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Indian Council of Medical Research Consensus Document for the Management of Pancreatic Cancer

Executive Summary

This consensus document may be used as framework for more focused and planned research programs 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 and while realizing the fact that some patients may require treatment strategies other than those suggested in these guidelines.

- Histological confirmation is mandatory before the commencement of definitive treatment
- All patients should be staged according to the tumor, node, and metastasis staging system, and risk should be assessed at diagnosis. A baseline contrast-enhanced computed tomography (CT) 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
- The indication for endobiliary stenting in patients with obstructive jaundice includes symptoms of cholangitis and/or sepsis, resultant coagulopathy and/or renal insufficiency, or if significant delays in surgery are anticipated
- The patient's malignancy should be classified as resectable, borderline resectable, or locally advanced on the basis of radiologic criteria at diagnosis and treatment plan discussed accordingly
- Resectable pancreatic cancer – Primary surgery remains the standard of care. Neoadjuvant therapy (NAT) (chemotherapy ± radiotherapy) should be considered in locally advanced and borderline resectable tumors 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 disease that has spread beyond 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 and 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 clinical trials
- Refer for early palliative care, if indicated.

Incidence

Pancreatic cancer currently ranks as the 12th most common cancer in the world but has the notorious distinction of being the 4th leading cause of cancer-related deaths.[1-4] There exists considerable regional variation in the age-standardized incidence rates of pancreatic cancer in the world. Places in Asia report incidences as low as 0.6/100,000 persons per year, while incidence rates as high as 12.6/100,000 have been reported from the West.[5] The age-standardized incidence rates for pancreatic cancer on an average are 8.2 and 2.7/100,000 among males in the developed and developing countries, respectively, and 5.4 and 2.1/100,000 among females in the developed and developing countries, respectively.[6]

In comparison to the West, India has a relatively lower incidence of pancreatic cancer. The rates in India vary from 0.5 to 2.4/100,000 persons per year among women to 0.2 to 1.8/100,000 persons per year among men.[7] The National Cancer Registry Programme (ICMR, Bengaluru)[8] has estimated that by 2020, there will be 8440 and 6090 new cases of pancreatic cancer afflicting Indian men and women, respectively.

Purpose

Although International Guidelines are available for the management of pancreatic cancer, it is not entirely feasible to apply these guidelines to the Indian population owing to differences in incidence of the disease in different parts of India, socioeconomic factors, and availability of resources. Therefore, it is essential to analyze the evidence pertaining to pancreatic cancer from India and the rest of the world[9,10] with an aim to formulate evidence-based guidelines that could be applicable to Indian patients. Taking into consideration peripheral oncology centers, regional cancer centers, and tertiary cancer centers in major cities, the set of recommendations includes two categories, namely desirable/ideal and essential.

Desirable/ideal

Tests and treatments that may not be available at all centers but the centers should aspire to have them in the near future

Essential

Bare minimum that should be offered to all the patients by all the centers treating cancer patients.

Diagnosis and Staging

In India, like most countries in the world, there is no screening program for the early detection of pancreatic

cancer. Furthermore, symptoms related to pancreatic cancer tend to be nonspecific including weight loss, abdominal pain, nausea, and dyspepsia. Both of the above contribute to the late presentation of the cancer and its notoriously poor outcomes. Thus, clinicians must be aware of specific clinical presentations linked with pancreatic cancer. Around 60%–70% of cancers arise in the head of pancreas, and these patients present with jaundice, pale stools, and itching. New-onset diabetes mellitus after 40 years or unexplained thrombophlebitis merits investigation. 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 (such as gallstones or alcohol ingestion). 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.

Recognizing these symptoms and initiating early investigation may help in the early detection of the cancer with corresponding improvement in outcomes.

Evaluation of a patient presenting with a pancreatic cancer should be aimed at pathological confirmation of the diagnosis and an accurate staging of the disease.

Diagnosis of Pancreatic Cancer

A CT scan of the abdomen and pelvis is essential in every patient suspected to have pancreatic cancer along with either a chest X-ray or inclusion of the chest in the same CT scan. Ideally, the scan of the abdomen should be carried out as per the pancreas protocol. While obtaining a tissue diagnosis of a suspected pancreatic cancer is not mandatory in a medically fit patient with disease amenable to a curative resection, a biopsy is required for any patient who is a candidate for neoadjuvant treatment, including borderline resectable patients. Endoscopic ultrasound (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.[11,12] In patients with locally advanced or metastatic disease, a percutaneous biopsy from an easily accessible site is preferred over EUS-guided sampling on account of its lower cost, wider availability in India, and wider applicability among sicker patients where sedation may be hazardous.

Initial biochemical evaluation of suspected or proven patients with pancreatic cancer should include the liver function tests, fasting blood sugars, HbA1c, and tumor markers such as serum carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen levels. CA19-9 levels may be elevated in conditions other than cancer, including benign or malignant biliary obstruction and cholangitis. For an accurate baseline, the CA19.9 levels should be measured after the bilirubin levels have normalized. CA19.9 may be undetectable in Lewis antigen-negative patients with pancreatic cancer. Preoperative CA19-9 levels correlate with both American Joint Cancer Committee (AJCC) staging and resectability.[13] A preoperative serum CA19-9 level ≥500 UI/ml indicates a worse prognosis after surgery.

Staging of Pancreatic Cancer

Pancreatic cancer is staged as per the AJCC system. However, a more clinically relevant way to classify pancreatic cancer is into the following categories:

1. Potentially curable
   - Resectable
   - Borderline resectable.
2. Unresectable, locally advanced
3. Metastatic.

Magnetic resonance imaging and MR cholangiopancreatography should be used to improve the characterization of indeterminate liver lesions on CT-scan or in patient who report severe allergy to intravenous iodinated contrast material. 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 tumor. These situations include unexplained dilatation or stricture of pancreatic and/or bile duct, raised CA19.9 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 borderline resectable. While the routine performance of a positron emission tomography-CT scan is not indicated, it may be considered after formal pancreatic CT protocol in high-risk patients to detect extrapancreatic metastases. These include patients with borderline resectable disease or those patients with a markedly elevated CA19-9, large primary tumors, or large regional lymph nodes. Staging laparoscopy may be considered in patients with resectable disease on preoperative imaging who harbor features suspicious for disseminated disease (high CA19-9, large primary tumors, large regional lymph nodes, body-tail tumors) as it can permit identification of peritoneal, capsular, or serosal implants that are radiologically inapparent even with conventional imaging, thereby avoiding morbid incisions in inoperable patients.

Staging should be performed as per the AJCC staging manual (8th edition, updated in 2016), and patients should be assigned a TNM stage.[14]

Treatment Plan

Treatment of each patient should ideally be undertaken by a multidisciplinary team. The intent of treatment is "curative" for patients deemed to have resectable disease (as discussed above) and "palliative" for patients with unresectable,

locally advanced disease or metastases. The treatment paradigms in the management of borderline resectable tumors are evolving and will be discussed in more detail.

Biliary Stenting

Biliary stenting should not be routinely performed in patients with pancreatic cancer except in selected indications such as in patients with obstructive jaundice in a pancreatic head or periampullary cancer who are symptomatic (with a serum bilirubin level of >15 mg/dl), septic, coagulopathic, patients who have renal insufficiency, or in whom surgical resection is significantly delayed.[15]

Biliary decompression is mandatory in jaundiced patients undergoing NAT before resection or who are receiving chemotherapy for advanced disease. Usually, bilirubin levels <3 mg/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 before confirmatory tissue diagnosis of malignancy.

Endoscopically placed biliary stents are preferred to surgical hepaticojejunostomy for relief of biliary obstruction.[16,17] SEMS has an advantage over plastic stents in terms of wider diameter, faster resolution of jaundice, and less need for reinterventions.

Resectable Pancreatic Cancer

Surgery remains the only option for cure in patients with resectable pancreatic cancer, so long as a complete resection with microscopically negative margins (an R0 resection) can be achieved. The optimal surgical resection for malignancies of the head and/or neck of pancreas is a pancreatoduodenectomy (PD). A distal or subtotal pancreatectomy is performed for malignancies involving distal neck and body, or the body and/or tail of the pancreas. Left pancreatic resections for cancer must include a splenectomy.[18] All patients must undergo a standard lymphadenectomy, that entails harvesting of lymph nodes situated to the right side of the hepatoduodenal ligament (12b1, 12b1, 12c), the posterior pancreaticoduodenal nodes (13a, 13b), lymph nodes situated along the right side of the superior mesenteric artery extending from the origin of the superior mesenteric artery down to the inferior pancreaticoduodenal artery (14a, 14b) as well as anterior pancreaticoduodenal nodes (17a, 17b).[19,20]

There is no evidence in literature to suggest the superiority of the pylorus-preserving PD over the Classic Whipple's procedure in terms of oncological outcomes.[21,22] A critical evaluation of the literature indicates that there exists no difference in the rates of POPF between PJ and PG, as well as their individual variations, except in a high-risk anastomoses where performing a PJ has its benefits.[23] The performance of an antecolic gastro-/duodeno-jejunostomy is likely to yield a significantly lower rate of delayed gastric emptying.[24-27] Multivisceral resections for pancreatic cancer are technically feasible.[28,29] Based on the limited data available, these resections are associated with a high morbidity and even mortality but an improved survival (5-year survival rates of 16%–22%)[30,31] when compared to no resection. Thus, such resections should only be performed if there exists a clear and objective possibility of achieving a complete resection (R0). Current evidence does not support the routine performance of intraoperative frozen section of the resection margin.[32] Laparoscopic resections for pancreatic tumors are technically feasible.[33-36] At the present time, the necessary evidence to suggest an advantage, or even comparability, of laparoscopic PD to open surgery in terms of overall survival is lacking.[33]

Borderline Resectable Pancreatic Cancer

Borderline resectable pancreatic cancers are those tumor "that have limited involvement of the mesenteric vessels such that resection is technically possible, but which carry a high risk of margin-positive resection unless NAT is employed before surgery."[37] There are currently numerous definitions of "borderline resectable" pancreatic cancer.[15,38-42] The ideal management strategy for these patients needs to be established.[43,44] The choice of management of these patients varies between neoadjuvant chemoradiotherapy followed by surgery[42] versus upfront surgery.[45,46] In patients diagnosed with borderline resectable disease based on radiological features, the next plan of action would entail the performance of a staging laparoscopy to determine the intent of treatment. The absence of distant metastatic disease would suggest an attempt at cure that would involve neoadjuvant chemoradiotherapy followed by reassessment. If the disease is stable or demonstrates regression on restaging,[47] a trial of resection with the possibility of a synchronous venous resection and reconstruction would seem prudent. Synchronous arterial resections for pancreatic cancer should not be performed as they are associated with increased morbidity and mortality and have a survival rate comparable to nonresected patients.[48,49]

Locally Advanced Pancreatic Cancer

Outstanding results with FOLFIRINOX in terms of downstaging of locally advanced tumors[50,51] – even rendering a proportion of them (30%–46%) amenable to resection – have prompted a more aggressive approach in this subclass of tumors, so long as the patient is medically fit for management. Chemotherapy with or without radiotherapy is the first line of management of locally advanced pancreatic cancer. In tumors that show a response to therapy (as has been seen with FOLFIRINOX-based therapy),[50] a trial of surgery may be considered.

Metastatic Pancreatic Cancer

There is no role for surgery in the management of metastatic pancreatic cancer. These patients should be considered for palliative therapies based on their functional status.

Palliative Surgery

Routine performance of palliative surgeries should be discouraged as they lead to increased morbidity with no survival benefit compared to aborted laparotomies.[17] Additionally, should the patient develop complications following the surgery - these complications have been shown to significantly impact survival.[52] Thus, in patients deemed clearly unresectable on preoperative staging, nonsurgical alternatives for palliation of biliary and gastroduodenal obstruction include SEMS. In patients with a reasonable life expectancy (>6 months) and a good performance status (ECOG = 0-2) in whom nonsurgical methods of palliation have been unsuccessful, and/or in patients who were following NAT underwent a surgically exploration (as part of the trial of resection) and were found to harbor nonmetastatic, but unresectable disease, performance of a prophylactic GJ, despite the absence of features of gastric outlet obstruction,[53,54] is supported by evidence in literature.

Adjuvant Therapy

While the ESPAC-1 trial laid the foundation for the beneficial role of adjuvant chemotherapy in terms of a survival benefit,[55] the findings of the ESPAC-3 trial demonstrated a lack of benefit of gemcitabine over 5-fluorouracil.[56] Despite this, gemcitabine remains the preferred (single agent) drug in the adjuvant setting.[57] At the recent meeting of the American Society of Clinical Oncology, the oncologists involved in the PRODIGE24 trial presented their results from the 30.5-month median follow-up.[58] mFOLFIRINOX (FOL – folinic acid (also called leucovorin, calcium folinate or FA) F – fluorouracil (also called 5FU), IRIN - irinotecan and OX-oxaliplatin) is safe and has a significantly better disease-free and overall survival compared to Gemcitabine when used in patients aged 18–79 years, with a WHO performance status ≤1, 21–84 days after a surgical (R0 or R1) resection, and in whom there were no hematologic, renal, or cardiac issues to preclude the use of the therapy.

Follow-up and Rehabilitation

Patients should be encouraged to maintain lead a healthy lifestyle and abstain from tobacco and alcohol. The aim of follow-up is to detect recurrences early as well as to assess any complication due to surgery/radiotherapy. Postsurgery, the follow-up is done every 3–4 months for the 1st year with each visit comprised of clinical examination (including history and physical examination). The follow-up in years 2–3 is every 6 months and annually, thereafter till year 5. At the end of each of the first 3 years, a CT scan of the chest, abdomen, and pelvis is recommended. For patients with advanced pancreatic cancer, the scans are symptom driven or for response assessment.

Shailesh V Shrikhande, Savio G Barreto, Bhawna Sirohi[1], Munita Bal, Raj Kumar Shrimali[2], Raju T Chacko[3], Vikram Chaudhari, Vikram Bhatia[4], Suyash Kulkarni, Tanvir Kaur[5], R S Dhaliwal[5], Goura Kishor Rath[5]

Tata Memorial Centre, Mumbai, Maharashtra, [1]Max Institute of Cancer Care, New Delhi, [2]Department of Surgical Oncology, All India Institute of Medical Sciences, [4]Department of Radiation Oncology, Institute of Liver and Biliary Sciences, [5]Department of Gatroenterology, Indian Council of Medical Research, New Delhi, [3]Department of Medical Oncology, Division of Non-Communicable Diseases, Christian Medical College, Vellore, Tamil Nadu, India

Address for correspondence:
Prof. Shailesh V. Shrikhande, Chief, Gastrointestinal and Hepato-Pancreato-Biliary Service, Deputy Director, Tata Memorial Hospital, Mumbai - 400 012, Maharashtra, India, E-mail: shailushrikhande@hotmail.com

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