlier received)
Poor PS
Nutritional support, Best supportive care

Adjuvant Therapy (within 8 weeks)
PT2 or less, R0 resection
Observe
More than PT2/ All Patients with NACT/RT
Chemotherapy
Locally inoperable/ R+ Resection
Chemo radiotherapy ± Targeted Therapy

Surveillance
Every 3 months for 2 years followed by every 6 months for 3 years then annually. Each visit S. CA 19-9, CT (A+P) & Thorax, CBC & Biochemistry

Recurrence
Confirm Tissue diagnosis
Early Local
CT/RT (If not received earlier)
Second line CT (Trial)
Late Local
CT/RT (If not received earlier
Chemotherapy (Trial)
Metastatic
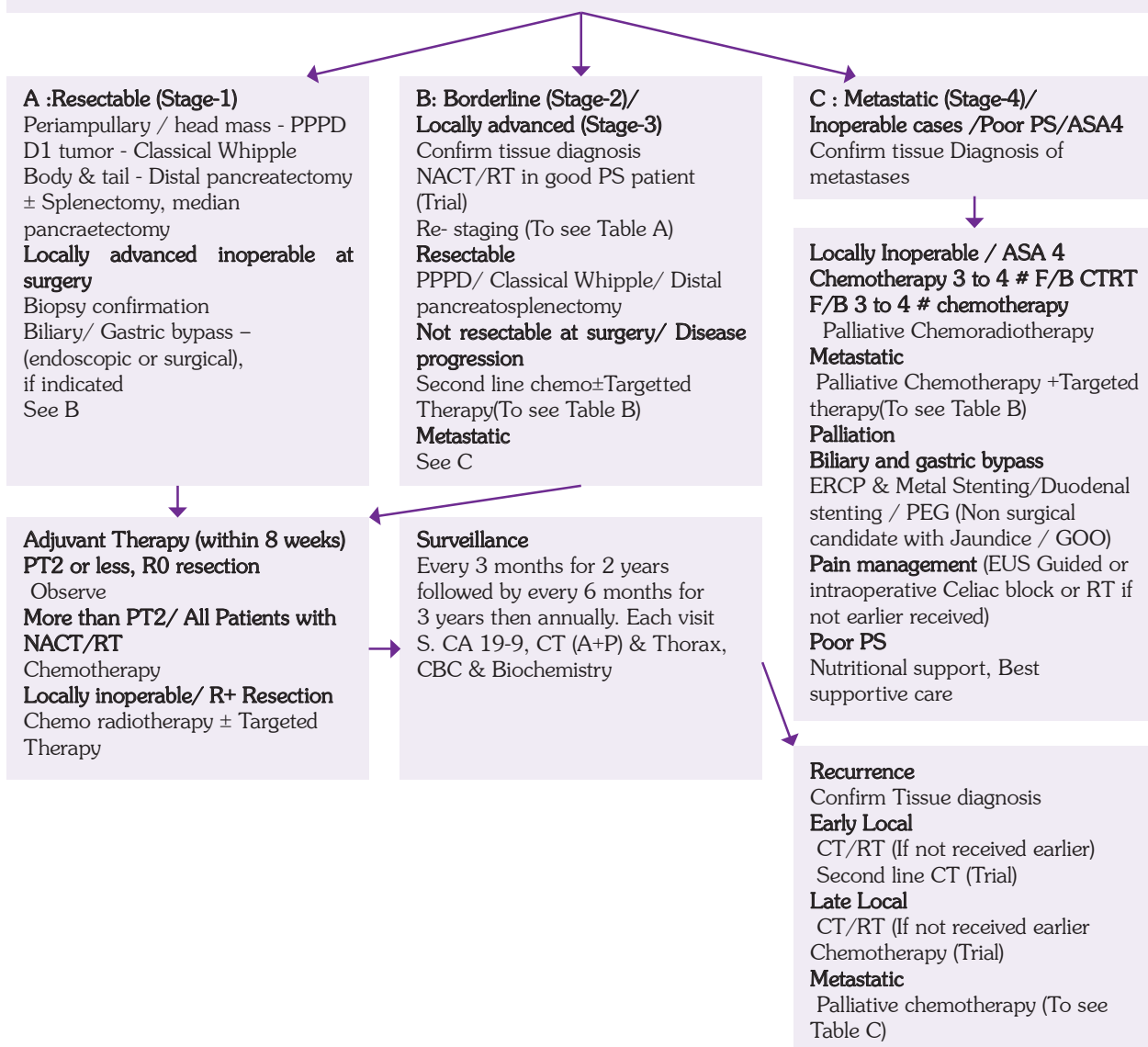Palliative chemotherapy (To see Table C)

Table A:	FOLFIRINOX 4 # OR GEMOX 4 #
Table B:	Gemox Gemcitabine + Erlotinib Gemcitabine + NAB Paclitaxel
Table C	Gemcitabine single agent Gemcitabine +Platinum Gemcitabine + Erlotinib Gemcitabine+ Nab Paclitaxel FOLFIRINOX FOLFIRI

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) Guidelines 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 these guidelines.

- Histological confirmation 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.

- Patients should receive multidisciplinary care under the care of a surgical, medical, and radiation oncologist.

- Patients should be classified as resectable, borderline resectable or locally advanced based on radiologic criteria at diagnosis and treatment plan discussed accordingly.

- Resectable Pancreatic Cancer - Primary Surgery remains the standard of care. Neoadjuvant therapy (chemotherapy +/- radiotherapy) should be considered in locally advanced and borderline resectable tumours to downstage the disease followed by reassessment for surgery in those with stable or partial regression radiological criteria. This may be followed by adjuvant chemotherapy.

- Patients with metastatic pancreatic cancer beyond the regional lymph nodes, should be assessed for chemotherapy versus best supportive care on an individual basis.

- Preferred first-line regimens for chemotherapy include –Gemcitabine-Nab Paclitaxel, FOLFIRINOX.

- 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.

3 EPIDEMIOLOGY

Pancreatic cancer is the 12th most common cancer and the 4th leading cause of cancer-related deaths in the world (1-3) (4). The age-standardized incidence rates of the cancer vary considerably in different parts of the world from as low as 0.6/100,000 persons per year in regions of Asia to as high as 12.6/100,000 in the West (5). The age-standardised incidence rates for pancreatic cancer on an average are 8.2 and 2.7/100,000 amongst males in the developed and developing countries, respectively and 5.4 and 2.1/100,000 amongst females in the developed and developing countries, respectively (6).

In India, the incidence rates of pancreatic cancer are low compared to western countries. In India, the incidence of pancreatic cancer is 0.5-2.4/100,000 persons per year in women - 0.2-1.8/100,000 persons per year in men (7). However, irrespective of the incidence of the disease, survival in patients with pancreatic cancer is generally low with the 1-year and 5-year relative survival rates for all stages being 29% and 7%, respectively (8). The cause for such poor long-term outcomes is possibly related to the fact that the disease is largely asymptomatic in the early stages and by the time symptoms do develop, the disease is locally advanced or metastatic. Only 10-20% of patients have resectable pancreatic cancer at presentation (9). In the midst of all the dismal statistics for pancreatic cancer, there are some aspects that need to be appreciated, viz. the 5-year survival rates for patients with localised disease who are amenable to curative resection is 22% as compared to 2% for those with distant disease (8).

Table 1 provides the age-adjusted / age-standardized rates for pancreatic carcinoma from different parts of India (10). Pancreatic adenocarcinoma is more common in men as compared to women. Pancreatic cancer tends to occur later in life in the Western countries as compared to India where it probably occurs a decade earlier (11, 12).

Table 1: Age-adjusted / age-standardised (ASR) pancreatic carcinoma incidence rates in India (expressed per 100,000 persons) (10)

Location	Males	Females
Chennai	1.4	0.7
Karunagapally	2.5	1.2
Mumbai	2.2	1.6
Nagpur	1.3	0.5
New Delhi	2.1	1.4
Poona	1.9	1.2
Trivandrum	1.7	1.0

Table 2 provides an estimate of the number of pancreatic cancer cases in India over the next few years based on the data from the National Cancer Registry Programme (ICMR, Bangalore) (13).

Table 2: Pancreatic Cancer estimates until 2020 in India

Year	Estimated number of new cancers (all ages)		Both sexes
	Male	Female	
2010	7304	5128	12432
2015	7851	5588	13440
2020	8440	6090	14530

The mortality figures from Indian registries suffer with problem of under-reporting because of problems in registration of death and in reporting of cause of death.

Risk factors for pancreatic cancer

Risk factors for pancreatic cancer can be divided into genetic and acquired. Pancreatic cancer has a familial component in about 10% of cases. The risk increases with the number of first degree relatives involved (14). The exact genetic basis of this inherited predisposition remains unknown in over 80% of cases (15). The most common inherited mutation in familial pancreatic cancer is probably in the BRCA2 gene. Other associated germline mutations include p16, ATM, STK11, PRSS1/PRSS2, SPINK1, PALB2, and DNA mismatch repair genes (16).

The defined familial cancer syndromes associated with an increased risk for pancreatic cancer include hereditary pancreatitis, Peutz-Jeghers syndrome, hereditary breast and ovarian cancer syndrome, Familial Atypical Multiple Mole Melanoma syndrome, Lynch syndrome, and Li-Fraumeni syndrome. A detailed description of these syndromes is beyond the scope of this document. However, a thorough family history should be taken of additional relatives with pancreatic cancer, pancreatitis, melanoma, and cancers of the colon and rectum, breast, and ovaries.

Acquired risk factors for pancreatic cancer include cigarette smoking, obesity, and diabetes (both type 1 and type 2). Recent onset after 50 years as well as long-term diabetes are considered as risk factors for pancreatic cancer (17, 18). Other factors including alcohol use and dietary habits have less rigorous risk association. Perhaps the most important risk factor for pancreatic cancer in our country is chronic pancreatitis, which should be considered as a pre-malignant condition (19, 20).

Pre-malignant lesions

Cystic neoplasia represent 10%–15% of cystic lesions of the pancreas (21). Intra-ductal papillary mucinous neoplasia (IPMN) and mucinous cystic neoplasia (MCN) are pre-malignant cystic lesions of the pancreas. The non-mucinous lesions have no malignant potential. With increasing use of abdominal imaging, incidental and often asymptomatic cystic pancreatic lesions are being detected with rising frequency.

The initial evaluation of cystic pancreatic lesions should be contrast enhanced magnetic resonance imaging (MRI). Endoscopic ultrasound (EUS) is also indicated in most cases, unless the decision for surgery is evident. EUS-guided cyst fluid aspiration should only be performed when the results of cyst fluid analysis are expected to alter management. Treatment decisions in patients with IPMN are based on clinical and morphological criteria. All MCNs should be resected in medically fit patients with reasonable longevity. Recurrences are not seen after resection, and surveillance is not needed (22). After surgery for IPMN, surveillance of the remnant pancreas is indicated.

Clinical features

The initial symptoms of pancreatic cancer may be non-specific including weight loss, abdominal pain, nausea, and dyspepsia. Around 60%-70% of cancers arise in the head of pancreas, and these patients present with jaundice, pale stools, and itching. Tumours of the body and tail are often diagnosed at a more advanced stage. Some patients may have new onset diabetes, depression, or thrombophlebitis.

Acute pancreatitis may be a manifestation of pancreatic cancer, especially when it occurs for the first time in an older adult without any obvious reason. Patients with chronic pancreatitis with super-added carcinoma may present with worsening pain, weight loss, and worsening diabetes control. In a long-standing diabetic patient sudden unexplained weight loss, or loss of blood sugar control may be features of pancreatic cancer.

4 DIAGNOSIS, CRITERIA AND INITIAL WORKUP

The baseline performance status, symptom burden, and comorbidity profile of patients with pancreatic cancer should be documented. Performance status of the patient is an important prognostic factor. An evaluation of patient beliefs and preferences, and available support systems should be carried out at the initial visits. An early palliative care consult should be encouraged. Disease management plans should be formulated with a multi-disciplinary collaboration.

The work-up of pancreatic cancer can be divided into confirmation of the diagnosis, and classifying the extent of the disease. Pancreatic cancer is staged as per the AJCC system. However, a more clinically relevant way to classify pancreatic cancer is into the following categories:

- Potentially curable
  - ○ Resectable.
  - ○ Borderline resectable.
- Unresectable, locally advanced.
- Metastatic.

At the time of diagnosis, pancreatic ductal adenocarcinoma is resectable in only 15%-20% cases. These are the only potentially curable patients, but even in this category 5-year survival rates are around 20% after surgical resection.

The subcategory of borderline resectable carcinomas include potentially curable patients in whom there is a higher likelihood of incomplete resection and positive surgical margins, when surgery is used as the initial treatment (23). Anatomic definitions of borderline resectable cancers are generally well accepted now (24). These patients may be considered for neoadjuvant treatment in preference to upfront surgical resection. If operated, the surgeon should be prepared for reconstruction of PV-SMV to achieve negative resection margins.

Unresectable, locally advanced cancers do not have distant spread, but surgical resection is still not possible because of vascular involvement of larger arteries like SMA, CHA, or celiac, and/ or non-reconstructible SMV/PV involvement. This category makes up 30%-40% of all pancreatic cancers at diagnosis.

Initial biochemical evaluation of suspected or proven patients with pancreatic cancer should include the liver function tests, fasting blood sugars, HbA1c, CA 19-9 and CEA levels.

CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 80% to 90% in symptomatic patients (25). CA 19-9 levels may be elevated in conditions other than cancer, including benign or malignant biliary obstruction and cholangitis. For an accurate baseline, the CA 19-9 levels

should be measured after the bilirubin levels have normalized. CA 19-9 may be undetectable in Lewis antigen-negative patients with pancreatic cancer.

Preoperative CA 19-9 levels correlate with both AJCC staging and resectability (26). A preoperative serum CA 19-9 level 500 UI/ml indicates a worse prognosis after surgery. However, there is no absolute CA 19-9 level that precludes surgery by itself. A decline in levels of CA 19-9 after chemotherapy in both neoadjuvant settings and advanced disease may be an independent prognostic factor for survival (27, 28). Conversely lack of normalization postoperatively is predictive of poor prognosis (29).

- CT scan: Pancreatic protocol CT scan is the key test for imaging confirmation of pancreatic cancer, and for staging of the disease. The CT scan should cover the pelvis, and may extend to the chest for complete staging. For patients with limited, potentially curable disease within the abdomen, a standard chest radiograph may be as effective as to exclude pulmonary metastasis (29, 30). A pancreatic protocol CT acquires sub-millimeter axial sections with images obtained in the pancreatic phase (40-50 seconds) and portal venous phase (65-70 seconds) of contrast enhancement. Neutral oral contrast is used to distend the bowel (31). In majority of cases, there is maximal contrast between the hypo-enhancing pancreatic cancer and enhancing surrounding parenchyma in the pancreatic phase. Hepatic metastasis and interface between the pancreatic tumour and portal and superior mesenteric veins are best evaluated in the portal venous phase.

- MRI: MRI should be used as a problem-solving tool for characterization of CT-indeterminate liver lesions, or in cases with severe allergy to iodinated intravenous contrast material. MRI is equivalent in its ability to detect and stage pancreatic cancer.

- PET/CT scan: The role of PET/CT is not established in pancreatic cancer. PET/CT scan may be considered after formal pancreatic CT protocol in high-risk patients to detect extra pancreatic metastases. Indicators of high-risk may include borderline resectable disease, markedly elevated CA 19-9, large primary tumours, or large regional lymph nodes. PET scan is not a substitute for high-quality, contrast-enhanced CT.

- Endoscopic ultrasound (EUS): EUS is complementary to CT scans, and is used selectively. It is most useful when a pancreatic cancer is suspected but CT and/or MR cannot demonstrate the tumour. These situations include unexplained dilatation or stricture of pancreatic and /or bile duct, raised CA 19-9 levels, unexplained acute pancreatitis in an older adult, or sudden unexplained worsening in a patient with diabetes or chronic pancreatitis. In CT- demonstrable lesions, EUS may be indicated to evaluate vascular involvement especially when the cancer is staged as resectable. The sensitivity of current CT scans is suboptimal for establishing resectability. On the other hand, CT can determine non-resectability of the tumours with a high positive predictive value (>90%) (32). In borderline resectable and locally advanced, unresectable tumours EUS may be indicated for obtaining tissue diagnosis, and pain palliation (see below). The overall accuracy of EUS for tissue diagnosis of pancreatic cancer is around 95%. In addition, EUS allows evaluation of distant nodal spread including aorto-caval and mediastinal nodes, and small CT- inapparent, small hepatic metastasis.

- ERCP: There is no role for diagnostic ERCP in the current era. Direct pancreatogram is now rarely needed for diagnosis of pancreatic cancer. The role of ERCP is restricted to biliary stenting. Cholangiogram done at time of stenting may suggest the diagnosis, and intra-ductal sampling (brushings) may be obtained for a tissue diagnosis before the stenting. Positive yield of biliary brushings is lower in cases of pancreatic cancer compared with cholangiocarcinoma.

- Laparoscopy: Among resectable patients, staging laparoscopy may be considered in patients at high risk for disseminated disease (high CA 19-9, large primary tumours, large regional lymph nodes, body-tail tumours). Laparoscopy can identify peritoneal, capsular, or serosal implants that are radiologically inapparent even with the use of a pancreatic CT protocol or EUS.

Tissue diagnosis

- When the imaging features are suggestive of a ductal carcinoma, tumour is clearly resectable, and the patient is medically fit, tissue confirmation is not indicated before surgery. The negative predictive value of a negative biopsy is too low to rule out cancer. In India, where a large proportion of pancreatic cancers arise in the background of chronic calcific pancreatitis, the sensitivity of tissue diagnosis is even lower.

- Biopsy confirmation is required for any patient who is a candidate for neoadjuvant treatment, including borderline resectable patients. EUS-guided biopsy is preferred over percutaneous image guided biopsy in these patients because of better diagnostic yield, safety and potentially lower risk of peritoneal seeding (33, 34).

- Patients who have locally advanced or metastatic disease should undergo biopsy confirmation initially. For easily accessible metastatic site(s) like liver metastasis a percutaneous approach is acceptable. Some patients have duodenal infiltration, and a biopsy can be obtained by standard gastroscopy. For other patients, an EUS-guided sampling may be considered, but offers no definite advantage over the image-guided percutaneous approach in this patient group. The advantages of percutaneous approach over EUS-guided sampling are its lower cost, wider availability in India, and wider applicability among sicker patients where sedation may be hazardous.

Summary

Essential investigation (minimum optimal)

Helical CT of the abdomen and pelvis plus chest radiography/CT

Ideal method (optimal with highest evidence)

MDCT of the chest, abdomen, and pelvis

EUS in select cases of borderline resectable tumours to assess relationship of the tumour to mesenteric vessels and for FNA in case of borderline resectable, locally advanced or metastatic tumours prior to commencing neoadjuvant / palliative therapy

MRI of the liver—only for problem solving

Medical management: Gastroenterologist's role

Biliary stenting

Indications for biliary stenting are controversial before upfront surgery. Most groups who perform resection without neoadjuvant treatment advocate selective use of decompression in patients who are symptomatic, septic, coagulopathic, have renal insufficiency, or in whom surgical resection is significantly delayed (23). Many surgeons also request for biliary decompression if the patient is deeply jaundiced, often with a bilirubin level of >15mg/dl. However, there is space data to support this practice.

For jaundiced patients undergoing neoadjuvant therapy before resection or chemotherapy for advanced disease, biliary decompression is mandatory. Usually bilirubin levels less than 3mg/dL are prerequisite for

chemotherapy. A self-expanding metal stent (SEMS) of short length is preferred to plastic stent(s) for this indication. Biliary stenting also relieves pruritus and improves the quality of life. Uncovered SEMS should never be placed prior to confirmatory tissue diagnosis of malignancy.

Endoscopically placed biliary stents are preferred to surgical hepatico-jejunostomy for relief of biliary obstruction. SEMS have an advantage over plastic stents in terms of wider diameter, faster resolution of jaundice, and less need for re-interventions. However, plastic stents are much cheaper and may be considered on an economic basis in patients who have advanced disease and limited life expectancy.

Enteral stenting

A proportion of patients with carcinoma of head-pancreas will develop obstruction of the first and second part of duodenum. Additionally, patients with advanced tumours of tail-pancreas can have instruction of the third and fourth parts of duodenum. Overall, symptomatic gastric outlet obstruction develops in 10%-25% patients with pancreatic cancer (34), and should be suspected in patients with persistent vomiting, bloating, and rapid decline in nutrition. Endoscopically placed enteral stents are preferable to surgical bypass for palliation in these patients, with median duration of stent potency of 6 months (35). Endoscopic re-intervention is possible when the stents block in surviving patients.

Relief of simultaneous biliary and general obstruction.

Biliary obstruction is usually tackled first before placing enteral stents across the papilla, as subsequent wire manipulation across the papilla can then become difficult. Some patients with inaccessible papilla due to duodenal obstruction may need percutaneous trans-papillary biliary stent placement. This can then be followed by endoscopic enteral stenting.

Pain relief

The pain in pancreatic cancer is because of retroperitoneal neural plexus invasion (neuropathic), pancreatic duct obstruction, biliary and/or enteric obstruction, or from metastatic sites. Pancreatic cancer has a propensity for peri-neural extension so that besides standard analgesics, medications like gabapentin, pregabalin, nortriptyline, or duloxetine may be added. Patients with pancreatic cancer may benefit from celiac plexus neurolysis (CPN) and palliative radiotherapy. Celiac plexus neurolysis should be carried out under EUS guidance. EUS-guided trans-gastric approach is much easier and safer than the posterior radiological approach. However, there is limited evidence of improved efficacy with any method of ablation.

EUS guided CPN can be combined with EUS staging and tissue confirmation in the same sedation. Absolute alcohol is the agent used, and injected around the base of the celiac trunk (CPN). Direct injection into the celiac ganglia (CGN) or around the superior mesenteric artery (broad plexus block) are recent refinements, that increase the efficacy of pain relief.

Pancreatic enzyme replacement

Pancreatic enzyme replacement for secondary exocrine insufficiency due to pancreatic ductal obstruction may be helpful. Enzyme replacement may be particularly indicated when there is underlying chronic pancreatitis or when more than half of the duct is blocked. In addition, after pancreatic resection, exocrine insufficiency is seen in >90% patients, and enzyme replacement is indicated in most (36). Consultation with a dietician, and appetite stimulant medications like magestrol acetate or dronabinol may be useful.

Pancreatic hormone replacement

Patients who develop diabetes mellitus as a result of the cancer or following resectional surgery for the cancer, will likely require insulin therapy. This decision should be made based on a case by case assessment by a Physician / Endocrinologist.

Prophylaxis and treatment of venous thromboembolism (VTE)

Patients with pancreatic cancer have increased risk of venous thrombosis. VTE leads to shortened survival, and is the second leading cause of death after the cancer itself (37). Low molecular weight heparin (LMWH) may be preferable to Warfarin for prophylaxis and treatment (38). LMWH use decreases the incidence of VTE (39), but there is lack of evidence regarding improvement in survival.

5 STAGING AND PROGNOSTIC CRITERIA

Staging

Please refer to *Appendix* for:

- Site specific staging

- Grading & Histological Classification

- Nomenclature

- Pathological reporting of Pancreatic cancer

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.

Treatment of the primary tumour

Extent of resection

Based on the staging of the pancreatic carcinoma by a combination of modalities, these tumours may be divided into the following groups in order of worsening prognosis (40-42):

• Resectable pancreatic cancer,

• Borderline resectable pancreatic cancer,

• Locally advanced pancreatic cancer, or

• Metastatic pancreatic cancer

Surgery offers the best outcome for tumours that are resectable, so long as a complete resection (R0) can be achieved. Surgical resection for carcinoma of the head and/or neck of pancreas involves a Pancreatoduodenectomy (PD) while a distal or subtotal pancreatectomy is performed for carcinomas of the body and tail and some tumours at the junction of the neck and body.

Resectable Pancreatic cancer

Pancreatoduodenectomy (PD)

PD has been subdivided into Classical and Pylorus-preserving depending on the inclusion, or exclusion, of the antrum and pylorus from the en bloc resection.

No difference in oncological outcomes has been noted between pylorus-preserving PD and the Classic Whipple (43, 44). As a result, in patients undergoing PD for periampullary and pancreatic head cancers, the performance of pylorus preservation or classic Whipple remains the prerogative of the surgeon. On the other hand, the performance of the classic Whipple should be reserved exclusively for duodenal cancers (part of periampullary tumours) or large pancreatic head tumours invading the gastric antrum and / or the first part of duodenum.

Reconstruction

While there has been considerable debate over the choice of the pancreaticoenteric reconstruction technique, the most recent meta-analysis has concluded that there exists no difference in the rate of overall and clinically significant post-operative pancreatic fistula (POPF), morbidity, mortality, reoperation, and intra-abdominal sepsis between PG and PJ (45). Further, there besides the reduction in hospital stay, the duct-to-mucosa PJ has not shown to reduce complication rates as compared to the invagination technique (46). Thus, the choice of pancreaticoenteric anastomosis should be based on the surgeon's experience so long as the technique is standardized, and meticulous (12) based on sound surgical principles and a low post-operative pancreatic fistula rate (47, 48).

Antecolic gastro-/duodeno-jejunostomy has been shown to be associated with a significantly reduced rate of delayed gastric emptying (49) possibly due to the avoidance of torsion or angulation that may occur with a retrocolic anastomosis.

A review of literature demonstrated that in order to improve outcomes of the anastomoses following PD, good vascularity, absence of tension, absence of main pancreatic ductal and distal obstruction, use of fine (4-0, 5-0, 6-0) sutures, main pancreatic duct to mucosa approximation and high-volume (including high surgeon-volume) were important factors (50).

Distal / Subtotal pancreatectomy

Brennan et al. (51) suggested an equally aggressive approach similar to PD when managing tumours of the body and tail of the pancreas. Current evidence supports the performance of a splenectomy along with a distal / subtotal pancreatectomy to attain a complete resection for carcinomas (52).

While the choice of closure of the pancreatic remnant has been a matter of debate, current evidence (53) concedes that although there is a trend towards the use of staplers (54), the available information cannot convincingly make a definite choice between sutures or staplers (55). The outcomes following hand-sewn closure of the pancreatic remnant after stapled or scalpel resection are comparable in terms of POPF, overall mortality and surgical time (56)

Extended resections

The term 'extended resections' encompasses numerous subclasses including, extended lymphadenectomy (discussed above), vascular resections, multivisceral resections and metastatectomies.

In the case of carcinomas of the body and tail, it has been found at the time of surgery that approximately 35% of patients (57) with tumours of the body and tail had evidence of involvement of surrounding structures either by tumour infiltration or inflammatory adhesions. In such circumstances, it is advisable to even resort to en bloc resections to obtain negative surgical margins. Shoup et al. (58), found that patients undergoing extended resections for the carcinomas of the pancreatic body and tail have long-term survival rates similar to those for patients undergoing standard resection for less aggressive tumours, and markedly improved long-term survival compared to those who are not considered resectable because of locally advanced disease.

Multivisceral resections

Although they are technically feasible, based on the limited data available, these resections are associated with improved survival (5-year survival rates of 16-22%) (58, 59) as compared to no resection and comparable survival to standard resections for lesions that do not involve adjacent organs when performed in high volume centres with the necessary expertise (60, 61). Given the high morbidity and even mortality

associated with these procedures, they should be performed only when the possibility of achieving R0 seems distinctly feasible.

Borderline resectable tumours

More recently an entity termed borderline resectable pancreatic cancer (BRT), has been proposed and its definition continues to evolve (62). The National Comprehensive Cancer Network (NCCN) describes borderline-resectable pancreatic head (and body) cancer as tumour abutment of the superior mesenteric artery (SMA), severe unilateral superior mesenteric vein (SMV) or portal vein (PV) impingement, gastroduodenal artery (GDA) encasement up to its origin from the hepatic artery, or colon and mesocolon invasion (63). The ideal treatment of patients with BRTs needs to be established. The choice of management of these patients varies between neoadjuvant chemoradiotherapy (42) versus surgery at the first instance (40, 64). If a patient presents with features clearly indicative of BRT as per radiological features, then such patients must be considered for a staging laparoscopy followed by neoadjuvant chemotherapy (if non-metastatic) followed by a trial of resection (if the disease remains non progressive) with the need for synchronous venous resection and reconstruction.

Vascular resections

While venous resections and reconstructions have been promoted as part of the en bloc resection of borderline resectable tumours (65), the most updated meta-analysis (66) has shown an increased postoperative mortality, higher rates of non-radical surgery and worse survival after such resections.

These findings are likely due to two pertinent factors, viz. (1) Depth of venous invasion (67) - Involvement of tunica media and intima was associated with poor outcomes even in a complete resection; and (2) Length of invasion (68) - Length of involvement more than 3 cm was associated with poor outcomes.

There is no data to support the performance of arterial resections at the time of surgery for pancreatic cancer. They have been found to be associated not only with increased morbidity and mortality, but a survival comparable to non-resected patients (69, 70).

The role of synchronous vascular resections thus needs to be more carefully studied and such resections performed in highly selected individuals preferably within the confines of clinical trials.

Technical refinements to improve resections in borderline resectable tumours and in vascular and multivisceral resections – the uncinate-first approach and the superior mesenteric artery (SMA)-first approach

The uncinate-first approach has been specifically described in 2007 (71) and is similar to the approach described by Hackert et al. (72). This approach seems to be more suitable for infiltration of the SMV or portal vein. The SMA-first approach seems to be suitable for infiltration of the arterial axis.

The operative technique of the SMA-first approach comprises of early dissection of the SMA (after performance of the Kocher's maneuver of the duodenum) along with the posterior pancreatic capsule. The potential advantage of this approach (73) is that technical difficulties which may be encountered either due to tumour infiltration of the superior mesenteric vein (SMV), main portal vein (MPV) or tumour proximity to the right of the SMA can be handled right at the initial stages of the resection. This may also help in reducing the chances of margin positive pancreatic head resections. Other reported advantages are improved lymph node yield by dissection of more lymph nodes along the right border of the SMV / MPV and SMA (74-76). Both these approaches aid in vascular resections, large uncinate process tumours and also in multivisceral resections.

Pancreatic resection in metastatic disease

Although technically feasible (77), there is no clear evidence to demonstrate an overall survival benefit of the performance of metastatectomy in patients with resectable pancreatic cancer (60, 78).

Laparoscopy for pancreatic carcinoma

Laparoscopic resections for pancreatic tumours are feasible (79-81). However, at present there is no high-level evidence to suggest that laparoscopic PD is equal or superior to open surgery in terms of overall survival (81). In the case of a complex procedure like PD, the appreciation that the morbidity of PD (pancreatic leak, haemorrhage, delayed gastric emptying) is not related to the length of the abdominal incision but to the extensive nature of the actual intra-abdominal surgery (82) deserves due consideration.

Laparoscopic distal pancreatectomy has also been demonstrated to be technically feasible with acceptable perioperative outcomes (83). The perceived short-term benefits of accelerated recovery have recently been questioned in a well conducted trial looking at readmission rates (83). The perceived benefit of reduced hospital stay appears to be completely offset by the high readmission rates following laparoscopic distal pancreatectomy. There is no long-term data demonstrating an improvement in survival of laparoscopic surgery over open surgery for carcinomas of the pancreas. The use of enhanced recovery clinical pathways with a shortened hospital stay (84) offset the proposed advantages of early recovery with laparoscopy in pancreatic cancer.

Treatment of lymph nodes / lymphadenectomy

As part of every oncological Pancreatic resection, a standard lymphadenectomy, i.e. removal of lymph nodes of the right side of the hepatoduodenal ligament (12b1, 12b1, 12c), posterior pancreaticoduodenal nodes (13a, 13b), nodes to the right side of the superior mesenteric artery from the origin of the superior mesenteric artery at the aorta to the inferior pancreatico-duodenal artery (14a, 14b) and anterior pancreaticoduodenal nodes (17a, 17b), has been shown to be associated with improved outcomes with no additional benefit conferred by the performance of an extended lymphadenectomy (85). Additionally, the extended procedure was associated with an increased rate of intractable diarrhoea in the early post-operative phase.

Locally advanced pancreatic cancer

Chemotherapy with or without radiotherapy is the first line of management of locally advanced pancreatic cancer. In tumours that show a response to therapy (as has been seen with FOLFIRINOX -based therapy) (86), a trial of surgery may be considered. A recent study has reported a 60% resectability rate with FOLFIRINOX that was better than gemcitabine in combination with radiation therapy (46%) (87).

Surgical Palliation of Pancreatic cancer

In pancreatic and periampullary cancers the symptoms that would need to be palliated include obstructive jaundice, uncontrolled vomiting from gastroduodenal obstruction and pain. Traditionally, the surgery performed in the case of a patient undergoing a laparotomy and found to have an inoperable tumour is the triple bypass surgery that includes a side- or end-to-side choledochojejunostomy with a retrocolic, side-to-side gastrojejunostomy and a side-to-side jejuno-jejunostomy.

However, palliative surgeries are associated not only with increased morbidity but no difference in survival compared to aborted laparotomies (88). Additionally, should the patient develop complications following the surgery, these complications have been shown to significantly impact survival (89).

Thus, in patients deemed clearly unresectable on preoperative staging, non-surgical alternatives for palliation such as SEMS for biliary and gastroduodenal obstruction must be considered. In patients with a reasonable life expectancy (more than 6 months) and a good performance status (ECOG = 0-2) in whom non-surgical methods of palliation have been attempted and have been unsuccessful, and / or in those who have received neoadjuvant therapy and on surgically exploration (with an aim for trial of resection) were found to harbor non-metastatic, but unresectable disease, the available evidence supports the creation of a prophylactic gastrojejunostomy in the setting of an inoperable pancreatic or periampullary cancer irrespective of the presence of features of gastric outlet obstruction (90) (91).

Recommendation

Pancreatectomy with standard lymphadenectomy is the current standard of care for non-metastatic, resectable pancreatic cancer.

The role of laparoscopic / robotic resections as well as synchronous vascular resections needs to be clarified.

Summary of the Surgical Recommendations

Primary tumour - Extent of resection

Resectable (including Borderline) Pancreatic cancer

Desirable / Ideal – PD / DP

Essential – PD/DP

Lymphadenectomy

Resectable (including Borderline) Pancreatic cancer

Desirable / Ideal – Standard lymphadenectomy

Essential – Standard lymphadenectomy

Metastases

Desirable / Ideal / Essential – No role for surgery in the presence of metastases

Surgical Complications and their management

The three most important complications of gastric cancer surgery are:

Post-operative pancreatic Fistula (POPF)

Delayed gastric emptying (DGE), and

Post-Pancreatectomy Haemorrhage (PPH)

The International Study Group of Pancreatic Surgery (ISGPS), an international panel of pancreatic surgeons, working in well-known, high-volume centers, has provided clear evidence-based definitions for each of the three complications to aid their identification, uniform reporting and management (92-94).

POPF – Despite diverse definitions, it is now generally accepted that if drain amylase levels are 3 times normal amylase levels on the 3rd post operative day onwards, if drain output is 10 ml, and drain colour is altered (non-serous), a diagnosis of pancreatic fistula must be strongly entertained. Sepsis and haemorrhage after PD, common sequelae of pancreatic anastomotic leakage, are associated with a mortality rate of 20 - 40% (95)

Management guidelines for POPF include:

- Ensure adequate drainage

- If abdominal drains already removed – CT guided percutaneous drains to be reinserted.

- Maintain adequate nutrition – total parenteral nutrition, enteral nutrition via nasojejunal tube or feeding jejunostomy

- Maintain haemoglobin, electrolytes

- Trial of octreotide treatment – discontinue if no response within 7 days of administration

- Close monitoring for complications of fistula – collections, abscess formation, haemorrhage – followed by appropriate treatment.

- In case above measures fail, high risk re-surgery to be undertaken*

* Abdominal lavage with repositioning of drains, disconnection of anastomosis and ligation of pancreatic remnant, completion pancreatectomy etc,

A consensus definition to aid the identification and management of DGE has been recently provided by the International Study Group for Pancreatic Surgery (93). Put simply, there are 3 grades of DGE which have been defined in Table 7. The management of grade A DGE is conservative, while patients with grade B DGE will benefit from prokinetic agents. Patients with grade C DGE, too, are best managed by the use of prokinetics and nutritional support. Very rarely, repeat surgery is warranted which has a low success rate and hence needs to be reserve as a last resort (96).

Table 7: Delayed gastric emptying (DGE) post gastric surgery

	Nasogastric drainage requirement
DGE grade A	up to 4-7th post-operative day
DGE grade B	7-14th post-operative day
DGE grade C	beyond the 14th post-operative day

7 MULTIDISCIPLINARY TREATMENT FOR ADVANCED CANCER (INCLUDING METASTATIC DISEASE)

Pancreatic Cancer: External Beam Radiation Therapy

Broad principles that are relevant to (both surgical and non-surgical) management of all pancreatic cancers are as follows:

- All patients with pancreatic cancer should be managed in a disease management group with multi-disciplinary collaboration.

- Appropriate imaging – sub-millimeter slice, triple-phase, contrast-enhanced, computed tomography (CT) for assessment of the pancreatic mass, the peri-pancreatic vessels and regional lymph nodes. Consensus Statement of the Society of Abdominal Radiology and the American Pancreatic Association should guide the staging of pancreatic cancer (97).

- Accurate staging – the report should classify the tumour as resectable, borderline resectable pancreatic cancer (BRPC), locally advanced pancreatic cancer (LAPC) or metastatic (98, 99).

- Precise resectability criteria, based on tumour location within the pancreas and the arterial or venous involvement, have been adopted in the NCCN and other guidelines (23, 100). Unresectable disease should indisputably be diagnosed if there is evidence of distant metastases, solid tumour contact with SMA and/or celiac axis >180 degrees. Controversy still surrounds and consensus is elusive for the definition of BRPC (98, 99).

- Achieving R0 resection is the main goal of pancreatic surgery, as R0 resection is one of the most important prognostic factors for patient outcome (101). However, R1 resections (<1 mm margin), exceeds 75% of all pancreatic surgery (102, 103).

Adjuvant Therapy

While the ESPAC-1 trial laid the foundation for the beneficial role of adjuvant chemotherapy in terms of a survival benefit (104), the ESPAC-3 trial confirmed the lack of a benefit of Gemcitabine over 5-FU (105). Despite this, single agent gemcitabine has been the preferred drug in the adjuvant setting (106). However, the results from the 30.5 month median follow up of the PRODIGE24 trial (107) were recently presented at ASCO. For patients aged 18-79 years, 21-84 days after R0 or R1 resection, WHO Performance status 1, adequate hematologic and renal function, and no cardiac ischaemia, mFOLFIRINOX has not only been shown to be safe, but associated with a significantly better DFS and OS compared to Gemcitabine.

Borderline Resectable Pancreatic Cancer (BRPC)

BRPC is used to describe pancreatic cancer with limited involvement of some vasculature, such that any resection, although possible, is likely to result in positive surgical margins (R1 resection). R1 resection is recognized as a negative prognostic factor for overall survival in patients with pancreatic cancer (101). However, neo-adjuvant therapy may lead to a R0 resection and promote long-term survival, and is

recommended in the NCCN guidelines. Other advantages of neo-adjuvant therapy are – earlier treatment of microscopic metastases, and that neo-adjuvant therapy is likely to be better tolerated than adjuvant therapy.

BRPC and Neo-adjuvant therapy

BRPC is an emerging entity, with no data from prospective randomized trials to guide the evaluation, diagnosis or management of this condition, but consensus based on multiple retrospective small series (42, 65, 100, 108). The available literature includes 3 meta-analyses. In the meta-analysis of 4394 patients from 111 studies, by Gillen et al, no separate analysis of BRPC or LAPC was carried out (109). The overall resection rate after neo-adjuvant therapy was 33.2% in the BRPC/LAPC group. The median survival in the resected patients after neo-adjuvant therapy in the BRPC/LAPC group was 20.5 months, which was comparable to 23.3 months seen with primarily resectable pancreatic cancer patients (109). Another meta-analysis of 536 patients in 14 phase-II trials, by Assifi et al, showed similar results with resectability after neo-adjuvant therapy in 31.6% patients from the BRPC/LAPC group (13). The median survival in the upfront resectable group of patients and the group resectable after neo-adjuvant therapy was 23 and 22 months, respectively (110). A third meta-analysis of 253 patients from 13 studies showed that down-staging after neo-adjuvant FOLFIRINOX-based therapy was noticeable in patients with BRPC/ unresectable LAPC, with a total R0 resection rate of 40% (86). Among patients with BRPC, R0 resection was possible in 63.5%.

Significant direct clinical advantage has not been conclusively shown by studies reporting neo-adjuvant treatments for BRPC and LAPC (109, 111). This is likely because of heterogeneous studies, with heterogeneous groups of patients, several of which are small series with < 25 patients each (112). The meta-analysis by Festa et al. (112), highlighted 2 interesting observations – the average survival with neo-adjuvant therapy and surgery was similar to that with adjuvant RT +/- chemotherapy after surgery.

A large single-centre series from the MD Anderson Cancer Center showed similar results. Of the identified 160 patients with BRPC, 125 (78%) completed preoperative therapy and restaging, and 66 (41%) underwent pancreatectomy. Vascular resection was required in 18 (27%) of 66 patients, and 62 (94%) underwent a margin-negative (R0) pancreatectomy. A partial pathologic response to induction therapy (< 50% viable tumour) was seen in 56% of patients. Median survival was 40 months for the 66 patients who completed all therapy and 13 months for the 94 patients who did not undergo pancreatectomy (p < 0.001). SBRT is evolving as an alternative to CRT in the neo-adjuvant setting for BRPC (111).

Neo-adjuvant therapy significantly decreases the accuracy of CT scan in determining operability, T-staging (39%, from 78%), and resectability R0 (58%, from 83%) of pancreatic head carcinoma (113). Overestimation of tumour size and vascular invasion significantly reduces CT scan specificity after preoperative treatment (113). Another study with 129 patients confirmed that radiographic down-staging was rare after neo-adjuvant therapy, and RECIST response was not an effective treatment endpoint for patients with BRPC (114). Most patients (69%) have stable disease after initial therapy, and the authors concluded that these patients should undergo pancreatectomy in the absence of metastases or significant disease progression (114).

Summary of recommendations:

- About one-third of initially unresectable cancers (BRPC/LAPC) were rendered resectable after neo-adjuvant therapy (109, 112).

- These cancers rendered resectable (R0) and underwent surgery after neo-adjuvant therapy had an

overall survival of 20 months, similar to resectable tumours at initial presentation and undergoing R0 resection (109, 112).

- Neo-adjuvant therapy using both chemotherapy and radiotherapy, before planned resection.

- Response to neo-adjuvant therapy is difficult to assess – radiologically or using CA 19-9.

- Patients with no evidence of disease progression after neo-adjuvant therapy must be considered for laparotomy with intent to resect the tumour.

BRPC and Adjuvant Chemoradiotherapy (CRT)

Of the patients who undergo resection, 80% suffer a relapse, locally or distant, and have a 5-year survival rate of 20% despite adjuvant chemotherapy (23, 30, 104). One randomized trial showed an improvement in survival with postoperative CRT (115), however, these results were not confirmed by an EORTC trial with the same design (116). In the ESPAC-1 trial, survival was actually shorter in patients who received CRT compared to those who did not (15.9 months versus 17.9 months; p = 0.05) (104). A meta-analysis of 875 patients, by Stoken et al, concluded that there was a benefit of CRT in patients with R1 resection, despite heterogeneity between trials with R1 resection patients from 18–83% (117).

A large retrospective study of 6165 patients, from the US National Cancer Data Base, with pT1-3N0-1M0 resected PC in revealed an improved OS provided by CRT (HR, 0.851; 95% CI, 0.793–0.913; P < 0.001) when compared to adjuvant chemotherapy alone (118). Subset analyses showed that CRT was associated with improved OS among patients with pT3 or pN1 disease and particularly among patients with R1 resection (118). In this analysis, the CRT was associated with an OS benefit when radiation therapy was delayed for 1–3 months after the beginning of chemotherapy.

Recommendations:

- To recruit patients in ongoing trials.

- Consider chemoradiotherapy – patients with pT3 or pN1 disease who underwent R1 resection.

Locally Advanced Pancreatic Cancer (LAPC)

LAPC – CRT versus chemotherapy alone

Multidisciplinary teams within the disease management group should assess and decide based on established guidelines whether the tumour can be considered as BRPC (see above) or is truly unresectable, defining LAPC (98, 99, 119). Survival of patients with LAPC without distant metastases is around 6-12 months (120), and chemoradiotherapy (CRT) using gemcitabine adds a modest benefit of 3 months (121).

Older trials showed improved survival with CRT when compared with chemotherapy alone, confirmed in a meta-analysis (HR 0.69; 95% CI: 0.51 – 0.94) (122). However, 5 randomized trials comparing CRT with chemotherapy were contradictory (120, 121, 123-125). Notable factors in some of these studies include use of obsolete chemotherapy regimens, obsolete radiation doses and inclusion of stomach cancers. Therefore CRT or chemotherapy alone are both acceptable treatment options in this setting (126).

Although gemcitabine could be considered a better agent for combination with radiotherapy based on the ECOG trial results (121), a phase II randomized trial favoured capecitabine over gemcitabine as less toxic and more active (127).

Summary of recommendations:

Acceptable treatment options include both CRT or chemotherapy alone.

LAPC – Induction Chemotherapy Before CRT

Up to 30% of patients with LAPC develop metastatic disease within 3 months, induction chemotherapy for 3–4 months could potentially select a subgroup of patients without early metastatic course who could benefit from CRT, as suggested by 2 large retrospective studies (128, 129). This strategy helps, firstly, address potential systemic disease (ie microscopic metastases) and secondly, limits the radiation therapy to a subgroup of patients with well controlled tumours (128, 129).

An international phase III trial, LAP07, has investigated this sequential approach of induction chemotherapy followed by CRT. The trial, although initially planned to include 722 patients with LAPC, was stopped for futility after recruiting 449 patients (130). Patients showing no tumour progression after 4 months of chemotherapy (n=267) underwent a second randomization to receive either two further months of gemcitabine or CRT. The OS was not significantly different between the two arms (15.2 versus 16.4 months, respectively; p = 0.8). However, the CRT resulted in improved PFS, and treatment-free interval (6.1 versus 3.7 months, p = 0.017) and less frequent loco-regional tumour progression (32% versus 46%, p = 0.035), confirming the efficacy of CRT for local control (130). More active combination regimens of chemotherapy used in metastatic disease, such as FOLFIRINOX or gemcitabine plus nab-paclitaxel, are evolving as options for these patients (131, 132). In a meta-analysis of induction FOLFIRINOX, in the subgroup of patients with LAPC (initially unresectable), the pooled rate of resection was 26.1% (95% CI, 18.2–35.9) and the pooled rate of R0 resection was 22.5% (95% CI, 3.3–35.4%) (86).

Summary of Recommendations:

- The standard of care remains 6 months of chemotherapy with gemcitabine (from LAP-07 trial).

- CRT is an option (resulting in better PFS and local control), to be considered in stable or responding patients after 3-4 months of chemotherapy.

- Options of concurrent chemotherapy during conventionally fractionated radiotherapy include weekly gemcitabine, continuous 5-FU infusion or oral capecitabine (twice daily dosage).

- Commonly used doses of RT are 50.4Gy or 54Gy in 1.8Gy per fractions.

LAPC – Radiation Therapy in LAPC (as part of CRT – concurrent or sequential)

Local progression of LAPC can lead to significant morbidity, pain and gastric outlet obstruction (133), therefore radiotherapy is important for these patients. New radiation techniques such as intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) enable better dose delivery to the tumour while sparing the organs-at-risk, thereby reducing the acute and late side-effects (134-136). A systemic review comparing toxicity after IMRT versus 3D-CRT for patients with pancreatic cancer found strongly significant reduction with IMRT of acute (grade-3) nausea/vomiting (7.8% vs 13.4%, p<0.001), acute (grade-3) diarrhoea (2% vs 11.6%, p<0.001) and late (grade-3) GI toxicities (5% vs 10%, p=0.017) (135).

Technological advances include respiratory motion management, image-guidance, better treatment planning and delivery systems. Treatment of gross disease with margins, excluding elective nodal coverage has shown improved toxicity whilst maintaining local control rates (137-141).

Stereotactic body radiation therapy (SBRT) is fast evolving as a very effective local treatment modality, as it is well-tolerated and can be given as a shortened course of radiotherapy, with minimal interruption in systemic therapy (111). SBRT aims to deliver high doses of radiation at bigger doses per fraction (hypofractionation) to a small target volume with tight margins and steep dose gradients. Respiratory

motion management have enabled customised (minimised) margins for PTV. SBRT allows steeper dose distributions and better sparing of organs at risk (OARs), despite the proximity of the duodenum and the stomach (111).

Respiratory motion management for pancreatic cancers can be carried out in one of the following ways:

- Greater margins in the cranio-caudal direction.

- Four-dimensional (4D) CT for characterizing tumour motion to generate an internal target volume (ITV).

- 4D-CT for respiratory gating.

- Tracking using orthogonal x-ray fluoroscopy.

Delineation of Target Volumes

Accurate delineation of target volumes and organs at risk, aided by high quality biphasic (arterial and portal-venous phases) contrast-enhanced CT and FDG-PET imaging should be carried out. Dilute oral contrast may help define the pancreatic head against the duodenum. Delineation based on most of the studies (111) is described as follows:

- CTV = Gross disease (based on contrast enhanced planning CT and PET/CT) + individualised margins (respiratory motion management).

- PTV = CTV + 2-3mm.

As tissues within the irradiated volume receive very high doses, areas at risk for microscopic disease and drainage nodes are not included in treatment volumes (111). The margins for PTV expansion is typically 2-3mm, for SBRT, and dose is prescribed to the periphery of the PTV. Metallic fiducial markers are often placed as surrogates for tumour position, to guide tracking or image verification.

Dose and Toxicity

Late toxicities include upper GI bleeds, ulceration and strictures (142-144) possibly related to the dose and volume of duodenum irradiated. GI toxicity has reduced with better understanding of duodenal tolerance and using a multi-fraction SBRT schedule (as opposed to single-fraction schedule) (145-147). Adaptive duodenal-tolerance based SBRT dose prescription has been used and reported at 3 dose levels, with no acute grade-3 toxicity and 8% late grade-3 GI toxicity (148, 149), as follows:

- 24Gy in 3 fractions (8Gy/fraction) – if the tumour approximated 1/3 or more of the circumference of the duodenum or stomach.

- 30Gy in 3 fractions (10Gy/fraction) – if the tumour abuts the bowel only in 1 area, in the axial, coronal or sagittal planes on the CT scan with oral contrast and/or the space between the tumour and bowel wall was <3 mm.

- 36Gy in 3 fractions (12Gy/fraction) – if the separation between the tumour and bowel wall is >3 mm.

In the largest series by Didolkar et al, severe late GI toxicity (grades 3 and 4) was 22.3%, and the statistically significant difference was noted only between the patients treated in the earlier years compared with more recent years, attributed to better delineation of target volume and OARs and technical advances in radiotherapy including respiratory motion management (150). A phase-I study showed that it was possible to irradiate a small volume of duodenum up to 22.5Gy with acceptable toxicity (151). In a recent

review of SBRT literature for BRPC and LAPC, the authors advocate fractionated SBRT with smaller doses per fraction, in order to reduce the risk of GI toxicity (111).

Techniques for Planning and Delivery of SBRT

After delineation of relatively small treatment volumes, the plan is generated using VMAT or tomotherapy (or cyberknife) and on-line image verification using modern IGRT (or real-time tracking) is used for treatment delivery.

Outcomes from SBRT

Data from 20 systematically included studies, in a recent overview of SBRT for pancreatic cancers, put the overall survival rates at 1 and 2 year at 59 to 80% and 29 to 74% respectively, and local control at 1 and 2 year ranges from 59 to 95% and 50 to 92%, respectively (111).

Summary of recommendations:

- Conventionally fractionated RT dose is 50.4Gy or 54Gy in 1.8Gy per fractions.

- SBRT is emerging as alternative RT modality, and is to be implemented carefully after careful consideration of the available literature, local technology / infrastructure and locally available expertise and experience.

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		SOCIAL
Pain, Nausea and vomiting, Constipation, Dysponea, Bowel Obstruction		Financial, education, job, social environment eg neighbours

HOLISTIC SUFFERING

PSYCHOLOGICAL		SPIRITUAL
-Stage of Grief (Denial, anger, bargaining, depression, acceptance) -Helpless, hopeless, lack of self		-Why me? -Meaning of disease

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.

FOLLOW-UP AND SURVIVORSHIP

Follow-up schedule after surgery / chemotherapy

Year	Time from start of chemotherapy (months)	Clinical examination	Elevated tumour marker levels, CA 19-9	CT CAP	Discharge
0	0	✓	✓	✓	
1	3	✓	✓		
	6	✓	✓		
	9	✓	✓		
	12	✓	✓	✓	
2	18	✓	✓		
	24	✓	✓	✓	
3	30	✓	✓		
	36	✓	✓	✓	
4	48	✓	✓		
5	60	✓	✓		✓

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.

RESEARCH AVENUES

Service

Reconfiguration of complex surgery to secondary and tertiary centres

Outcome data for pancreatic cancer – 1-y survival and 5-y survival data

Education

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

- Interventional radiology training

12 APPENDIX

A. Pathology reporting of Pancreatic Cancer

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 pancreatic cancer include:

Macroscopic

1. Type of specimen

2. Site of tumour

3. Maximum tumour dimension

4. Resection margins

5. Superior mesenteric vein (SMV) or portal vein (PV) involvement (if included in the specimen)

6. Background pathology

Microscopic

1. Histological type

2. Tumour grade

3. Maximum extent of local invasion

4. Perineural invasion

5. Lymphovascular emboli

6. Vessel (SMV, PV) involvement

7. Tumour regression grading score (specify grading system used)

8. Lymph node status (number present, number involved)

9. Resection margin status

10. Pathologic staging (UICC/AJCC TNM 8th edition)

Explanatory notes

Relevant Surgical anatomy

Knowledge of the surgical anatomy is critical in grossing pancreatic resections. A few anatomical aspects pertinent to evaluation of pancreatic resections are given below:

a) Relationship of pancreatic head and superior mesenteric vessels

The head of pancreas shares a close anatomical relationship with the superior mesenteric vessels and absence of invasion of these blood vessels by the pancreatic head tumour is an important criterion that determines tumour resectability. The SMV, together with the superior mesenteric artery (SMA) on its left, passes along the anterior surface of the uncinate process whereupon they curve underneath the pancreatic neck to reach the posterior surface. Herein, the SMV indents the pancreatic surface which is identifiable as a smooth, curvilinear tract, referred to as 'the SMV groove' (also referred to as SMV margin, see under section -margins). The SMA courses to the left of SMV and is closely applied to the uncinate process. During pancreaticoduodenectomy (PD), a surgeon has to sharply dissect the SMA off the uncinate process which produces a rough area on the uncinate process which is referred to as the 'SMA margin'. This surface/margin has also been referred to previously as 'the retroperitoneal margin' or the 'uncinate margin' by different authors.

b) Pancreatic head surfaces

The head of pancreas encompasses four important landmarks which are relevant to evaluation of PD resections for pancreatic cancer:

1. Anterior surface, which is smooth bulging anterior face of the pancreatic head.
2. Posterior surface, which is also a flat, fibrous surface on the posterior aspect of pancreatic head.
3. SMV surface- Between the anterior and posterior surfaces of the pancreatic head, and beneath the pancreatic neck cut margin is the SMV surface of the pancreatic head. It is a shallow curvilinear groove with a fairly glistening, smooth surface. This groove reflects the tract of the superior mesenteric vein (SMV).
4. SMA surface- Flanking to the left of the SMV surface is a relatively small, some-what triangular area of rougher texture that *in vivo* faces the superior mesenteric artery (SMA).

Types of specimen for pancreatic cancer

The type of surgical specimen received depends on the site and size of the tumour and includes:

1) Standard Kausch-Whipple's pancreaticoduodenectomy specimen
    This comprises of distal two-thirds of the stomach, the gall bladder and its cystic duct, the common bile duct, the head of the pancreas, duodenum, proximal jejunum, and regional lymph nodes.

2) Pylorus preserving pancreaticoduodenectomy (PPPD)
    This is a modification of Whipple's resection wherein the stomach is not included.

3) Distal pancreatectomy - consists of the body and tail of pancreas, with or without the spleen.

4) Median pancreatectomy- resection of the mid-body segment of body of pancreas

5) Total pancreatectomy- is a combination of PD and distal pancreatectomy

6) Enucleation specimen- in which tumour is removed with its capsule from the pancreatic parenchyma

Site of tumour

Pancreaticoduodenectomy is performed for not only pancreatic cancer but also for tumours originating in the ampulla of Vater, periampullary duodenum and terminal end of common bile duct. Making a distinction between these 4 cancer types is essential as these are biologically distinct malignancies with different outcomes. This may be especially difficult to determine when the tumour is located in close proximity to, or is large and involving more than one of these adjoining sites. Therefore, during macroscopic evaluation it is vital to document the epicentre of the tumour (i.e. the site of tumour centre). This should be later corroborated with microscopic findings.

Tumour size

Tumour size should be recorded in all three dimensions. This should be later confirmed or altered on the subsequent microscopy.

Histologic type

Histologically, PDAC is characterized by malignant glands infiltrating in a typical desmoplastic stroma. Many morphologic variants of ductal adenocarcinoma are recognized that differ in prognosis (Table 1)

Table 1 Histologic types of exocrine carcinoma of pancreas (WHO Classification) (152)
Ductal adenocarcinoma • Mucinous (colloid) carcinoma • Medullary carcinoma • Signet-ring cell carcinoma • Adenosquamous carcinoma • Undifferentiated (anaplastic) carcinoma • Undifferentiated carcinoma with osteoclastic giant cells Mucinous cystadenocarcinoma (non-invasive) • Mucinous cystadenocarcinoma (invasive) Intraductal papillary mucinous carcinoma (non-invasive) • Intraductal papillary mucinous carcinoma (invasive) Acinar cell carcinoma • Acinar cell cystadenocarcinoma • Mixed acinar endocrine carcinoma Mixed ductal endocrine carcinoma Serous cystadenocarcinoma Solid-pseudopapillary carcinoma

Colloid (mucinous) carcinoma and medullary carcinomas are associated with better outcome while other variants such as adenosquamous carcinoma and undifferentiated (anaplastic) carcinomas are associated with a poorer prognosis. Medullary carcinomas are characterized by solid syncitial growth pattern and a rich intratumoural lymphoid infiltrate. These variants are likely to display microsatellite instability and display a better prognosis. Acinar cell carcinomas are aggressive tumours however exhibit a slightly better prognosis than conventional PDAC. Adenosquamous carcinoma is a rare neoplasm characterized by the presence of variable proportions of glandular and squamous components. The squamous component should account for at least 30% of the tumour tissue (152).

Undifferentiated (anaplastic) carcinomas are highly lethal carcinomas which lack any ductal differentiation are composed of large pleomorphic cells, anaplastic, sarcomatous, or rhabdoid cells that grow in poorly cohesive formations supported by scanty fibrous stroma. High mitotic activity as well as perineural, lymphatic, and blood vessel invasion is seen in most cases (152). Undifferentiated carcinoma with osteoclastic giant cells has pleomorphic mononuclear cells with scattered osteoclastic giant cells; latter mark with histiocytic markers.

Mixed ductal-endocrine carcinoma is characterized by an admixture of ductal and endocrine cells. By definition, the endocrine cells should comprise at least 1/3rd to 1/2 of the entire tumour. The ductal cells are highlighted by the presence of a ductal marker such as CEA while endocrine cells are reactive for the neuroendocrine markers (152).

Invasive adenocarcinoma can arise in the background of pre-invasive neoplasms, namely, intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). Awareness of the pre-invasive nature of these neoplasms also has a bearing on sampling and reporting. If on microscopy, an IPMN or MCN is encountered, complete sampling and evaluation of the tumour is warranted in order to exclude the possibility of any missed invasive carcinoma focus. It is also essential to document if an invasive carcinoma is arising in a background of IPMN or MCN as the prognosis of these cancers is better than conventional PDACs (153, 154)

Role of IHC in diagnosis of pancreatic carcinoma is very limited. On IHC, pancreatic adenocarcinomas are positive for ductal markers on IHC- CK7,8,18,19 and also for mucins- MUC1, MUC5AC and negative for MUC2. These markers are not specific for pancreatic origin however may be useful when other non-ductal neoplasms are being considered as differential diagnoses. Acinar cell carcinomas are positive for trypsin and chymotrypsin (152).

Tumour grade

Grade signifies the inherent biologic aggressiveness of a tumour. Histological grading of PDAC into well, moderately and poorly differentiated has been found to be of prognostic significance (Table 2) (155). The tumour is graded according to the least differentiated area, regardless of the amount.

Table 2: Tumour grading according to Kloppel's criteria (155)

Differentiation	Duct structures	Nuclei	Mitotic count	Mucin
Well	Well formed	basal	< 5/10 HPF	Marked
Moderate	Somewhat well formed	Loss of basal polarization	5-10/HPF	Variable
Poor	Poorly formed or absent	Marked nuclear atypia	>10/10 HPF	Minimal

Abbreviation: HPF- high power fields

Background pathology

It is essential to document if a tumour is arising from a cystic precancerous neoplasm. Invasive carcinomas arising from IPMN or MCN tend to exhibit a better prognosis compared with conventional ductal adenocarcinoma (154). Further, presence or absence of communication with the pancreatic ductal system, (main duct or branch duct) supports the diagnosis of IPMN and MCN, respectively. Dilatation of main pancreatic duct with papillary growth and mucoid secretions is characteristic of IPMN. Female preponderance and cystic tumour devoid of contact with ductal system and ovarian stroma in the cyst wall on histology is typical of MCN.

Pancreatic intraepithelial neoplasia (PanINs) are common incidental precursor lesions found in >80% of PDAC cases. While recording their presence merely serves documentation purpose as these do not carry any therapeutic or prognostic significance.

Neural invasion

Invasion of the nerve sheath or nerve substance by tumour cells is referred to as perineural invasion (PNI). Presence of PNI is significantly correlated with extrapancreatic plexus invasion and risk of local recurrence (156).

Vascular invasion

Infiltration of superior mesenteric artery or celiac plexus is a contraindication for surgery. On the other hand surgery (with or without venous reconstruction) is performed in a proportion of cases of SMV or PV involvement. When a named vessel is included in the specimen, pathology report should indicate whether there is histological evidence of tumour infiltration. If so, the venous cut ends should be submitted as margins and assessed for presence of tumour.

Resection margins

1. Pancreaticoduodenectomy

Resection are (RM) status is a key prognostic factor in pancreatic cancer. Tumours are classified as R0 when margins completely free of tumour microscopically, R1 when margins are involved microscopically but free macroscopically, and R2 when margins are involved macroscopically. Traditionally, only transected (en-shave) margins, as enlisted below, were sampled. However, recent studies have shown that inclusion of additional circumferential resection margin (CRM) assessment into a standardized pathology protocol has resulted in a significant increase in the R1 rates for pancreatic cancer, from 14–53% to 76–85% (103, 157);moreover, the R1 rate thus derived correlated better with survival.

The resection margins evaluated for pancreatic cancer are as follows:

A. Transected margins (*en-face*) margins:

a. Proximal duodenal/ stomach cut margin

b. Distal enteric cut margin

c. Pancreatic neck cut margin

d. Common bile duct cut margin

e. Venous (SMV or PV) cut margins-proximal and distal (if vessel included)

B. Circumferential margins:

a. Anterior margin

b. Posterior margin

c. SMV margin

d. SMA margin

A margin is regarded as involved if tumour is identified   1mm away from the margin (i.e. 1 mm clearance is needed for R0). The anterior surface is an anatomic surface and not a surgical margin; however studies have shown that anterior surface involvement is associated with increased local recurrence and decreased

survival, hence documenting its involvement, is of prognostic significance rather than of surgical relevance. Presence of tumour within 1 mm within a lymph node, or a perineural/lymphovascular space is also regarded as incomplete excision however, if these form the only reason for reporting a case as R1, the mode of margin involvement must be clearly documented in the report (158).

It is notable that the margin evaluation and rates of involvement have varied between different studies. This is attributable to lack of standardized nomenclature and pathologic examination protocol and of a consensus on R1 definition (103, 157). Implementing a standardized pathologic evaluation protocol is a crucial means of reducing this disparity prevalent in R1 reporting and generating meaningful data. Local audits can provide clinical validation of the data thus accrued. Till further evidence accumulates, documenting involvement of all margins and recording microscopic distance of tumour from margins is recommended.

2. Distal Pancreatectomy

Margins sampled are as follows:

a. Pancreatic neck cut margin.

b. Anterior margin (anterior pancreatic surface)

c. Posterior margin (posterior pancreatic surface)

3. Median pancreatectomy

Margins sampled are as follows:

a. Right pancreatic neck cut margin

b. Left pancreatic neck cut margin

c. Anterior margin (anterior pancreatic surface)

d. Posterior margin (posterior pancreatic surface)

Lymph node sampling

Lymph node metastasis is an important negative prognostic marker in pancreatic cancer (159). Evaluation of 15 lymph nodes is regarded minimum adequate number for optimal pathologic staging. The total and metastatic lymph nodes examined should be reported in the pathology report. The regional lymph nodes in the PD specimens are sampled from the following regions:

a. Anterior pancreatoduodenal groove

b. Posterior pancreatoduodenal groove

c. Inferior (includes nodes around SMV and SMA)

d. Anterior pancreatic surface

e. Posterior pancreatic surface

f. CBD region

g. Infra-pyloric

h. Superior

i. Celiac (sent separately)

j. Hilar and peripancreatic nodes (distal pancreatectomy)

All of the lymph nodes dissected from the specimen should be examined histologically. Direct infiltration of the primary tumour into lymph nodes is also classified as lymph node metastasis. Use of IHC for detecting metastasis in a histologically negative node is not currently recommended for routine practice.

Tumour regression grading score

As neoadjuvant therapy is increasingly being administered in borderline resectable pancreatic cancer patients, specimens with prior therapy related changes are becoming common. Hyalinization, necrosis, foam cells, calcification and inflammation in the tumour area are histologic features of tumour regression/ response. Various grading systems are available for application, however the most commonly used method to grade response is the modified Ryan's regression grade (Table 3) (160). Tumour regression is assessed only in the primary tumour. Acellular pools of mucin in specimens from patient receiving neoadjuvant therapy are considered to represent completely eradicated tumour and are not used to assign pT stage or counted as positive lymph nodes

Table 3: Tumour Regression grade (Modified from Ryan et al) (160)

Description	Tumour Regression Grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumour kill; extensive residual cancer	3 (Poor response)

Pathologic staging

Pathologic tumour stage is the most significant factor in predicting survival in pancreatic cancer. UICC TNM staging requires assessment of the maximum size of the tumour and extent of local invasion beyond the pancreas (Table 4). It is important to note that involvement of the intra-pancreatic common bile duct by pancreatic carcinoma should be staged as pT3.

Table 4: UICC TNM staging (161)

pT stage	Description
T1	Maximum Tumour diameter < 2 cm
T2	Maximum Tumour diameter > 2 4 cm
T3	Maximum Tumour diameter > 4 cm
T4	Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)

Grossing technique

Currently, several different techniques are employed for dissecting PD specimens both with its attendant merits and limitations. First involves bi-valving of the specimen through the Ampulla of Vater with resultant two mirror image slices through the pancreatic and CBD. The second technique which is discussed below involves the axial dissection method which has several advantages. It is easy to perform, and allows key anatomical structures (e.g. ampulla, common bile duct, main pancreatic duct) to be seen in the same slices, and facilitates radial sampling of margins with respect to tumour.

Steps in grossing

1. State the type of specimen

2. Orient the specimen and identify the various components of the specimen as well as the different surfaces of pancreatic head (anterior, posterior, neck, SMV groove and SMA surface).

3. Take dimensions of each component of the specimen.

4. Document the presence of a named vessel (e.g. portal vein, superior mesenteric vein) if any.

5. The external surface of the specimen should be examined for any abnormality.

6. Remove all the staples meticulously.

7. Paint the different margins of the pancreas using multi-colour inking, in accordance with an agreed colour code. This is preferably done when the specimen is fresh (but can also be undertaken when fixed), however, before blocks are taken. Allow adequate time for drying of paints before fixing the specimen.

8. Open the intestinal segment with a scissors. Expose the ampullary region and inspect the ampulla and duodenum for presence of tumour.

9. Make serial cuts in the pancreatic head in an axial plane, perpendicular to the long axis of the duodenum.

10. Determine the origin of the tumour–whether ampullary, duodenal, terminal bile duct or pancreatic head. In cases involving more than one subsite, determine the location of the tumour centre.

11. Fix the specimen by placing in a large volume of formalin for 24-48 hours.

12. Serially slice/ bread-loaf the pancreatic head in an axial plane from superior to inferior surface (along the cuts made previously for fixation). The slices should be approximately of equal thickness, with each slice measuring 3 to 5mm in thickness. The slices thus obtained are sequentially placed in order from top to bottom on a board for examination.

13. Identify the tumour and record its size, appearance, extent, and relation to the resection margins

14. Measure the distance of tumour from the various cut margins and surfaces.

15. Sections to be taken:

    a. Tumour, minimum of 4 sections. The sections should include tumour with ampulla, with CBD, with duodenum and with pancreatic head.

    b. Transected margins;

        i) the proximal duodenal/ stomach resection margin,

        ii) the distal enteric resection margin,

        iii) pancreatic neck resection margin, and

        iv) common bile duct resection margin

        v) Venous- proximal and distal margins (if vessel included)

    c. Circumferential margins:

        i)   Anterior margin

        ii) Posterior margin

        iii) SMV margin

        iv) SMA margin

    d. Adjacent pancreas

    e. Infrapyloric, anterior and posterior pancreatoduodenal, uncinate, anterior, posterior, inferior pancreatic and pericholedochal nodes along the specimen.

    f. Separately sent lymph nodes, sent by the surgeon

The slices showing tumour closest to inked circumferential margins/surfaces should be chosen for sampling. If *no tumour* is identified, as can happen in post-chemotherapy or post-radiotherapy specimens, multiple sections should be taken from areas showing firm or hard areas. The slices, from which these sections are taken, should be recorded.

Pancreatoblastoma

Pancreatoblastomas are rare paediatric tumours originating from the epithleial exocrine portion of the pancreas. They tend to present as large, retroperitoneal masses in children (mean age 5 years) that are often unresectable at presentation. Biopsy of the tumour is warranted to prove the diagnosis and imaging for staging is recommended. While complete surgical (R0) resection is the treatment of choice along with adjuvant chemotherapy, unresectable tumours may benefit from NACT with cisplatin and doxorubicin.

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CHAPTER

14 ABBREVIATIONS

AAR	Age-adjusted incidence rate	IV	Intravenous
AJCC	American Joint Cancer Committee	LAPC	Locally advanced pancreatic cancer
ASA	American Society of Anaesthesiologists	LMWH	Low molecular weight heparin
BD	Twice daily	LVEF	Left ventricular ejection fraction
BMI	Body mass index	MCN	Mucinous cystic neoplasia
BRPC	Borderline Resectable Pancreatic Cancer	MDCT	Multi-detector computed tomography
BSC	Best supportive care	MEN	Multiple endocrine neoplasia
CAPOX	Capecitabine and oxaliplatin	MPV	Main portal vein
CDK	Cyclin-dependent kinase	MRI	Magnetic resonance imaging
CECT	Contrast-enhanced computed tomography	NACT	Neoadjuvant chemotherapy
		NCCN	National Comprehensive Cancer Network
CF	Cisplatin and 5-FU		
CGN	Celiac Ganglion	NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
CI	Confidence interval		
CPN	Celiac plexus Neurolysis	OD	Once daily
CRT	Chemoradiotherapy	PD	Pancreatoduodenectomy
CT	Computed tomography	PET	Positron emission tomography
CTV	Clinical target volume	PFS	Progression-free survival
DGE	Delayed Gastric Emptying	PO	Per oral
ECHO	Echocardiogram	POPF	Post-operative pancreatic fistula
ECOG	Eastern Cooperative Oncology Group	PPH	Post-pancreatectomy haemorrhage
EMR	Endoscopic mucosal resection	PPI	Proton pump inhibitor
EUS	Endoscopic ultrasonography	PRRT	Peptide radionuclide receptor therapy
5-FU	5-Fluorouracil	PS	Performance status
FDG	Fluoro-deoxyglucose glucose	QDS	Four times a day
FNA	Fine needle aspiration	RR	Relative risk
GDA	Gastroduodenal artery	SC	Subcutaneous
GEP-NET	Gastroenteropancreatic neuroendocrine tumours	SEER	Surveillance, Epidemiology, and End Results Program
GI	Gastrointestinal	SEMS	Self expanding metal stent
Gy	Gray	SMA	Superior mesenteric artery
GOO	Gastric outlet obstruction	SMV	Superior mesenteric vein
5-HIAA	5-hydroxy-indole acetic acid	SPECT	Single photon emission computed tomography
HPF	High-power field		
ICMR	Indian Council of Medical Research	TDS	Thrice daily
IHC	Immunohisotchemistry	ULN	Upper limit of normal range
IPMN	Intraductal papillary mucinous neoplasia	VTE	Venous thromoboembolism
ISGPS	International Study Group for Pancreatic Surgery	WHO	World Health Organization